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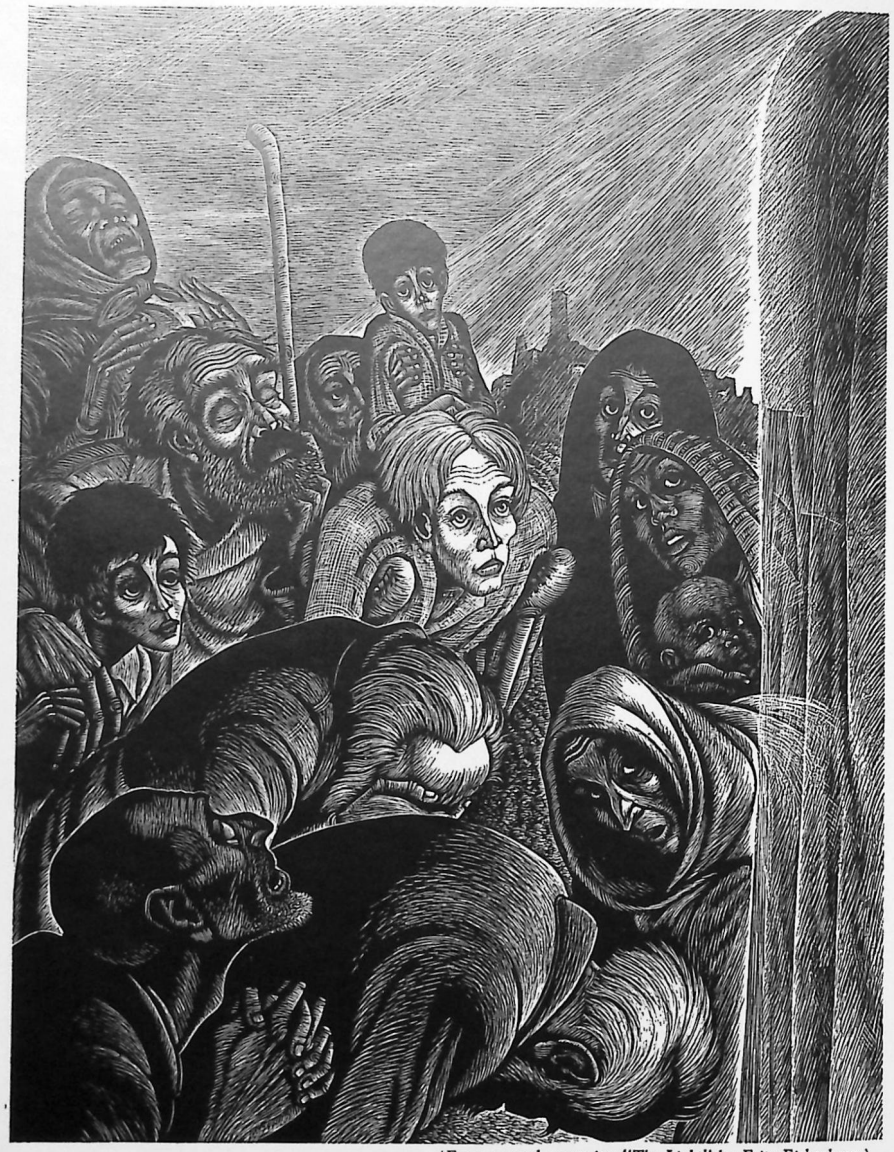

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RELIEF FROM STRESS

Our facts must be correct. Our theories need not be if they help us to discover important new facts.

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The Physiology and Pathology of Exposure

to

STRESS

A treatise based on the concepts of the

GENERAL-ADAPTATION-SYNDROME

and the

DISEASES OF ADAPTATION

by

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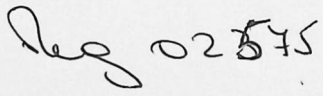

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HANS SELYE

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This book is dedicated to those who suffer from stress.

To THOSE WHO — IN THEIR EFFORTS FOR
GOOD OR EVIL, FOR PEACE OR WAR —
HAVE SUSTAINED WOUNDS, LOSS OF BLOOD
OR EXPOSURE TO EXTREMES OF TEMPERATURE,
HUNGER, FATIGUE, WANT OF AIR,
INFECTIONS, POISONS OR DEADLY RAYS.

TO THOSE WHO ARE UNDER THE
EXHAUSTING NERVOUS STRAIN OF PURSUING
THEIR IDEAL — WHATEVER IT MAY BE.
TO THE MARTYRS WHO SACRIFICE THEM-
SELVES FOR OTHERS, AS WELL AS TO THOSE
HOUNDED BY SELFISH AMBITION,
FEAR, JEALOUSY,
— AND WORST OF ALL BY HATE

For MY STRESS STEMS FROM THE URGE TO HELP
AND NOT TO JUDGE.

BUT MOST PERSONALLY,
THIS BOOK IS DEDICATED TO MY WIFE,
WHO HELPED SO MUCH TO WRITE IT,
FOR SHE UNDERSTOOD THAT I CANNOT, AND
SHOULD NOT, BE CURED OF MY STRESS
BUT MERELY TAUGHT TO ENJOY IT.

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I should like to use this opportunity to thank all my co-workers who helped me with the original experiments described in this book. It will not be necessary to mention them by name here, since their contributions have been discussed in much detail throughout the present volume.

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My special gratitude is also due to my long-time friend and collaborator, M. Kai Nielsen, who — aided by Mr. Robert Gagnon and Mr. N. Schierbeck — contributed all the illustrations pertaining to work done in this Institute. But Kai Nielsen helped me in many other ways, too varied and numerous to be listed here. Let me merely mention that he was my assistant during those first years of 1936-37, when the G-A-S concept began to crystallize, he helped me with the first adrenalectomies and hypophysectomies which were to show the rôle of the pituitary and suprarenal in the alarm-reaction, but most important of all, his sound judgment and perpetual equanimity helped me to avoid doing a number of things which — though entirely unrelated to science — would have wrecked this effort many a time. — God bless his smiling, even-minded Scandinavian soul!

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The present chief librarian of the Institute Miss Marie Atkinson, as well as her predecessor, Mrs. A. Jait and their staff, have made the task of compiling the literature on stress a comparatively simple matter for the author. If the reader turns to the reference pages at the end of this volume, he will realize the immensity of the work done by our library staff who had to procure the originals or photostats of every publication perused, not only the 5500 which were actually selected for special mention.

The kind co-operation of the U.S. Army Medical Library in Washington has been of extraordinary value to us since it is only as a result of it that I was able to obtain photostatic copies of publications otherwise quite unavailable here.

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FOREWORD

Adaptability is probably the most distinctive characteristic of life.

In maintaining the independence and individuality of natural units, none of the great forces of inanimate matter are as successful as that alertness and adaptability to change which we designate as life — and the loss of which is death. Indeed there is perhaps even a certain parallelism between the degree of aliveness and the extent of adaptability in every animal — in every man.

There are many ways of studying life:

— There is the tabulation of simple facts, such as the registration of structural detail or of biochemical changes produced by an experimental intervention. — This work is safe; it is **the book-keeping of Nature.**

— There is the descriptive characterization of complex facts, such as clinical syndromes or intricate tissue-reactions. — This work is inspired; it is **the landscaping of Nature.**

— Finally, there is the correlation of facts into a unified system, a Science. For the explorer of Nature this yields a practically useful (though not necessarily complete or even correct) map of navigation. It helps him to remember the points he saw and to discover new ones along the roads of abstractions which connect them. — This work is creative; it may lead far astray, but apart from procreation, this is the closest man can come to **the making of Nature.**

It is well to realize that the value of a scientific theory does not depend as much upon its correctness as upon its fertility, its usefulness in discovering data. Indeed, when a theory says "nothing but the truth and all the truth" about a certain subject, it has lost its heuristic value and hence is no longer a theory.

These thoughts are my apology for devoting an entire book to the concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation.

As it stands the map is certainly both incorrect and incomplete, but let us hope that it possesses that critical degree of truthfulness which stimulates to rectify the misdrawn boundary lines and to fill out the spaces where uncharted territories are shown to lie.

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REVIEWS

In order to familiarize himself with different points of view the reader is referred to several earlier reviews, concerning the General-Adaptation-Syndrome and allied phenomena, which appeared in **English.**[1]

Readers more familiar with other languages may find it convenient to consult translations of the above reviews and similar surveys published in: **Afrikaans,**[2] **Czech,**[2a] **Danish,**[3] **Dutch,**[4] **French,**[5] **German,**[6] **Hebrew,**[7] **Hungarian,**[8] **Italian,**[9] **Portuguese,**[10] **Spanish,**[11] **and Swedish.**[12]

Finally, let us mention a few among the relevant articles which appeared in the **lay press,** to illustrate the various techniques used to present this material in a manner understandable to the non-medical public.[13]

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[1] Albright **84530/42-3. B309/43.**
Anonymous
editorial **B37484/48. B44424/50.**
Dosne **95270/42.** Goldzieher **B126/44.**
Ingle **A55580/42.** O'Connor **98364/47.**
Selye **38798/37. A8401/37.**
A8048/40/46. B223/44. B1204/46.
B1205/46. 97491/47. B18831/47.
B1433/48. B4165/48. B19380/48.
B28243/49. B32003/49. B41241/49.
Sundstroem and Michaels **83691/42.**
Tepperman et al. **A58184/43.**
Ungar **B4934/47.**

[2] Selye **B1207/46.**

[2a] Schovanec **B41797/47.**

[3] Selye **97492/48.**

[4] Overbeek **B1846/47.** Groen **B41893/48.**

[5] Albeaux-Fernet et al. **B44601/49.**
Bacq **B27654/48.**
Dontigny and Prado **B2608/48.**
Feyel and Varangot **99211/42.**
Leblond **A30385/39.**
Lichtwitz et al. **B27062/48.**
Mach **B41928/49.**
Manceaux and Jorda **B23176/48.**
Mauriac **B3307/47.**
Mosinger **B44600/47-48.**
Rentchnick **B41988/49.**
Selye **B1209/46. B19698/48.**
Theiler et al. **B41852/49.**
Toupin **B43690/49.**

[6] Constantinides and Selye **B4167/48.**

[7] Selye **B4166/48.**

[8] Karády et al. **A9072/38.**

[9] Patrono **B40255/49.**
Selye and Timiras **B26481/48.**
Tarantino **B28538/48. B38360/49.**

[10] Flosi **B32317/48.**
Prado and Dontigny **B1661/48.**

[11] Balze **92262/46.** Rodriguez **B38732/49.**
Selye **A37308/41.**

[12] Overbeek **B28174/48.**

[13] Anonymous B38211/46. B38212/47. B38213/48.
Boardman B38214/47.
Constantinides and Carey B36277/49.
Gray B46312/50. Lal B38215/47.
Kaempffert B38216/48. Maisel B38217/49.
Waltz B38218/47. B38219/47. B38220/47.

HISTORY

At about the middle of the XIXth century the great French physiologist *Claude Bernard* [1] had already realized that to maintain life, the constancy of the **"milieu intérieur"** must be preserved in spite of changes in the environment.

Subsequently, the American investigator *Walter Cannon* [2] introduced the term **"homeostasis"** to designate the maintenance of this steady state and directed attention to the rôle of adrenaline and of the autonomic nervous system in bringing about the internal adjustments upon which it depends. He examined a number of specific reactions, which are important in maintaining the constancy of the milieu intérieur during certain "emergencies", such as result from muscular work, nervous irritation, variations in the surrounding temperature, etc.

Also in the United States, *Frank Hartman* and his co-workers [3] prepared purified adrenal cortical extracts; experiments with these led them to the **"general tissue hormone"** theory of the corticoids. They concluded that cortical hormone is necessary for the function of all cells, because it raises the resistance of tissues to infection, combats fatigue of muscles and nerves and maintains the normal temperature and hydration of tissues.

In the meantime, ever since 1913, the Belgian histologist *A. P. Dustin* [4] studied the mitosis and pycnosis-producing effect of certain drugs. He named these **"poisons caryoclasiques"**, since he found that their fundamental action is to cause "caryoclasia" or pycnosis of nuclei (especially in the thymico-lymphatic apparatus), an effect which he believed to be specific of this pharmacologic group.

The seemingly quite unrelated observations of the French surgeon *René Leriche* [5] led him in 1934 to describe a clinical syndrome accompanied by characteristic blood-chemical changes which appeared after all kinds of severe surgical interventions and was consequently named **"maladie postopératoire".**[6]

Many other investigators described important morphologic, functional or biochemical changes following exposure to certain agents (drugs, infections, nervous stimuli, trauma, burns, etc.), however, they regarded them as due to the specific actions of each causative agent, respectively, and hence there was no reason to suspect any correlation between all these scattered observations.

Even in the most ancient medical texts, we find evidence that physicians have long suspected the curative value of pain, starvation and many other non-specific damaging agents. However, it was probably the Austrian psychiatrist *Wagner-Jauregg* [7] who first evaluated such observations in modern

[1] A9982/867, 38305/880.
[2] 13711/22, A19828/29.
[3] 9126/32.
[4] 53735/33, A30579/39.
[5] B18459/34.
[6] Dubois 99368/45, König B19947/41, Lambret A32628/43, Lambret and Driessens A2914/37.
[7] B19911/887, 92264/46.

scientific terms. In a series of publications, ever since 1887, he related experiences concerning the **therapeutic action of fever** in various mental diseases, especially, general paralysis. These observations stimulated much further research on so-called "non-specific therapy", "foreign protein therapy", "malaria therapy", etc., but the mechanism through which artificial fever exerts its beneficial effect, and the possible relationships between these and the previously mentioned observations, remained shrouded in mystery.

The Japanese pathologist *M. Masugi* [8] working along entirely unrelated lines, observed that animals treated with renal extracts develop antibodies against kidney-tissue. If their **"nephrotoxic sera"** are injected into another individual they eventually produce nephrosclerosis and malignant arteriolosclerosis with hyalinization of the vessel walls, such as is observed in malignant hypertension and certain allergic diseases.

Almost at the same time, in 1934, the American investigator *Harry Goldblatt* [9] described his first observations concerning the **production of experimental hypertension by partial constriction of the main renal artery.**

At first sight, it would seem that all these observations have little in common and there was no reason to believe that they could be integrated into a unified system of physiologic and pathologic events. However, in 1936 [10] it was noted that animals exposed to a variety of non-specific damaging agents respond with a discharge not only of adrenaline, but also of adrenal cortical hormones; simultaneously their resistance to numerous damaging agents is increased. The most striking feature of this response was its extreme non-specificity. Any stress was apparently met by an increased discharge of corticoids. This suggested that perhaps in man also all the systemic diseases, indeed all the stresses and strains of normal life, are met by a similar defensive corticoid production. Thus developed the realization that here we are dealing with one of the fundamental adaptive reactions of vertebrate organisms.

It was not immediately obvious how the adrenal cortex is alerted during emergencies. Various surgical interventions on the two great integrators of bodily functions, the nervous and endocrine systems, failed to prevent the activation of the adrenal cortex by stress. However, during the following year, in 1937,[11] it was noted that if the hypophysis is removed, animals can no longer respond with any adreno-cortical secretion even when exposed to severe, lethal stress. Simultaneously the resistance of these hypophysectomized individuals fell to very low levels. It was concluded that normally exposure to stress causes both damage (shock) and defense (counter-shock) phenomena. In the absence of the pituitary, manifestations of damage (e.g., gastric ulcers, hypothermia, hypoglycemia, hypotension) become even worse, while most of the presumably defensive changes (e.g., fever, hyperglycemia, hypertension, dissolution of lymphatic tissue) are eliminated.

These observations suggested that Nature herself has foreseen a general defense mechanism in which corticotrophin production plays an important part and that hence **a promising way to treat the stress-factor of disease would be to "imitate the physiological counter-shock phenomena"**, e.g., by administering supplements of ACTH or corticoids when required.[11a] It was hoped that

[8] B36588/34, B36589/33.
[9] Goldblatt B29301/48. Goldblatt et al. B36287/34.
[10] Selye 36031/36.
[11] Selye 38798/37.
[11a] Selye et al. A32768/40.

by thus supplementing the natural systemic defense reaction, it may be possible to develop a new, and rather universally applicable, approach to therapy. In addition to the conventional efforts to eliminate pathogens (e.g., by surgical means, drugs, sera or rays) we may succeed in rendering the body indifferent to their damaging actions.

Only several years later did it become evident that, under certain circumstances, increased endogenous production during stress, or exogenous administration of ACTH and corticoids can in itself become the cause of disease (e.g., hypertension, arteriosclerosis, diabetes, gout, myocarditis and various rheumatic-allergic conditions). Here we were apparently dealing with diseases due to excessive or abnormal adaptive reactions.[11b] These findings led us to formulate the theory of the **general-adaptation-syndrome** and of the **diseases of adaptation.**

It is the object of this volume to relate the personal observations which were inspired by this theory and to correlate these with the numerous, often quite independently acquired data, described in the scientific literature of many nations and in journals devoted to almost every branch of medicine.

In retrospect, we feel that the main results of this work were to show that:

(1) Any systemic stress (viz., one affecting large portions of the body) elicits an essentially similar *syndrome with general manifestations.*[12]

(2) *This syndrome helps adaptation.*[13]

(3) *Adaptation can cause disease.*[14]

Especially important clinical contributions to this field were made only a few months ago when adequate amounts of a potent gluco-corticoid hormone and corticotrophin became available. *Hench and his colleagues* at the Mayo Clinic [15] found that **rheumatoid lesions and perhaps even acute rheumatic fever, show a truly dramatic improvement upon treatment with cortisone or corticotrophin.** Almost simultaneously *Perera and Pines* [16] reported that the **hypertension which can be elicited with desoxycorticosterone in man is abolished by an adrenal extract containing gluco-corticoids and that spontaneous hypertension is reduced by cortisone.**[17] It was found, furthermore, that certain experimental similes of rheumatic and allergic conditions in animals are aggravated by mineralo-corticoids and ameliorated by gluco-corticoids [18] and that a derangement in steroid metabolism exists in patients suffering from rheumatoid arthritis.[19]

These findings appear to support the seemingly far-fetched view that the adrenal cortex plays a rôle in the pathogenesis of the above-mentioned diseases; at the same time they give us hope that a better understanding of the general-adaptation-syndrome may furnish us with powerful new weapons in the treatment of disease.

[11b] Selye A75044/44, B1204/46.
[12] Selye 36031/36.
[13] Selye 38798/37.
[14] Selye A75044/44, B1204/46.
[15] B27892/49, B37402/49.
[16] B37746/49.
[17] Perera et al. B36595/49.
[18] Selye B41762/49, B39702/49, B39703/49.
[19] Sommerville et al. B44426/50.

GENERAL PHYSIOLOGY AND PATHOLOGY OF SYSTEMIC STRESS

PRINCIPAL FACTS AND THEORIES UPON WHICH THE G-A-S CONCEPT IS BASED

A brief outline of the principal facts observed, and of the conclusions derived from them, may act as a guide and introduction to the study of the "general-adaptation-syndrome".

First the main **facts:**

(1) Various stresses, which affect large portions of the body (cold, fatigue, infections, intoxications, etc.), produce a number of somatic changes conjointly as a *syndrome.* Prominent among these are the involution of the thymico-lymphatic apparatus, the appearance of gastrointestinal ulcers and the enlargement of the adrenal cortex (with discharge of its hormones, lipids and ascorbic acid).

(2) Some manifestations of this syndrome, especially the adrenal-cortical changes, proved to be *useful.* There is an *increased corticoid-hormone production,* as judged by urinary bioassays; *this helps adaptation* since adrenalectomized animals are very inefficient in adapting themselves to a change, or in maintaining an already acquired adaptation, unless they receive corticoid substitution-therapy.

(3) *Non-specific stress* (e.g., exposure to cold, protein intoxication) *can cause malignant nephrosclerosis, hypertension, and hyalinization with inflammatory changes in the arteries and in the hearts* of experimental animals. Some of the changes so produced resemble those characteristic of acute *rheumatic fever* or of *allergic* tissue reactions.

(4) *Similar changes, of "hyalinosis" with hypertension, can be produced by anterior-pituitary preparations or corticoids* (e.g. desoxycorticosterone).

(5) *Sodium deficiency* (or the artificially induced loss of sodium caused by the administration of "acidifying" salts) protects the body against "hyalinosis" caused by any of the above-mentioned agents.

(6) *Protein* (or amino-acid) deficiency protects only against the hyalinosis caused by stress or by crude pituitary extracts, not against that elicited by pure ACTH or corticoids.

(7) In the kidneys of experimental animals exposed to non-specific stress, pituitary extracts or corticoids, many nephrons assume the appearance of solid endocrine tissue, the *"endocrine nephron".*

(8) Using a special surgical technique it is possible to transform the entire kidney into a structure having the aspect of a solid endocrine gland, an *"endocrine kidney".*

(9) *The endocrine transformation of one kidney produces nephrosclerosis in the contralateral organ, as well as hypertension and hyalinization with inflammatory changes* in the arteries and in the heart.

(10) *In animals bearing an "endocrine kidney" the sodium and protein content of the diet remains without effect* upon the resulting hypertension and hyalinosis.

(11) ACTH or gluco-corticoids (e.g., cortisone) inhibit the production of hyalinosis by crude pituitary extracts or mineralo-corticoids (e.g., desoxy-corticosterone) in animals.

(12) ACTH or gluco-corticoids exert a beneficial effect in the "spontaneous" hyalinoses (rheumatic-allergic collagen diseases) of man.

These are the main observations from which the concept of the general-adaptation-syndrome was developed to the point at which it stands today; conversely, most of these facts were found by using preliminary sketches of this concept as a guide. No doubt sooner or later all these data could have been discovered by hit-or-miss experiments merely registering results; this would have obviated all speculations which involve the risk of error, but theory led us to them at a time when other approaches failed to do so.

Let us now review the principal **theories** and thoughts derived from observations concerning the general-adaptation-syndrome.

(1) In addition to many specific defense-reactions (e.g., maintenance of a constant body temperature, osmotic pressure, blood-pressure) there is an *integrated syndrome* of closely interrelated adaptive reactions to non-specific stress itself; this has been termed the *"General-Adaptation-Syndrome" (G-A-S)*.

(2) The G-A-S does not merely represent a transitory "emergency" adjustment to changes in the environment, but is an *adaptive reaction*, which comprises the "learning" of defense against future exposure to stress, and helps to maintain a state of adaptation once this is acquired.

(3) The process of *adaptation may itself become the immediate cause of diseases*, namely of derangements due to maladaptation (hypo-, hyper- or dysadaptation). Among these are some of the most common fatal diseases of man, such as the hypertensive, the "rheumatic" and the "degenerative" or "wear-and-tear" diseases of old age; the psychosomatic syndromes probably also belong to this group.

(4) In the G-A-S the manifestations of *passive non-specific damage are intricately intermixed with those of active defense* to it.

(5) We must henceforth keep in mind that in every aspect of experimental or clinical medicine (e.g., in all observations concerning the specific effects of drugs, diets, surgical interventions and diseases) some manifestations of the G-A-S will unavoidably be superimposed upon the specific changes caused by the agents under study. This is necessarily so, since all these agents cause some degree of systemic stress. Hence, *in order to recognize truly specific actions we must compare the changes produced by a stimulus not only with the "untreated normal control"*, but also with the *"stress control"*, that is, an individual exhibiting the non-specific effects of a comparable degree of systemic stress produced by different means.

In other words, the G-A-S appears to be the appropriate standard of comparison from which the specific effects of all diseases, drugs, physical agents, diets, etc., must be delimited. There is no purely specific effect in biology without simultaneous manifestations of non-specific stress. The former can only be recognized as such by subtracting the manifestations of the G-A-S from the total picture.

(6) The G-A-S — as the absolutely "normal" man — is an abstraction, which never occurs in its pure form. All agents capable of eliciting this syndrome have some specific actions of their own which they do not share with other types of stress. *In identifying individual manifestations as belonging to the G-A-S we must, therefore, always verify that they are elicited by any agent causing a comparable degree of systemic stress.*

(7) *The pressor action of the kidney can be stimulated directly by corticoids.* It can also be augmented indirectly by hypophyseal corticotrophin, which increases corticoid-production and still more indirectly by stress, which stimulates the secretion of corticotrophin.

(8) Apart from their well-known pressor effect, *the renal hormone(s) exert important humoral actions upon protein metabolism.* This manifests itself by their ability to cause a generalized disease, a *"hyalinosis"* or *"fibrinoid diathesis"* characterized by the deposition of so-called hyalin or fibrinoid protein material in various organs, especially the cardiovascular system.

DEFINITIONS AND TERMINOLOGY

A — Definition of the terms commonly used in connection with the G-A-S

In discussing a relatively new concept it is almost always necessary to create new terms or to use old ones in a novel sense; to avoid misunderstandings in such cases it is indispensable to give clear definitions of the terminology to be employed.

In general "definitions" applied to biologic concepts are not very satisfactory. It must be admitted that in the final analysis most concepts in biology — as that of life itself — are embraced by experience and not by rational delimitation.

In some sciences (e.g., mathematics) definitions are unchangeable laws which make a concept what it is; in biology "definitions" are merely given as concise descriptions of phenomena as they are conceived at the time, realizing that they may have to be modified when further observations necessitate it. — It is in this sense that the following "definitions" are presented.

To begin with, it is most important to state clearly what we understand by *"non-specific"*. The meaning of this commonly used term has never been carefully analyzed and we believe that the resulting lack of precision in terminology was one of the most severe handicaps to the development of our knowledge concerning the non-specific biologic phenomena.

Firstly we must sharply differentiate between *non-specific changes* and *non-specific agents*. The two have often been confused due to the use of such broad terms as "non-specific actions", which may mean either.

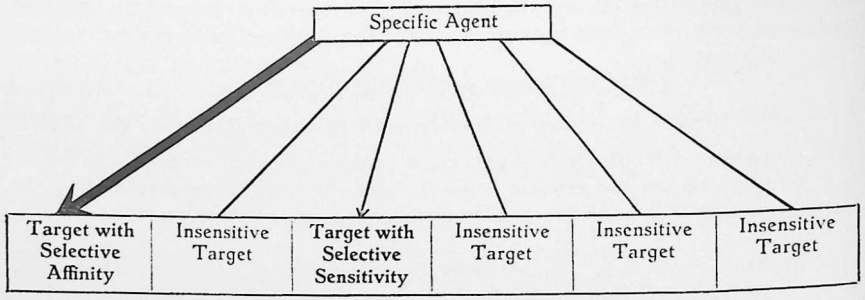
Non-specific changes are those which can be elicited by many agents. There are degrees in the specificity of biologic effects; few, if any, are produced by one agent only (absolute specificity) or by all agents (absolute non-specificity). The response of the thyroid to thyrotrophin is an example of a highly specific change, one not known to be produced by any other compound: the cell-destroying effect of x-rays represents a non-specific change, probably the most non-specific of all, since it is shared by any biologic agent providing a sufficiently high dose is administered.

The systemic or *general non-specific changes* — which are the main subject of this study — must be distinguished from the localized or *topical non-specific changes*. It is noteworthy that most of the systemic non-specific changes bear a striking resemblance to the topical non-specific reaction to local injuries. although, the former affect the whole body, the latter only one region. Especially important among these non-specific changes are derangements in mem-

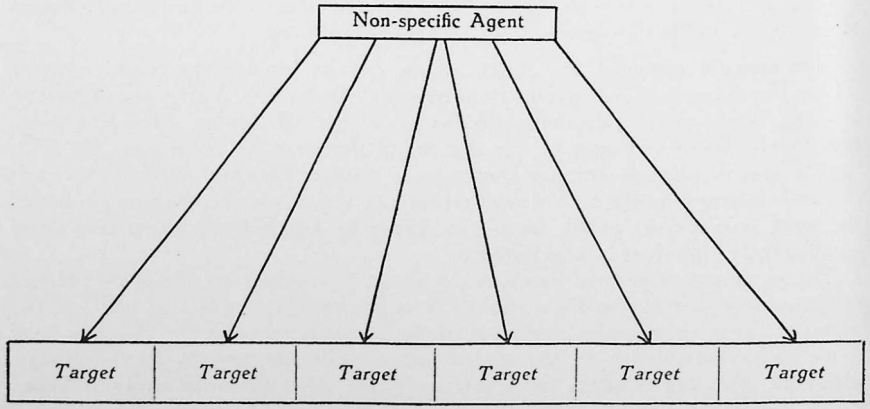
brane-permeability affecting both capillaries and cell surfaces. They lead to an equalization of the chemical composition of the intra- and extracellular spaces, egress of blood-constituents into the tissues, degenerative changes and necrosis of cells, infiltration of tissues of fibroblasts and leucocytes, etc.

Non-specific agents are those which affect many tissues and are devoid of the ability to act selectively upon any one.

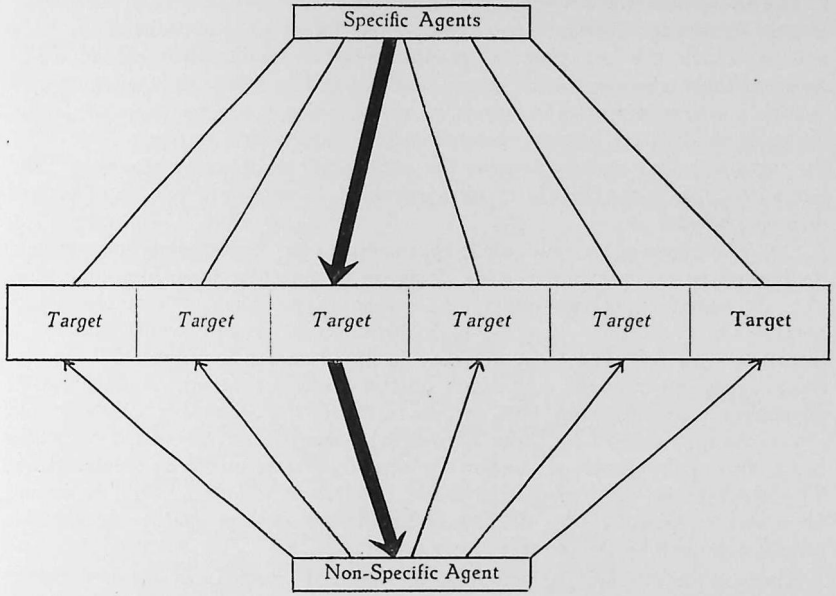
The following graphs may simplify the discussion of the principal mechanisms through which specific and non-specific agents can exert their respective actions when placed in contact with all cells of the body (e.g., intravenous injection of a drug or total body-irradiation with penetrating x-rays).



(A) — A specific agent has the ability to single out a limited number of cells for action. This can be accomplished in two ways: (1) Through a selective affinity of certain cells for the agent (bold arrow). In this case the cells selectively attract the agent and this results in a disproportionately high concentration of it within their protoplasm (e.g., intravenously administered bacteria or radioactive colloidal particles accumulate in the phagocytic elements of the reticulo-endothelial system and selectively attack these cells which have a particular affinity for them). (2) Through a specific sensitivity of certain cells for the agent. In this case some cells are more sensitive to its biologic actions than the rest of the body, hence, even if the actual concentration is the same throughout the organism, only they respond (e.g., effect of light upon the retina).



(B) — Non-specific agents have no selective action upon cells through either of the above mechanisms (e.g., anoxia or exposure to extremes of temperature affect almost every cell in the body).



(C) — Even specific agents may possess secondary non-specific effects. This may be due to various reasons: (1) The agent can cause systemic stress through the liberation of a compound by a target organ; the latter responds specifically, due to selective affinity or sensitivity (e.g., the thyroid is specifically sensitive to thyrotrophin, but under its influence liberates excessive amounts of thyroid hormone, which in turn may cause severe non-specific damage due to its influence upon general metabolism). (2) The tissue which responds selectively to the agent is destroyed by the latter and the resulting deficiency itself may represent an important systemic stress (e.g., the kidney has a selective affinity for mercury but its destruction in mercurial intoxication results in uremia with systemic stress).

The expression **systemic stress** is used here to denote a condition in which — due to function or damage — extensive regions of the body deviate from their normal resting state. In accordance with the common usage of the word "stress", the term "systemic stress" is sometimes loosely employed also to denote the stimuli which cause systemic stress. In this sense, it is preferable however, to speak of alarming stimuli or "stressors".

The term **alarming stimulus** has been employed to denote any agent capable of eliciting first an alarm-reaction and, if its action is prolonged, the entire general-adaptation-syndrome.[1] It is the **"stressor"** resistance to which requires a systemic effort on the part of the organism. The transition is imperceptible between the condition of absolute rest and a fully developed alarm-reaction; hence it is correct to say that, at least in principle, any change will evoke at

[1] Selye A8048/40, B1204/46, 94572/47.

least some mild manifestations of the alarm-reaction. The most powerful alarming stimuli are agents which affect large portions of the body without causing death due to selective (specific) damage to vital organs.

The **alarm-reaction** (A-R) is defined as the sum of all non-specific phenomena elicited by sudden exposure to stimuli, which affect large portions of the body and to which the organism is quantitatively or qualitatively not adapted.[2] Some of these phenomena are merely passive and represent signs of damage or "shock"; others are manifestations of active defense against damage. In the event of moderately severe systemic stress, from which recovery is possible, the signs of injury usually precede the appearance of defense-phenomena. The alarm-reaction may, therefore, be subdivided in turn into two more or less distinct phases:

(1) *The phase of shock.* This is characterized by: hypothermia, hypotension, depression of the nervous system, decrease in muscular tone, hemoconcentration, deranged capillary and cell-membrane permeability, generalized tissue-breakdown ("catabolic impulse"), hypochloremia, hyperkalemia, acidosis, a transitory rise followed by a decrease in blood-sugar, leucopenia followed by leucocytosis, eosinopenia and acute gastrointestinal erosions. A discharge of adrenaline, corticotrophin and corticoids (with the secondary metabolic and organ-changes caused by these hormones) are early defense-reactions, which begin during the shock-phase but are actually characteristic of counter-shock. The shock-phase may vary from a few minutes to about 24 hours, depending upon the intensity of the damage inflicted, but (unless death ensues), it is always followed by the counter-shock phase.

There is no satisfactory definition of shock. In most cases one or the other sign of the shock-syndrome was singled out as its basic feature and the condition was then defined as one characterized by that manifestation (e.g., hypothermia, hypotension, hemoconcentration, capillary permeability, depression of the nervous system). Such definitions are not satisfactory because under certain conditions any one of the so-called "characteristic" signs may be manifest, although there is no shock, and conversely, shock may develop in the absence of one or the other of these signs.

We therefore prefer to consider shock as a condition of suddenly developing, intense, systemic (general) damage. Although this definition is not very instructive, it is necessarily correct since it merely represents a brief outline of those essential phenomena which induced physicians to coin the term. Shock is always a rapidly developing condition; damage caused by chronic ailments cannot be thus described. The term also implies that the damage is systemic (general); localized lesions, no matter how severe, are not designated as shock, unless they secondarily lead to generalized damage.

It is customary to distinguish between *"primary" and "secondary" shock.* It has been claimed that such a distinction is all the more important since primary shock is due to nervous stimuli, while secondary shock is the result of intoxication with endogenous substances. However, this is not definitely proven and, in any case, since we know now that nervous impulses are humorally transmitted, the distinction is not as sharp as was assumed at first. Furthermore, even in the event of exposure to stressors which lead to fatal shock within less than an hour, the pathologic and biochemical changes may be practically the

[2] Selye A8048/40, B1204/46, 94572/47.

same as those seen in secondary shock. It is questionable therefore whether these two types should be considered as essentially different, or as an acute and a delayed form of the same process. Whether the customary sharp separation between *"reversible" and "irreversible" shock* distinguishes essentially different conditions is likewise debatable. The data available at present merely suggest a difference in severity.

(2) *The phase of counter-shock.* This phase is characterized by phenomena of defense against shock. There is an enlargement of the adrenal cortex with signs of increased activity, acute involution of the thymico-lymphatic apparatus and generally speaking, the reversal of most of the changes seen during the shock phase (e.g., a rise in blood-pressure, hyperchloremia, hyperglycemia, rise in blood volume, alkalosis, increased diuresis and often hyperthermia). These changes are not only synchronous with the stimulation of adrenal-cortical activity but largely dependent upon the discharge of corticoids into the blood. Counter-shock phenomena may explain cases in which a distinct period of "primary shock" was followed by "secondary shock" after an intermediate stage of relative well-being. It is possible that here the intermediate shock-free period is merely the equivalent of the counter-shock phase, which cannot be maintained (cf. "exhaustion" below) and gives way to fatal shock.

The counter-shock phase of the A-R represents a transition to the stage of resistance (see below) and imperceptibly merges into the latter in the event of chronic exposure. The principal reason for recognizing this as a distinct phase of the G-A-S is that under the impact of short, sublethal, systemic stresses, some manifestations of the initial shock phase are eventually reversed although, in the absence of repeated exposure, a stage of resistance cannot become manifest.

In clinical medicine, the equivalent of this counter-shock phase has been studied particularly in connection with the so-called "malignant syndrome". Speaking about the latter, Manceaux and Jorda [3] state that here "... this phase of counter-shock is especially clear-cut and characterized by clinical and biologic changes absolutely comparable to those encountered in the counter-shock phase of Selye's syndrome".

When the A-R, as outlined above, was first described (1936) we knew only that the organism responds with the same set of symptoms to a great variety of systemic stresses. The term alarm-reaction was coined to intimate that this response represents a "call to arms" of the body's defense forces.[4] It should be mentioned, however, that the expression "alarm-reaction" has also been used by some investigators to describe certain nervous phenomena whose relationship to the general-adaptation-syndrome is questionable.[5]

The **stage of resistance** represents the sum of all non-specific systemic reactions elicited by prolonged exposure to stimuli to which the organism has acquired adaptation. It is mainly characterized by an increased resistance to the particular stressor agent to which the body has been exposed and a decreased resistance to other stimuli. Thus the impression is gained that during the

[3] B23176/48.
[4] Selye 36030/36, 36031/36.
[5] Klein 34211/36, Wolff et al. A55923/42.

stage of resistance, adaptation to one agent is acquired "at the expense of" resistance to other agents.[6]

Most of the morphologic and biochemical changes of the A-R disappear during the stage of resistance and indeed in some instances the direction of the deviations from the normal is reversed (e.g., hypochloremia during the A-R, hyperchloremia during the stage of resistance; loss of lipids from the adrenal cortex during the A-R, deposition of lipids into this gland during the stage of resistance).

The **stage of exhaustion** represents the sum of all non-specific systemic reactions which ultimately develop as a result of prolonged over-exposure to stimuli to which adaptation has been developed but could no longer be maintained.

It was found that even a perfectly adapted organism cannot indefinitely maintain itself in the stage of resistance. If exposure to abnormal conditions continues, adaptation wears out and many lesions characteristic of the A-R (e.g., involution of the thymico-lymphatic system, loss of adrenal-lipids, gastro-intestinal ulcers) reappear as a stage of exhaustion develops and further resistance becomes impossible.[7]

The **general-adaptation-syndrome** (G-A-S) is the sum of all non-specific systemic reactions of the body which ensue upon long-continued exposure to systemic stress. One of the most fundamental observations in connection with the G-A-S was the finding that many of the morphologic, functional and biochemical changes elicited by various systemic stressor agents are essentially the same irrespective of the specific nature of the eliciting stimulus. We coined the inclusive term "general-adaptation-syndrome" to denote the whole response of which the A-R, the stage of resistance, and the stage of exhaustion are merely three successive phases.

The reaction is *general;* it is elicited only by those stresses which are generalized (in that they affect large portions of the body) and it in turn evokes generalized, systemic defense phenomena.

The reaction is *adaptive;* it helps the acquisition and maintenance of a state of inurement.

The reaction is a *syndrome;* its individual manifestations are co-ordinated and partly even inter-dependent.

The G-A-S must be distinguished from the specific adaptive reactions, such as the hypertrophy of the musculature after prolonged exercise, the allergic or immunologic phenomena elicited by certain foreign proteins or micro-organisms, etc. These latter responses are not evoked by systemic stress. They usually endow the body with a great deal of resistance against one particular agent (that to which it had previously been exposed), but, both the manifestations of such specific adaptive reactions and the resistance which they confer upon the organism are limited to the agent which elicited them.[8]

Perhaps because historically the A-R was the first to be described, or because of its striking name, it received the greatest attention in the literature pertaining to the G-A-S. Indeed, some workers fail to distinguish clearly between the A-R

[6] Selye 38798/37, A8049/38, A9375/38, 75441/38.
[7] Reynolds and Phillips B4516/47, Selye 36032/36, 38798/37, 36030/36, A15800/38, B1204/46, B223/44.
[8] Selye 38798/37, A8048/40, B1204/46.

and the G-A-S as a whole. We wish to re-emphasize, therefore, that the former is merely the first stage of the latter and that if an organism is continuously subjected to severe systemic stress, the resulting G-A-S always evolves in three successive stages, namely, first "the alarm reaction", then the "stage of resistance" and finally the "stage of exhaustion".

Specific resistance denotes that type of inurement which increases tolerance only to the particular kind of stimulus to which the body had been exposed.[9]

Non-specific resistance (or "crossed-resistance") designates the ability of the body to withstand a stressor agent qualitatively different from that to which it had been adapted.[10]

Adaptation energy (or adaptability) is the ability of the organism to acquire resistance to changes in its internal or external medium.[11]

This is closely related to what has been called the *"reserve capacity* of the human body" [11a] in clinical medicine. It probably accounts for the decreased life expectancy of people who previously suffered from chronic illness.[11b]

The term **"conditioning factors"** is used in connection with the G-A-S to designate circumstances which influence the course of this syndrome but are not necessarily an integral part of it. For example, sodium conditions the response to mineralo-corticoids, protein, the discharge of ACTH.[11c] The corticoids and ACTH themselves are integral parts of the G-A-S and not its conditioning factors. Of course even the various constituents of the G-A-S may mutually influence each other's actions. Thus many effects of mineralo-corticoids can be counteracted by gluco-corticoids although both these types of hormones are secreted as part of the G-A-S response. Hence in a broad sense of the term, we may also speak of mutual conditioning between the various stimuli which arise in the course of a typical G-A-S.

B. — Definition of terms commonly used in connection with the Diseases of Adaptation

The **diseases of adaptation** are defined as maladies referable to an abnormality of the adaptation-process itself, to maladaptation. These diseases can be further subdivided into three sub-groups comprising the diseases due to hypo-, hyper- and dysadaptation respectively, that is to say, an insufficient, excessive or abnormal adaptive reaction.[12]

Except for the interpretation of "shock" the clinical importance of the G-A-S did not become evident until recently when it was shown that non-specific stress can elicit a sudden dissolution of lymphatic structures (e.g., thymus, lymph-nodes, Peyer's patches, appendix) with secondary edema and inflammatory changes and, under special experimental conditions, stressor agents (e.g., cold) cause hypertension and nephrosclerosis in animals.[13] This hypertension and nephrosclerosis was found to be accompanied by an enlargement of the adrenal cortex and the question arose whether the increased production of corticotrophin, during the G-A-S, could be of pathogenic importance.

[9] Selye 38798/37, B1204/46.
[10] Selye 38798/37, B1204/46.
[11] Selye A9210/38, A8049/38, A9375/38, 75441/38, A8406/38. A32153/40.
[11a] Chatterjee B40830/46.
[11b] Ciocco 93263/46.
[11c] Selye B4165/48, 94572/49.
[12] Selye A75044/44, B223/44, B1204/46, **B4165/48, 94572/49.**
[13] Selye A62756/43, **B1204/46.**

Further experiments showed that pure synthetic desoxycorticosterone acetate,[14] as well as corticotrophic anterior-pituitary extracts,[15] are particularly active in eliciting nephrosclerosis and hypertension in animals. These changes are not infrequently accompanied by myocarditis and arthritides, similar to those seen in patients with rheumatic fever.

It becomes increasingly more obvious, however, that "conditioning" to the production and effectiveness of the hormones, by diets and metabolic changes, is also of great importance. Both the production of hormones during stress and their activity depend upon metabolic conditions, especially the diet. Nevertheless all experimental observations are most readily compatible with the view that during the G-A-S certain anterior-pituitary and adrenal-cortical hormones are produced in excess. This defensive endocrine response is useful since it raises resistance to stress (e.g., infections, intoxications, nervous stimuli, cold), but the resulting endogenous hormone-overdosage may cause certain cardiovascular, renal and joint diseases. Thus developed the concept that many of the most common maladies of man are "Diseases of Adaptation", that is to say, the by-products of abnormal adaptive reactions to stress.[16]

Perhaps the strongest argument against our type of reasoning is the fact that the same degree of damage or stress does not necessarily always elicit the same response. Even lesions which are manifestly not the specific result of one particular pathogenic agent, may be more prone to occur following exposure to one or the other type of damage. For example, nephritis may be caused by a variety of micro-organisms, by exposure to cold or by treatment with various drugs, but it is particularly frequent in patients suffering from streptococcus infection with tonsillitis, scarlet-fever or sepsis. This does not mean that the pathogenic agent of nephritis is a streptococcus, in the sense in which the pathogenic agent of tuberculosis is the tuberculosis-bacillus. It merely means that streptococcus-infection elicits a somatic response which produces especially favorable conditions for the development of nephritis. We have seen that numerous factors can specifically sensitize or desensitize, that is, "condition" the body to one or the other manifestations of the G-A-S. Thus we noted that sodium sensitizes, while ammonium chloride desensitizes the kidney to the nephrosclerotic action of cold; glucose-administration desensitizes, while exposure to cold sensitizes, the gastric mucosa to the ulcer-producing effect of spinal-cord transection. The dissociation of symptoms, resulting from such selective sensitization or desensitization to one particular lesion, helps to understand that the same degree of stress or damage does not always result in the same symptomatology.

Of course all diseases are the result of a conflict betwen the organism and a pathogenic agent; [17] hence it is obvious that — apart from instant death (e.g., that caused by a lesion to a vital center) — some manifestations of the G-A-S will accompany all pathologic processes. This conclusion is inescapable if we consider that our definition of the "stressors" includes all pathogenic agents. To arrive at a practically useful classification it appears desirable, however, to separate from the other diseases those whose manifestations are so preponderantly due to abnormal adaptative reactions that the direct consequences of

[14] Selye and Hall A57551/44, Selye et al. A72284/44.
[15] Selye A75044/44.
[16] Selye B223/44, B1204/46, B17771/48, 94572/47.
[17] Bauer 89907/28, Forbus B4213/45.

the eliciting pathogenic agent assume a secondary position. Thus the growth of a malignant tumor, the muscular paralysis due to destruction of a nerve center and the convulsions resulting from tetanus-toxin or parathyroidectomy, are disease-manifestations in which abnormal adaptive processes are relatively unimportant. Conversely, in psychosomatic syndromes, many types of nephrosclerosis, hypertension, gastric ulcers or "allergic" diseases, the abnormal adaptive response to the agent is the major cause of disease. This is especially obvious if we remember that the same pathogenic stimulus, which produces such changes in one person, elicits no significant disturbance in others whose adaptive mechanism functions normally.

It would be expedient to distinguish between **primary and secondary diseases of adaptation.** The former are due to lesions originating in the organs of adaptation (e.g., destruction of the pituitary or adrenals by tumors, compression of the renal artery by a scar); the latter are caused by abnormal responses of these same organs to a stressor which requires adaptation. Each of these two main categories could be further subdivided into diseases due to *hyper-, hypo- or dysadaptation,* according to whether the derangement is chiefly due to a deficiency, an excess, or a distortion of the adaptive response.

Accordingly, the principal diseases of adaptation might perhaps be classified as follows:

I. *HYPERFUNCTIONAL AND DYSFUNCTIONAL*:

A. Primary Diseases of Organs of Adaptation:

(1) Cushing's disease (pituitary hyperfunction)
(2) Adrenal tumors with "Cushing's syndrome" (adrenal-cortical hyperfunction)
(3) Chromaffinomas (adrenal-medullary hyperfunction)
(4) Coarctation of the renal artery and other primary diseases of the kidney conducive to hypertension (renal hormonal hyperfunction).

B. Secondary Diseases Due to Excessive (or Abnormal) Responses of Organs of Adaptation:

(1) Some types of hypertension
(2) Periarteritis nodosa (also arteriosclerosis and other vascular lesions ?)
(3) Nephrosclerosis
(4) Some types of nephritis
(5) Rheumatic diseases
(6) Eclampsia (?)
(7) Accidental thymus-involution
(8) Some types of appendicitis (?)
(9) Some types of tonsillitis (?)
(10) Gouty arthritis
(11) Some types of diabetes
(12) Various psychosomatic disorders.

II. HYPOFUNCTIONAL:

A. Primary Diseases of Organs of Adaptation:

(1) Simmond's disease (pituitary hypofunction)

(2) Addison's disease ("status thymico-lymphaticus" ?) (adrenal-cortical hypofunction)

B. Secondary Diseases Due to Insufficient Responses of Organs of Adaptation:

(1) Secondary shock (relative hypocorticoidism) (?)

(2) Acute gastrointestinal erosions ("Curling's ulcer")

(3) Waterhouse-Friderichsen syndrome.

This would be a simple and natural system, but unfortunately, in many instances we do not understand the pathogenesis of these diseases sufficiently to justify such a classification according to etiology. Hence, at present, we prefer to discuss the diseases of adaptation in conjunction with the most severely affected targets (e.g., cardiovascular system, joints, metabolism) until further research permits a more logical etiologic classification. Accordingly, later in this book, the diseases will be considered together with the more physiologic manifestations of the G-A-S in the chapters devoted to each target. Here, we shall merely attempt to give a general introduction to the concept of the diseases of adaptation and to familiarize the reader with the most commonly employed terms.

The term **"hyalinosis"** has been coined in keeping with the use of the suffix "-osis" (plural "-oses") for those "thesauroses", or storage diseases, in which there is abnormal deposition of some material in many structures throughout the body (e.g., amyloidosis, lipoidosis, calcinosis, glycogenosis). It is synonymous with "fibrinoid diathesis" and is used to designate diseases characterized by the deposition of hyalin, "fibrinoid" material in many organs especially in the cardiovascular system and the connective tissue. Examples of pertinent syndromes in human pathology are: *periarteritis nodosa, temporal arteritis, rheumatic arteritis, malignant hypertension, malignant nephrosclerosis, "fibrinoid necrosis" of arteries, diffuse collagen-disease, disseminated lupus erythematodes and Libman-Sacks' disease.* The great resemblance of these diseases to the various types of experimental hyalinosis (which can be produced in animals by stress, pituitary extracts, corticoids or renal-pressor-substances) raises the possibility that their pathogenic mechanism may also be similar. If this were true then, both in human and in experimental pathology, intoxication with renal hormones may be the ultimate cause of that disturbance in protein-metabolism which leads to the deposition of the so-called hyalin material, since the experimental hyalinoses are apparently mediated through the kidney (see experimental data below).

When hyalin material is deposited in tissues, it causes irritation and this tends to produce local inflammatory reactions. The hyalin deposits may become surrounded by a granuloma which often contains leucocytes and giant cells, but sometimes it is gradually replaced by lipids, calcium salts or sclerotic connective tissue. If the endothelium is severely damaged, thrombosis ensues. Only rarely is hyalin completely absorbed without leaving a scar; indeed frequently the secondary changes are so predominant that original hyalin deposition is hardly detectable. Hence, we envisage the possibility that several other, hitherto

unexplained, spontaneous diseases of man are **derangements related to the hyalinoses.** Depending upon the histologic characteristics of the lesions and their distribution in the various organs, the resulting clinico-pathologic picture may assume widely different aspects. In this sense, *thromboangiitis obliterans (Buerger's disease), endarteritis obliterans, brain-rheumatism, hypertensive encephalitis, allergic encephalitis, dermatomyositis, serum sickness,* and several of the *erythemas (erythema multiforma, erythema nodosum, etc.)* should be considered as perhaps belonging to this group. As we shall see later, there is some evidence that even various *allergic, anaphylactic* and *rheumatic* changes as well as the hyalinizing necrosis of *eclampsia* (which is so largely dependent upon the Na-intake) are also related.

The so-called **"serous inflammation"** of Eppinger (cf. Glossary) is primarily characterized by loss of the selective permeability of capillaries and cell-membranes with the formation of a serous transudate between the capillaries and the epithelial cells of various parenchymatous organs. This condition is very similar to that seen in experimental animals during the A-R or after overdosage with anterior-pituitary, corticoid, or renal-pressor-substances. The large body cavities (pleura, peritoneum, pericardium, the joints) are likewise frequently the site of "serous inflammation". If the lesions happen to be predominant in these locations, we speak of *polyserositis.* We must also consider the possibility, therefore, that here we are again dealing with diseases of adaptation, in the sense of the definition given above.

There are many other diseases in whose etiology an exposure to systemic stress — and more particularly a defective or excessive corticoid production — appears to play a rôle. Among these, we might mention the formation of **peptic ulcers** in the digestive tract, the precipitation of an attack of **gout** in a predisposed subject, certain **menstrual anomalies,** some types of **leanness** or **adiposity, neuroses,** various **psychosomatic disturbances** and perhaps even some of the **psychoses,** the acute **accidental thymus-involution** of infants, certain types of **pancreatitis, parotitis, tonsillitis** and **appendicitis,** the occasional case of acute **Grave's disease,** precipitated by some physical or emotional shock, etc. All of these diseases will be discussed later in this volume, in the chapters dealing with the response of the corresponding target organs during the G-A-S. As we shall see there, the evidence that some of these maladies are actually diseases of adaptation is very convincing, as regards others, it is quite hypothetical. We felt, however, that it should be one of the major objectives of this book to analyze the literature concerning every pathologic entity which has been considered, on the basis of reasonable evidence, as possibly a disease of adaptation.

It should be pointed out in this general survey that, in spite of their apparent diversity, many of the derangements listed above have been grouped together in the past because of certain common characteristics. Thus it has been claimed that certain metabolic derangements (leanness, adiposity, diabetes mellitus, Grave's disease), as well as gastrointestinal disorders and cardiovascular diseases (especially essential hypertension), menstrual disorders and sterility are essentially **"diseases of civilization",** since they are comparatively uncommon in primitive societies. Allegedly their development is promoted by food-habits and stresses inherent in civilized life, to which the hypothalamus-hypophysis-system cannot adequately adjust itself.[18] It has also been stated that "three

[18] Bertram **B36279/48.**

diseases stand out as striking and universally acknowledged examples of stress casualties: thyrotoxicosis, duodenal ulcer and non-renal hypertension". Their development has been attributed to "the conditions under which a great proportion of the inhabitants of the older and more civilized communities live, and these are the conditions that are causing them to break down and are producing a group of diseases that we may call the **stress diseases**".[19] A monograph on the pertinent geriatric literature states, in discussing the **"diseases of the aged"**, that "under continued stress, the weakest part of the body shows the result of strain. Influenced by hereditary tendencies, the following conditions may result from, or be aggravated by stress: hypermetabolism, hyperglycemia, arterial hypertension, peptic ulcer, autonomic nervous system imbalance, endocrine disturbance, cardiovascular disease, and anemia".[20] Essentially this same group of diseases, as well as leanness, obesity and arthritis are also frequently described as **"degenerative diseases"** or **"wear-and-tear diseases"**. All these terms are selected to emphasize the stress-element in their pathogenesis.[21]

Of course not only the stresses "characteristic of civilized life" can provoke such maladies. **"Focal infection"** is another example of a continuously acting systemic stressor to which maladaptation can occur. A great deal of evidence has been adduced to show that rheumatoid diseases, allergy, hyperthyroidism, diabetes mellitus, menstrual disorders, peptic ulcers, hypertension, neuralgias and certain types of nephritis can develop as a consequence of an, in itself relatively unimportant, focus of infection.[22]

The so-called **"exaggeration phenomena"** are especially pertinent to this problem. It was found that a sudden exaggeration of previously existing disease-manifestations may occur in patients under the influence of a surgical operation or other stressful procedures (e.g., mental shock, infections). This has been interpreted as a secondary effect of the G-A-S.[23] It may be that damage by systemic stress causes particularly pronounced lesions in those organs sensitized by a pre-existent, though latent, derangement. This hypothesis may also help us to understand why the same systemic stress-reaction can cause so widely different manifestations depending upon the "terrain" (especially racial, constitutional, infectious or dietary factors), which could create a weak point in one or the other organ system and thus render it hypersensitive.

It is noteworthy, in this connection, that locally applied non-specific damage (e.g., trauma, freezing, burns, x-rays) affects most targets in a qualitatively similar manner as the G-A-S does. Hence, it is not unreasonable to assume that the actions of local and systemic stress can be cumulative, thus selectively concentrating the effects of systemic stress in a certain organ. Contrary to earlier concepts, the body exhibits only a limited number of reaction-types to injury. Among these are: inflammation, sclerosis, increased capillary-permeability and the loss of the normal "selective permeability" of cell-membranes to certain substances. The latter change leads to the entrance of plasma-proteins and Na into the cell, with a discharge of K into the extracellular spaces; thus it tends to equalize the composition of the intra- and extra-cellular fluids.

[19] Ogilvie **B36284/49.**
[20] Thewlis B17900/46.
[21] Hirsch **B26303/27,** Moore et al. B36752/45, McCay B37495/39, Thewlis B17900/46.
[22] Goia **B25571/46.**
[23] Wilensky B3270/46.

The apparent polymorphism of the responses to systemic stress is largely due to local factors in various organs, which influence the end-results of such simple reactions. For instance, injury to the gastric or duodenal mucosa rapidly leads to the formation of an ulcer, because the damaged surface-epithelium can no longer protect itself against self-digestion by the gastrointestinal juices; injury to the hepatic cells tends to cause fatty degeneration of the liver because, owing to local enzymatic conditions, fat-storage happens to be a characteristic response of the hepatic cells to many types of injuries. During the G-A-S, as we shall see, gastro-intestinal ulcers may develop in one case, hepatic steatosis in another, while in a third both these lesions may evolve simultaneously, depending upon the sensitivity of these two targets. Yet, every organ, if it responds at all, does so in its own characteristic way, the reactions in the various tissues are by no means haphazard. Under no conditions will systemic stress cause steatosis of the stomach or ulcer-formation on the liver surface!

It may appear rather far-fetched to consider some of the above-mentioned derangements as diseases of adaptation. The arguments for and against such an interpretation will be critically analyzed in those chapters of this book which are devoted to the organs principally affected by these maladies. However, to prevent the reader from losing patience with us before he reaches these chapters, let us remind him of the reserve with which — only a few years ago — he would have considered the suggestion of an etiologic relationship between the adrenal cortex and rheumatoid arthritis, hypertension or accidental thymus involution.

C — Glossary of Terms and Concepts commonly used in connection with the G-A-S and its Diseases.

It is surprizing that such a common biologic phenomenon as the G-A-S was not discovered long ago. Apparently previous investigators whose work touched upon this field invariably became so absorbed in certain individual manifestations that they failed to recognize the general syndrome of which the object of their particular attention merely formed a part. Usually such observations were limited to the isolated description of a change which occurred under the influence of an experimental intervention, hence the former was considered to be the specific effect of the latter. For instance a number of investigators noted adrenal-enlargement following treatment with certain drugs, hence they described their observations to show that these compounds are distinguished by a specific pharmaco-dynamic action upon the suprarenals. Many observations of this type will be mentioned in the section "Course of the General-Adaptation-Syndrome" in connection with the affected metabolite or target-organ. There we shall also endeavour to show that these are not direct, specific pharmaco-dynamic actions, but part of a syndrome elicited by the systemic stress which they cause. Spontaneous diseases, which may have some pathogenic relations to the G-A-S, will also be discussed in the chapters devoted to the predominantly affected targets.

In the present "Glossary" we merely wish to enumerate those terms and concepts which were created to group under one heading certain less well-known clinical and experimental syndromes, or complex tissue-reactions, which in the light of present-day knowledge may belong to the G-A-S.

Homeostasis. — This has been defined by Cannon [24] as: "The coördinated physiological processes which maintain most of the steady states in the organism". This rather broad term comprises all specific reactions involved in the maintenance of a constant "milieu intérieur"; it does not differentiate between specific and non-specific defense-phenomena. Thus Cannon [25] distinguishes as separate homeostatic mechanisms those assuring the constancy of the blood-sugar, blood-proteins, blood-calcium, body-temperature, etc. By contrast the G-A-S co-ordinates such individual homeostatic mechanisms into a balanced defense-reaction to non-specific stress. Moreover, it comprises all those consequences of systemic stress, which are merely expressions of damage, not of defense. To deal conjointly with damage and the defense against damage is theoretically somewhat unsatisfactory, but in practice unavoidable until we learn to delimit these intricately intermixed phenomena better than we can at present.

Tachyphylaxis. — In 1911, Cesa-Bianchi [26] made an observation which may have been the first evidence of "crossed resistance" during the counter-shock phase. He noted that rabbits receiving intravenous injections of a toxic tissue-extract, become more resistant to subsequent injections, both of the same and of different organ-extracts. This phenomenon was also studied by Champy and Gley [27] — who named it "tachyphylaxis" ("rapid readiness") — and by numerous subsequent investigators.[28]

The term *"skeptophylaxis"* ("lightening readiness") has been coined by Ancel et al.[29] to describe this same phenomenon.

Biophylaxis. — This designation was introduced by Tzanck et al.,[30] to denote all non-specific defense-mechanisms (e.g., phagocytosis, inflammation) exclusive of true immune-reactions. These authors limited themselves, almost entirely, to theoretic considerations and gave so little factual evidence that it is almost impossible to determine exactly what phenomena they observed. It is probable, however, that their concept came close to Cannon's interpretation of homeostasis.

Trophophylaxis. — It has been claimed [31] that injection of such "nutrients" as 40% glucose, rice water, beer, wine, organ extracts, milk, etc., increases the resistance of mice to cobra-venom. This phenomenon has been described as "trophophylaxis" (nutritive readiness) and may be related to the so-called "crossed resistance" or "non-specific resistance" as defined by us.

Caryoclastic crisis. — Dustin [32] claimed that certain drugs, the "poisons caryoclasiques" (cell-nucleus-splitting drugs), increase the number of pycnoses and decrease mitotic proliferation, especially in the lymphatic organs. This phenomenon was designated as the "crise caryoclasique". However, in later stages of the response to these drugs, there is regeneration with an increase in the number of mitoses. Thus the same substances appear to stimulate both

[24] 13711/22, A19828/29, A32208/39, A32209/39, B14905/39.
[25] B14905/39.
[26] 35415/11, A32533/11.
[27] 35537/11, 35398/11.
[28] Fastier and Smirk A59076/43, Page A31299/39, Rietschel A31106/39, Winder and Anderson B17781/48.
[29] Ancel 35427/11, Lambert et al 35379/11.
[30] Abrami and Tzanck A32621/31, Neret-Cauchy A17037/38, Tzanck A32618/32, Tzanck and Klotz A32622/35.
[31] Lassablière A6258/37.
[32] 53735/33, A30579/39.

destruction and regeneration of cells. Some investigators claimed that certain caryoclastic drugs act more specifically on pycnosis, others on mitosis.[33]

All of the "caryoclastic drugs", which we had occasion to examine, produce typical A-R changes. This has been demonstrated especially clearly for colchicine,[34] one of the most active compounds of this group. It was also noted that waves of pycnoses in the thymus and lymph nodes are produced by all alarming stimuli, not only drugs but also spinal or surgical shock, exposure to cold, muscular exercise, etc.[35] Thus it appears rather likely that, in the caryoclastic crisis, we are merely dealing with one aspect of the A-R and not with the specific pharmacologic action of a special class of drugs. Of course the mitosis-arresting effect of certain caryoclastic drugs is independent of the A-R and, incidentally, unaffected by adrenalectomy.[35a] The relationship between the caryoclastic drugs and other alarming stimuli is extremely close, however.[35b]

Hemoclastic crisis. — Widal et al.[36] gave a detailed description of a clinical syndrome which they termed "crise hémoclasique" (crisis of blood-breakdown). This was first observed in patients with cold-hemoglobinuria and later in many other clinical conditions, such as allergic reactions, infectious diseases, etc. The outstanding features of this syndrome are leucopenia, a decrease in the refractive index of the serum, decrease in blood-clotting time and hypotension. Albuminuria and fever are sometimes also observed, but these are less constant. Since both Widal's reaction and the A-R are largely catabolic responses to acute systemic stress, there probably exist close relationships between them.[37]

The **"malignant syndrome".** — With the designation "Le syndrôme malin des maladies infectueuses" the French school has long recognized the fact that many manifestations of grave infectious diseases (stupor, derangement of thermoregulation, dehydration, azotemia, albuminuria, a hemorrhagic diathesis, cardiovascular disturbances, etc.) are independent of the pathogenic organism and common to diverse infections which cause severe stress.[38] The relationship of this "malignant syndrome" to the G-A-S has recently been the subject of considerable study.[39]

"Chronic shock" and "medical shock". — The term chronic shock has been applied to a condition characterized by weight loss, decreased blood-volume, decreased blood-protein content and increased interstitial fluid volume. Frequently it is accompanied by anemia and edema. A variety of wasting systemic diseases (chronic infections, malignant tumors, peptic ulcers, malnutrition, hepatic insufficiency, etc.) may elicit this condition.[39a] It corresponds essentially to what has been termed by others "medical shock".

[33] Brock et al. 81456/39, Cavallero 78616/39, Chodkowski 78617/39, Delcourt 78615/39, Dustin B5348/38, 78614/39, Grégoire 85577/45, Grégoire and Lison 85578/34.
[34] Leblond and Segal A50424/38.
[35] Selye 38798/37.
[35a] Mascart B38797/49.
[35b] Dustin **B38553/47**, Selye B1204/46.
[36] 12298/21.
[37] Dellamartina A99218/40.
[38] Marquézy and Lodet B26289/38, B26290/38, Sedallian and Monnet B37944/47, B29085/45, Tardieu and Tardieu B19961/48.
[39] Manceaux and Jorda B23176/48.
[39a] Clark et al. B1401/47, B1402/47, B1403/47, Lyons and Mayerson B46016/47.

"Toxic destruction of protein". — This term describes the sudden protein-catabolism seen in many acute febrile infections, acute hemorrhage, traumas and other types of acute systemic stress. It refers to the participation of protein in the "catabolic impulse" of the A-R and is closely related to the "syndrome polypeptidotoxique" (see below). The term is still in use to designate the repercussions upon protein-metabolism of syndromes such as those described under the names of post-operative disease, caryoclastic crisis, etc.[40] It corresponds to the "Eiweisszerfallsvergiftung" of the German investigators.[40a]

"Toxic aminemia". — Under the name of "l'aminémie toxique" Loeper et al.[41] described a syndrome of protein-catabolism, caused by systemic stress, in which the clinical signs were ascribed to the formation of amines (histamine, tyramine, etc.) from protein-cleavage products. It is closely related to the *"syndrome chimique d'histolyse massive"* described by the same authors as characteristic of patients in whom much tissue is destroyed by x-rays, trauma, burns, etc.[42]

Syndrome polypeptidotoxique. — This syndrome is characterized by an unusually high blood-polypeptide-content e.g., in acute hepatic insufficiency, after burns, traumas and other severe systemic injuries. It is obviously related to, if not identical with, the so-called "catabolic impulse" of the A-R, in which there is a conspicuous, sudden protein-breakdown and — especially if renal function is impaired — a concomitant increase in the blood-concentration of protein-split-products.[43] An increase in blood-polypeptides is often found in *"toxic uremia"* and has been claimed to play an important rôle in producing the uremic syndrome.[44]

Post-operative disease. — Under the name of: "Maladie postopératoire" Leriche et al.[45] described a syndrome which appears in patients following a variety of surgical interventions. Its characteristic manifestations were listed as: (1) humoral (hypochloremia, hypochloruria, decrease in blood-alkali-reserve, increase in blood-N.P.N.), (2) vascular (hypotension, tachycardia, extra-systoles, cyanosis, cold sweats, collapse) and (3) hematologic (transitory fall followed by an increase in blood-platelets with a maximum on the tenth day, leucocytosis, hypercalcemia, hyperkalemia, and a great tendency to the formation of thromboses).

Non-specific therapy. — Since the A-R confers a certain degree of non-specific resistance upon the organism it probably plays a part in the so-called "non-specific therapy." In spite of the very voluminous literature concerning this subject,[46] little is known about the underlying mechanism. It has been claimed that administration of certain non-specific agents leads to the production of "metabolites" which exert a beneficial action in various diseases. The nature of these metabolites has not been elucidated, but the mobilization of the endocrine defense-mechanisms during the G-A-S may be involved.

The terms *"Leistungssteigerung"* (increased efficiency) and *"Protoplasmaaktivierung"* (protoplasma-activation) have been widely used in the German literature to describe this phenomenon. The various types of *"shock therapy"*,[47] including the *malaria-therapy* [48] as well as other types of *"fever-therapy"*,[49] *"protein-therapy"*,[50] *"insulin-shock-therapy"*,[51] *"metrazol-shock-therapy"*,[52] *"electro-convulsive therapy"* [53] need only be mentioned here with key-references to the literature where extensive compilations of the pertinent bibliography can be found. (Cf. corresponding agents in section on "Alarming Stimuli".) It is probable that all these phenomena are closely related to the increase in resistance seen during the "phylactic" reactions (see above) and correspond to the "crossed-resistance" during the G-A-S. Significantly, artificial fever mitigates anaphylaxis in sensitized guinea-pigs.[54]

Focal infection.[55] — This term is applied to infections in which pathogenic micro-organisms settle in circumscribed areas and although the local manifestations may be negligible, these foci tend to cause severe pathologic changes in distant organs. The favorite sites of focal infections are the tonsils, periodontal tissue, nasal sinuses, fallopian tubes and the prostate. Allegedly the most common changes caused by focal infections are the following: acute rheumatic fever, chronic "rheumatism", lumbago, neuralgias, hypertension, arteritis, acute or chronic nephritis, aplastic anemia, allergic manifestations such as uticaria purpuras, and perhaps even Grave's disease. It is characteristic of focal infections that they tend to cause systemic changes periodically, with comparatively symptom-free intervals, and that removal of the causative primary focus of infection almost invariably results in a cure. Many investigators ascribe the systemic manifestations of focal infections to periodic invasion of the blood-stream by micro-organisms, others regard them as due to the discharge of toxic products or to some allergic reactions. It is possible that any one of these pathogenic mechanisms may be operative in different cases, but in any event either of them would lead to systemic stress. It is tempting to assume, therefore, that the lesions in distant organs, caused by focal infections, are merely another example of the diseases of adaptation, in the sense of a severe maladaptation to a comparatively unimportant pathogenic focus.

Anoci-association. — Crile and Lower [56] coined this term to describe "an operative technique, which will exclude from the brain the stimuli of the special senses and the stimuli of common sensation." They clearly recognized that intense nervous stimuli, such as fear and pain before or during an operation, may in themselves be very damaging; hence they emphasized the importance of avoiding such stressors in surgery, as far as possible, to diminish the likelihood of shock. In subsequent largely speculative writings Crile [57] attempted to extend this concept of damage through pain to various "Phenomena of Life". As regards the G-A-S, the chief interest of his books lies in their excellent descriptions of psychosomatic manifestations.

The reactional state. — Guieysse-Pellissier [58] described as *"l'état réactionnel"*: "a state of reaction against slightly injurious agents, which cause a change

[40] Peters B19934/46.
[40a] Eppinger **B37085/49.**
[41] B19724/44.
[42] Loeper et al. B19724/44.
[43] Liegeois and Terache A6268/37.
[44] Puech and Cristol A32660/29.
[45] Lambret A32628/43, Lambret and Driessens A2914/37, Dubois-Ferriere 99368/45, Leriche B18459/34.
[46] Hicks A60110/36, Weichardt 62468/36, Weichardt and Schmidt A32623/34.
[47] Himwich B23656/44, Wilcox B19967/48.
[48] Wagner-Jauregg 92264/46, B19911/887, B19912/895.
[49] Simpson et al B18193/37.
[50] Petersen B4433/22.
[51] v. Braunmuehl B31231/47, Sakel B19918/36, B19920/38, Squires and Tillim B23840/44.
[52] Meduna and Friedman B19919/39.
[53] Cleghorn et al. B19125/48, Delay et al. 99465/44.
[54] Gottschall et al. B656/44.
[55] Goia **B25571/46.**
[56] 97296/15.
[57] 96642/36.
[58] **99224/32.**

in the structure of normal organs, stimulating the growth of their elements without killing them." He states that "the reactional state manifests itself by cellular hyperplasia which affects almost exclusively the lymphatic tissue." The designation especially referred to such excessive proliferations of lymphatic elements as occur under the influence of local irritations, for instance in the appendix or tonsils. This condition is not sufficiently defined to permit a profitable discussion of its possible relationship to the G-A-S.

Serous inflammation. — Under the name of *"Seröse Entzündung"* Rössle,[59] Eppinger [60] and their respective schools, described the fact that under the influence of various noxious agents the normally low protein-concentration of the intercellular fluid rises due to migration of plasma into the intercellular spaces. This migration — which is referred to by Eppinger as *"albuminuria into the tissues"* — is the result of increased capillary permeability. It is accompanied by blood-plasma imbibition of parenchymatous cells, with a rise in their NaCl, Ca and water content and a decrease in their PO_4 and K content. Thus the chemical composition of the intra and extracellular fluids becomes equalized. This is presumably due to a loss of the characteristic "selective permeability" of cell-membranes which helps to keep certain compounds inside, others outside the cell. A-R changes in the adrenals [61] and in the intestinal tract,[62] accompany this syndrome in man. These observations emphasize the close correlations between the concepts of "serous inflammation" and of the A-R.

The anamnestic reaction. — This is probably an integral part of the G-A-S. The term "anamnestic reaction" (reaction of recalling) has been defined as: "The enhancement of antibody titer which follows the injection of a variety of non-specific substances other than the original antigen".[63] Such reactions may explain some of the manifestations of "crossed-resistance".

The "Shwartzman Phenomenon". — The term *"phenomenon of local tissue-reactivity"* has been introduced by Shwartzman.[64] He found that if a rabbit is first prepared by intradermal injection of active bacterial filtrate and 24 hours later receives an intravenous provocative injection of the same filtrate, severe hemorrhagic necrosis occurs, after another four hours, in the region of the preparatory intradermal injection. The substances used respectively for preparing the skin and for provoking the reaction need not be the same nor do they have to be bacterial filtrates. For instance, after preparation of the skin with a coli-bacillus filtrate the phenomenon can be elicited by intravenous injection of agar or starch. Yet, only those substances can be used for preparation which cause an inflammatory swelling that lasts at least 24 hours.

Sanarelli [65] showed that even the preparatory injection could be made intravenously. If a first intravenous injection of active bacterial filtrate is followed 24 hours later by a second similar intravenous injection, the latter elicits the thrombo-hemorrhagic lesions typical of the "local phenomenon". These are manifest in various internal organs, especially the kidneys. This response was named the *"general phenomenon" of Sanarelli-Shwartzman*. The renal lesions are characterized by arterial necrosis, fibrin thrombi in the glomerular loops,

[59] A32624/08, A32627/35.
[60] A9304/37, **B37085/49.**
[61] Dworacek B29025/45.
[62] Manzini 76996/39.
[63] Dougherty et al. B142/45.
[64] B19913/37.
[65] B25271/26, B25272/36.

glomerular hemorrhages, tubular necrosis and often extensive bilateral cortical necrosis with severe hemorrhages. Simultaneously, multiple, mural vascular thrombi are formed in the bone-marrow, spleen, liver, lungs and occasionally there is extensive adrenal-necrosis.[66] The so-called *"phenomenon of non-specific allergy"*, commonly seen in tuberculosis or typhoid fever, is closely related to, if not identical with the "Sanarelli-Shwartzman phenomenon".[67] Allegedly the Sanarelli-Shwartzman phenomenon is due to endogenous histamine-liberation.[68]

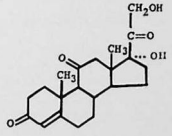
All these changes resemble those often encountered in man, in association with infectious purpuras. The "general phenomenon" is claimed to be closely related to the sudden death which sometimes occurs following intravenous injection of typhoid-vaccine in man.[69] In such cases, post-mortem examination revealed numerous purpuric spots in the pericardium, endocardium, peritoneum and skin, hemorrhages in the kidneys and lungs as well as necrotic foci in kidneys, liver and adrenals. The morphologic changes in the kidneys, adrenals and the cardiovascular system, are sufficiently similar to those of experimental (e.g., hormonally produced) "hyalinosis" to suggest the possibility of pathogenic relationships between them. The discovery of such connections between the diseases of adaptation and "allergic-pathergic" lesions would open an intriguing new approach to the problem of allergy.

Thrombosis, with the formation of fibrin, endows the plasma with vasopressor activity (see: "Spätgift"), hence the possibility should be envisaged that in the Sanarelli-Shwartzman phenomenon the thrombosis itself is the immediate reason for the local vasoconstriction which leads to necrosis. If numerous thromboses are simultaneously formed in many branches of the vascular tree — as is also the case in the experimental "hyalinoses" — the resulting formation of vasopressor material may perhaps even suffice to raise the systemic blood-pressure. (Cf. Serologic reactions.)

D — Abbreviations, Symbols and Special Technical Terms

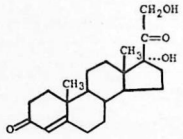
(For a more detailed characterization of metabolites, especially hormones, cf. chapter: "Metabolism")

ACTP = adreno-corticotrophic polypeptide; a hydrolyzate of ACTH.
ACTH = adreno-corticotrophic hormone or corticotrophin.
ADP = adenosine-diphosphate.
A-R = alarm-reaction.
A-R changes = changes characteristic of the A-R.
ATP = adenosine-triphosphate.
B.M.R. = Basal metabolic rate.
Corticoids = substances simulating the activity of the adrenal-cortex.
The following are some members of this group to which reference is made in the text. For a detailed review of these and other steroids see Selye: (A57606/43).

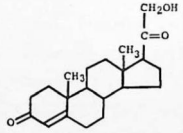


CORTISONE (Reichstein's cpd. "Fa 6", Kendall's cpd. "E", Wintersteiner's cpd. "F", 17-hydroxy-11-dehydro-corticosterone).

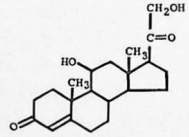
[66] Shwartzman et al. **B19914/38.** Urbach and Gottlieb **B2133/46.**
[67] Albert-Weil 99346/46.
[68] Gangitano and Bondi B37974/47.
[69] Love and Driscoll B19916/45, Urbach et al. B19915/44.



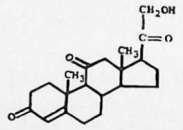
DESOXOCORTISONE (Reichstein's cpd. "S", 11-desoxy-17-hydroxy-corticosterone).



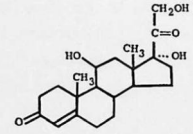
DESOXYCORTICOSTERONE ACETATE (acetate of Reichstein's cpd. "Q", Kendall's desoxy cpd. "B", 21-hydroxy-progesterone).



CORTICOSTERONE (Kendall's cpd. "B", Reichstein's cpd. "H", 11-21-dihydroxy-progesterone).



DEHYDROCORTICOSTERONE (Kendall's cpd. "A").



17-HYDROXYCORTICOSTERONE (Kendall's cpd. "F", Reichstein's cpd. "M").

Cortisone; see corticoids, above.
DCA = desoxycorticosterone acetate; see corticoids, above.
Desoxocortisone; see corticoids, above.
Dopa = dihydroxyphenylalanine.
Endocrine kidney = a kidney which has been so modified that it ceases to produce urine but continues to secrete RPS.
Endocrine nephron = a nephron which has been so modified that it ceased to secrete but continues to produce RPS.
E.S.R. = erythrocyte-sedimentation rate.
Folliculoids = compounds simulating the hormonal activity of an ovarian follicle.
G-A-S = general-adaptation-syndrome.
G-C = gluco-corticoids.
G-CT = gluco-corticotrophic effect.
Gluco-corticoids = corticoids particularly effective in raising the liver-glycogen and blood-sugar concentrations (e.g., cortisone).
Gluco-corticotrophic action = stimulation of G-C production (not necessarily due to separate hormone).
Kendall's compounds; see: Corticoids, above.
LAP = lyophilized anterior-pituitary tissue.
Lipo-corticoids = corticoids particularly effective in causing fat-deposition (especially in the liver).
Luteoids = compounds simulating the hormonal activity of the corpus luteum.
M-C = mineralo-corticoids.
M-CT = mineralo-corticotrophic effect.

Medulloids = adrenergic substances simulating the hormonal activity of the adrenal medulla (adrenaline, nor-adrenaline).
Mineralo-corticoids = corticoids particularly effective in causing sodium-retention and potassium-loss (e.g., DCA, desoxocortisone).
Mineralo-corticotrophic action = stimulation of M-C production (not necessarily due to separate hormone).
N.P.N. = non-protein-nitrogen.
Reichstein's compounds; see: Corticoids, above.
RPS = renal pressor substance(s).
R.E.S. = reticulo-endothelial system.
Stress = systemic stress. If the term is used in another sense in this book, this will be specifically stated.
Stressor = an agent producing systemic stress.
Target = that which reacts to a stimulus. Both structural (e.g., heart) and chemical (e.g., blood-sugar) receptors of stimuli are thus designated.
TEA = tetraethylammonium (usually administered as the chloride).
Testoids = compounds simulating the hormonal activity of the testis.
VDM = vaso-depressor material.
VEM = vasi-excitor material.
17-KS = 17-ketosteroids.

FACTORS WHICH ELICIT THE G-A-S

(The "Alarming Stimuli" or Stressor Agents)

As previously stated (see: Definitions and Terminology) the term "alarming stimulus" denotes a "stressor" agent, that is, one which causes systemic stress. The latter may be defined as a deviation from the normal resting condition, in extensive regions of the body. Any change affecting a living organism is a stressor, as it elicits some efforts to resist and hence at least mild manifestations of an A-R.

Agents whose action is localized and requires no important general adaptive adjustment (e.g., selectively acting drugs, amputation of limbs), are relatively mild alarming stimuli, even if they maximally stimulate, or actually kill, limited cell-groups. Conversely, agents which, even though mildly, affect large portions of the body (e.g., extensive trauma, muscular exercise, cold, hemorrhage, solar or roentgen radiations) evoke an intense G-A-S.

It must be especially emphasized — since the point has so often been misinterpreted in the literature — that the A-R is not necessarily a pathologic phenomenon. In the case of mild exposure to stress, there is no "shock" in the ordinary sense of that word. Slight hyperglycemia, tachycardia and leucocytosis may be the only detectable signs of "alarm". There is a continuous series of transitions between the definitely physiologic adaptive processes to the strains of everyday life and the most severe alarm-reactions which cause death in the shock-phase.

In view of these considerations it hardly seems useful, or even feasible, to mention each stressor agent which can produce an A-R or, upon prolonged exposure, an entire G-A-S. Nevertheless, it was considered desirable to characterize each of the principal alarming stimuli in a few words, since many investigators are interested in the G-A-S only as regards its influence upon the effects of one or the other stressor which happens to be the principal object of their study (e.g., trauma, x-rays, anoxia, emotional stimuli).

The following discussion is therefore meant to serve a dual purpose: it will survey those agents which are particularly active in producing a G-A-S and it will attempt to delimit the truly specific from the non-specific actions of such agents. Among the innumerable pertinent publications we tried to select mainly those suited to act as guides to the general literature concerning the non-specific effects of each alarming stimulus and those in which the relationships with the G-A-S were specifically considered.

Trauma.[1] — Direct mechanical injury to large portions of the body (e.g., accidental trauma or major surgical interventions), is eminently endowed with the two most important attributes of alarming stimuli: (1) many cells are affected, (2) the change requires much adjustment and adaptation. The number of cells affected depends partly upon the extent of the trauma itself (direct injury), and partly upon the resulting humoral and nervous derangement (secondary injury). The necessity for adaptation and repair is occasioned by the widespread cell-destruction, the loss of blood, etc. Conversely, purely mechanical trauma to tissues does not appear to possess any important specific actions of its own, if we disregard the changes caused by interference with the functions of directly injured organs. It is for this reason that the syndrome of *"traumatic shock"* furnished us with the earliest good descriptions of what we now realize to be the first phase of the G-A-S to non-specific, systemic stress. The previously-mentioned publications on the "post-operative disease" (see Glossary) contain many interesting pertinent observations.

In the light of these considerations it is understandable that simple surgical trauma also proved to be one of the most useful stressors in the experimental investigations which led to the discovery of the A-R [2] and the G-A-S.[3] In these early experiments trauma was produced by crushing of intestines or the muscles of the anterior abdominal wall, fractures of bones, etc. It was found that such interventions regularly produce an enlargement of the adrenal-cortex (with discharge of its lipid-granules), gastrointestinal erosions (with hemorrhages into the gastrointestinal tract) as well as acute involution of the thymus, lymph-nodes and spleen. As in alarm-reactions produced by other systemic stressor agents, these morphologic changes were accompanied by the characteristic biochemical manifestations of the "catabolic impulse". The thymico-lymphatic involution (but not the other organ lesions) could be prevented by adrenal-ectomy. Shortly speaking, the reaction was similar in all important points to that elicited by any alarming stimulus.

Since it is difficult to subject experimental animals to frequently repeated surgical trauma, the technique of producing mechanical tissue-injury had to be modified for chronic experiments. A rotating drum was constructed which contained projections on its inner surface. Small laboratory rodents (rats, guinea pigs) were placed in this drum with their paws taped together to prevent climbing. Thus they could be exposed to the repeated trauma of falling off the projections against the wall of the drum. Rats traumatized in such rotating drums developed typical adrenal enlargement, thymico-lymphatic

[1] Best and Solandt **A34670/40**, Blalock **B19949/30**, **B19948/40**, Cannon **A32617/23**, Frank et al. **93252/46**, Gregersen **96515/46**, König **A32639/32**, Krogh **12532/21**, Moon **A16304/38**, **B19951/48**, Parsons and Phemister **B19950/30**, Raven **B36453/42**, Scudder **A32530/40**.

[2] Selye 36032/36.

[3] Selye 38798/37, B1204/46.

atrophy, gastrointestinal ulcers and other manifestations of the A-R. However, upon chronic exposure, they revealed the interesting fact that a certain degree of adaptation can be acquired even to the shock-producing action of mechanical injury.[4]

Obstetric shock.[5] — This condition, which is usually seen after complicated deliveries, is probably closely related to other types of traumatic shock. The syndrome is but vaguely defined by such postulates as "that the patient shall have died of shock in connection with obstetrics, no matter what the cause of the shock".[6] The only important characteristic of this condition, which differentiates it from the usual response to intense systemic stress, is the frequently mentioned predominance of multiple hemorrhages and ischemic necroses in various organs, particularly the pituitary. Infarcts in the anterior-hypophysis after complicated deliveries may permanently impair adaptation and are a frequent cause of Simmonds' cachexia.

Surgical interference with vital organs. — Suffice it merely to mention that in addition to the direct systemic stress produced by trauma, considerable injury may be inflicted upon many cells of the organism, indirectly, through traumatic (mechanical or chemical) interference with the function of vital organs. Injury to the glands involved in the regulation of the metabolism, for instance the liver or kidney, may derange their function and thus cause particularly pronounced systemic stress due to the ensuing changes in the chemical composition of the "milieu intérieur". A minor traumatic injury to the hypothalamus can cause intense systemic stress by interfering with the nervous regulation of metabolic functions.

All these types of lesions are clear-cut examples of non-specific damage secondary to the selective effect of a specific agent upon a target which in its turn influences the organism as a whole.

These interventions incidentally illustrate lesions in which there is marked "distortion" of the G-A-S, due to the addition or subtraction of certain specific changes. For instance destruction of the liver causes systemic stress with a typical G-A-S, except that there is no increase in fibrinogen-formation, since the latter is made in the liver. After renal injuries, the specific actions of uremia are superimposed upon the G-A-S manifestations while the characteristically increased nitrogen-excretion of the catabolic phase may be inhibited by anuria. With hypothalamic injuries various specific nervous manifestations (their nature depending upon the extent of the lesion) will be added to the non-specific G-A-S.

A few other examples deserve special mention. Thus, *ligature of the common bile-duct* produces typical and very intense G-A-S changes in the rabbit, presumably because of the resulting liver-insufficiency and the retention of toxic bile.[7]

Complete evisceration is a very intense alarming stimulus. This proves that none of the intraperitoneal organs are indispensable for the development of the

[4] Neufeld et al. A63529/43, Noble A56868/43, Noble and Toby B3012/45, Toby and Noble 85127/44, Ungar A57983/43.

[5] Matthews A30867/39, Paucot and Bedrine B29887/47, Russell A33116/40, Sheehan A31726/39, Snaith A33084/40, Solomons A33086/40.

[6] Sheehan A31726/39.

[7] Rosselli del Turco and Matteini B37478/49.

A-R and that absorption of toxic products from the intestine is likewise not a necessary prerequisite for its production.[8]

In agreement with expectations general peritonitis causes severe A-R changes especially if it results in marked *intestinal atony*. It is interesting, however, that "a stage of shock may occur during the healing stage of peritonitis when intestinal function suddenly is resumed" [8a] and the organism has to readapt to it.

Temporary occlusion of blood vessels.[9] — Cannon [10] described the case of an unwounded man who suffered merely a compression of the thigh, between fallen timber, for twenty-four hours; after being released he went into shock and died in thirty-two hours. Since this report, many similar cases have been observed both in man and in experimental animals.[11] In animals the technique usually employed is either to ligate the artery directly or merely to place a tourniquet around a part of the body. The resulting damage to all the cells distal from the occlusion is presumably caused by temporary anoxia and lack of nourishment rather than to direct mechanical damage; yet the ensuing A-R changes are similar to those elicited by direct trauma.

The principal value of this technique was to suggest the humoral mediation of shock. Only a blood-borne, chemical transmission of the shock-producing impulse could explain: (1) that shock ensued after release of the occlusion but not during interruption of the circulation, (2) that release of a temporary occlusion of the limb-vessels is followed by shock even if all other connections between body and limb are severed. The tourniquet technique also proved to be very valuable in studies concerning the chemical composition of blood coming from a limited injured area. For this purpose it was used in the cat, dog and monkey.[12]

Hemorrhage.[13] — Loss of blood almost invariably accompanies traumatic injuries and adds to the systemic stress caused by the latter. But even by itself, massive hemorrhage acts as an intense alarming stimulus, since it represents a severe stress for nearly all tissues of the body. Therefore, experimental hemorrhages have been extensively employed in the study of the A-R. Using suitable precautions this agent lends itself especially well to the production of graded degrees of stress.[14]

The lesions produced by massive hemorrhages are essentially the same as those caused by other systemic stressor agents, but the specific effects of blood-loss (e.g., hemodilution, stimulation of bone-marrow-activity) are superimposed upon the ordinary G-A-S manifestations.[15] It is possible that the therapeutic efficacy of "blood-letting" was due to the "crossed resistance" or "shock-therapy" effect to this systemic stressor agent.

As we shall see later, ascorbic-acid-depletion of the adrenal (and to a lesser extent of other tissues) is rather characteristic of the G-A-S. It is noteworthy,

[8] Selye A8052/38.
[8a] Sandblom and Hahn B40795/47.
[9] Allen A18905/39.
[10] A32617/23.
[11] Allen A18905/39, 76347/38, Hungerland A32726/34, A32727/35, 37521/36, Scott 93258/46, Seligman et al. 93251/46, Selye and Dosne A35802/41, Wilson and Roome A32728/36.
[12] Selye and Dosne A35802/41.
[13] Gellhorn B27006/43, Glasser and Page B28222/48, Klemperer B19258/48, Rukstinat A32657/32, Shwartzman et al. B19246/48.
[14] Dosne 94398/46, Huizenga A59447/43.
[15] Gregersen B19252/48, Wiggers and Ingraham 93253/46.

therefore, that even in the rat, which can synthesize ascorbic-acid, hemorrhagic shock causes marked losses of this vitamin from the adrenals and liver.[16] In the guinea pig, which depends upon a nutritional intake of ascorbic-acid, intraperitoneal injections of it allegedly raise resistance to hemorrhagic shock.[17] Perhaps in this species the availability of ascorbic-acid is a limiting factor in shock-resistance.

The commonly observed post-hemorrhagic leucocytosis is presumably also merely a manifestation of the G-A-S. It has been claimed that after hemorrhage the blood itself acquires leucotactic properties, demonstrable by injection into a normal animal of blood taken from one in hemorrhagic shock. This has not been confirmed, however.[18]

Burns.[19] — It has long been known that severe burns, affecting a large portion of the body-surface, produce characteristic changes at a distance from the site of injury. Among these are adrenal-cortical hyperemia sometimes with hemorrhages, hemorrhagic gastrointestinal erosions (the so-called "Curling's ulcer") and biochemical changes which are now recognized to be part of the G-A-S. More recently it has been claimed that death in such cases "may be attributed to adrenal exhaustion and renal failure".[20] Glendening et al.[21] summarized analogous observations in their paper "Study of the Alarm Reaction in burned human subjects and its possible significance in war injuries".

The endocrine factors involved in defense to burns also appear to be essentially those of the G-A-S. It has been shown [22] that "after the production of standardized scalds in anesthetized rats there was a significant fall in the total cholesterol of the adrenal gland (e.g., from a normal concentration of 4.2 mg. per 100 mg. of adrenal weight to as low as 0.7 mg.). This fall did not occur in hypophysectomized rats, indicating that the effect of the burn may not be directly on the adrenal gland but mediated by the pituitary gland, possibly by a stimulation of the production or the outpouring of adrenotropic hormones".

Among the more or less specific changes which tend to complicate a G-A-S produced by burns are: (1) enormous plasma-loss through oozing from the injured area, (2) particularly sudden and intense proteolysis in the burned region and consequently, auto-intoxication with tissue-decomposition-products, (3) poisoning by drugs (e.g., tannic acid) of which excessive quantities are applied to the rapidly absorbing wound surface.

Temperature.[23] — Exposure to extremes of temperature likewise causes a stress affecting most tissues of the body. In agreement with expectations, exposure to severe **cold** elicits typical A-R changes such as adrenal-enlargement, thymico-lymphatic atrophy, gastrointestinal ulcers, generalized tissue breakdown, leucopenia, etc.[24] Indeed exposure to low surrounding temperature

[16] Sayers et al. B512/45.
[17] Dosne 94399/46.
[18] Feenders 37979/36.
[19] Bardeen B19953/897, B19954/897, Cameron 89885/45, Christophe **B19955/39**, Colebrook et al. B26911/42-43, Erb et al. A57594/43, Ficarra and Naclerio **B808/44**, Hilgenfeldt **38008/36**, Moon **B19951/48**, Pack A15632/26, de Mesquita Sampaio and Rocha Azevedo **B24444/44**, Walker and Shenkin 89895/45, Wallace **B36452/42**.
[20] Ficarra and Naclerio B808/44.
[21] 84678/44.
[22] Harkins 91182/44.
[23] Brobeck 96504/46, Gagge and Herrington 97656/47, Muirhead et al. A67426/42.
[24] Leblond et al. A18194/39, Muirhead et al. A67426/42, Puchkov A14663/37.

proved to be such an excellent means of producing almost purely non-specific damage that it was routinely used as a standard systemic stressor agent in the earliest studies concerning the G-A-S.[25]

Frost-bite due to local cooling may also produce systemic A-R changes.[26] Here, the most noteworthy facts are: (1) the similarity of the local lesions in the exposed area to those occurring systemically during an A-R produced by any means, (2) the resemblance of the "immersion foot" or "trench-foot" type of frost-bite to the experimental hormonal arthritides.[27]

It has been claimed that tissues exposed to cold form a "histotoxin", similar to that allegedly produced by otherwise damaged tissues. This metabolite is supposed to play an important rôle in the development of the systemic changes caused by cold,[28] but these observations have not been confirmed.

Exposure to extreme **heat** produces the well-known syndrome of "heat-stroke".[29] In man there may be erosions in the stomach and duodenum with bleeding into the gastro-intestinal tract, typical A-R changes in the adrenal-cortex ("tubular degeneration"), involution of the thymico-lymphatic apparatus, elevation of blood N.P.N., hypochloremia, formation of transudates in various serous cavities and — upon prolonged exposure — focal myocardial degeneration with renal changes similar to those seen in the "crush syndrome".[30] Brain-lesions, such as edema, hyperemia and hemorrhages,[31] are more prominent in acute heat-stroke than in most other stress-situations and hence may be regarded as somewhat specific of heat.

Pertinent observations were also made in rats in which artificial fever was produced by treatment with ultra-high frequency radio-emanations. Here, the adrenal-cortical lipids were depleted at first, but this was followed by increased storage during the phase of resistance. It was concluded that " . . . fever induced by ultra-high frequency radio-waves may have acted as a thermal stimulus which induced the chain of effects which accompany the alarm state".[32] Observations in man revealed that DCA prevents the NaCl-loss in sweat and urine as well as the excess urinary elimination of nitrogen normally occurring during exposure to humid heat. From this it was concluded that the adrenal-cortex is important for adaptation to heat.[33]

X-rays.[34] — The penetrating nature of x-rays renders them eminently suitable to produce the systemic stress so essential in evoking the G-A-S. Accordingly, many investigators, who studied the morphologic and metabolic derangements caused by x-rays, came to the conclusion that "radiation sickness" produces lesions strikingly similar to those elicited by other types of systemic stress, notably: involution of the thymico-lymphatic apparatus, gastro-intestinal

[25] Selye 36032/36, B1204/46.
[26] Csáky and Magyary-Kossa B37945/47.
[27] Vagliano B29862/48.
[28] Shimada 39049/35.
[29] Eppinger B37085/49, Gore and Isaacson B41903/49, Moon B19951/48, Schickele B37921/47, Terbrüggen and Deneke B38040/47.
[30] Malamud et al. B18019/46.
[31] Malamud et al. B18019/46, Haymaker et al. B37920/47.
[32] Bernstein 78168/40.
[33] Conn et al. B4468/46.
[34] Bloom **B31225/48**, Ellinger **68685/35**, Hirsch and Petersen A32674/23, Hoshi 23951/28, Kikuchi 10149/31, Kroetz A16087/24, Moon et al. A31861/40, Podljaschuk 20989/27, Prosser B26618/47, Prosser et al. 98573/47, Reding **39925/35**, Tullis B27010/48, Warren B27893/46, Weichert A56943/42.

ulcers, hemoconcentration, a derangement in the blood-clotting mechanism, etc.[35] This soon led to the suspicion that endocrine reactions may play a part in radiation sickness [36] and, more specifically, that a "relative" corticoid-deficiency exists in cases of acute, severe, systemic x-ray damage.[37]

Significantly, and in agreement with what is known about other alarming stimuli, in the rat, adrenalectomy almost completely prevents the thymico-lymphatic atrophy produced by systemic x-ray-damage if the thymus itself is shielded. However, direct irradiation of the thymus causes it to involute irrespective of the adrenals.[38] After total-body-x-irradiation, there is, furthermore, an early decrease in adrenal-cholesterol which is similar to that caused by adrenotrophic hormone administration.[39] In mice it was shown that total-body-x-irradiation causes involution of the thymico-lymphatic apparatus, fall in circulating blood-lymphocytes, rise in serum-protein and γ-globulin with signs of the "anamnestic response". Only after mild total-body-x-irradiation is the occurrence of such changes prevented by adrenalectomy. "It is suggested that x-rays exert both a direct and an indirect effect on lymphocytes. The direct action may be manifested even in the absence of the pituitary or adrenals, whereas the indirect action is mediated via the pituitary-adrenal-cortical mechanism".[40]

It has been demonstrated furthermore that in mice mild total-body-x-irradiation (3 weekly exposures of 144 r. followed by a 30 day rest) increases resistance to a subsequent lethal dose of x-rays. "It is difficult to visualize that cellular resistance to x-ray was actually increased. It is more plausible to consider that the previous sublethal exposure increased the non-specific resistance as defined by Selye or perhaps increased the specific resistance by developing protective bodies against the products of cellular destruction".[41]

Among the rather specific effects of x-rays and other ionizing radiations (see below) are: (1) the often rather prolonged latent-period between exposure and the full development of a G-A-S, (2) the derangement in blood-clotting and the gastrointestinal lesions are unusually severe, (3) the lympholytic effect is largely independent of adrenal-mediation.

Other ionizing radiations.[42] — In mice total-body-irradiation with effective doses of neutron rays leads to a "clinical, bacteriological and anatomical picture similar to that following roentgen irradiation".[43] Those investigators who examined the radiation-syndrome particularly with regard to its possible relationship to the G-A-S came to the conclusion that "nearly every organ system is affected by a single 30 day LD_{50} dose of any type of ionizing radiation. The most sensitive systems are the blood forming organs, the gastrointestinal tract and the gonads." . . . "there are striking similarities to anaphylactic shock and to the non-specific (alarm) reactions to a variety of diverse toxic agents

[35] Moon et al. A31861/40, 81503/41, Thygesen B1683/47.
[36] Reding 39925/35, A2443/36.
[37] Riml 75159/39.
[38] Halberstaedter and Ickowicz B3383/47, Leblond et al. A18194/39, Leblond and Segal A17235/38, 82724/42, Segal and Leblond A17236/38.
[39] Patt et al. B3611/47.
[40] Dougherty and White 95612/46.
[41] Cronkite et al. B26980/48.
[42] Anonymous B26330/48, Bloom **B31225/48**, Brues B38697/48, Cronkite B24051/48, B24042/48, Demole B38704/47, Liebow et al. **B41902/49**, Tobias et al. B4455/48, Tullis B27010/48, B41901/49.
[43] Lawrence and Tennant B19922/37.

given in sublethal amounts (Selye). Many of the delayed effects of irradiation can be duplicated by various toxic chemicals, . . .".[44]

In other experiments on mice, in which neutron bombardment of the tissues was accomplished by the administration of U^{235} there was: atrophy of the spleen, lymph-nodes (especially the germinal centers) and liver, with patchy tubular necrosis in the kidneys, diminution in the circulating leucocytes and anemia; the similarity of this syndrome to that produced by massive x-irradiation was re-emphasized.[45] All investigators who described the biologic effects of nuclear fission-products emphasized that multiple hemorrhages, due to incoagulability of the blood, largely dominate the picture.

The systemic damage caused by *radium* is similar to that caused by other radioactive elements or x-rays.[46]

Solar radiation. — Exposure to intense solar radiation likewise produces A-R changes. If shaved guinea-pigs are exposed to intense sunlight, they exhibit hyperemia of various internal organs, hemorrhages into the gastro-intestinal tract and the pleural cavities as well as interstitial pneumonias. The latter are perhaps more frequent than could be expected on the basis of a purely non-specific stress-effect.[47] The complex nature of this stressor agent makes it impossible to determine the relative rôles played by various rays and heat. Exposure of rabbits to mild ultraviolet-irradiation caused only slight adrenal-enlargement and thymus-atrophy after six weeks.[48] In man intense ultraviolet-irradiation caused biphasic blood-chemical changes typical of the shock — and counter-shock elicited by other stressor agents.[49] Particularly marked A-R changes occur upon exposure to light in individuals pretreated with *photodynamic substances* (cf. "Drugs", below p. 44).

Electric injury.[50] — The participation of neuro-endocrine mechanisms in electro-shock has long been suspected [51] and several investigators discussed the possibility that the humoral changes characteristic of electro-shock-therapy are due to the resulting G-A-S and not to any specific effect.[52] Experiments on frogs led to the conclusion that a toxic factor may be involved since occlusion of the vessels supplying the legs prevents shock in animals whose legs are exposed to electric injury. The first change here was a slight decrease, followed by an increase, in the blood-clotting time. It was assumed that the toxic factor may be "in the nature of a thrombin or thromboplastin".[53] Recent observations in man led to the conclusion that electro-convulsive therapy causes an activation of the adrenal-cortex which is similar to that seen in the G-A-S.[54]

Nervous stimuli.[55] — Nervous commotions are extremely effective alarming stimuli. Through its complex ramifications the nervous system readily transmits impulses to many parts of the body and if these stimuli are strong, they cause systemic stress. Even mere *emotional stress,* for instance, that caused by

[44] Painter et al. 98568/47, Painter and Brues B39627/49.
[45] Tobias et al. B4455/48.
[46] Ellinger **68685/35.**
[47] Pinner and Margulis 37822/36.
[48] Grant and Gates 17596/24.
[49] Kroetz A16087/24.
[50] Braun et al. B35551/49, Delay **B29861/46,** Delmas-Marselet **B26881/46,** Riess B35595/48.
[51] Delay **B29861/46.** Delay et al. 99465/44.
[52] Delay et al. B26884/43, B26883/44, Delay and Soulairac B26882/43, Delmas-Marselet B26881/46.
[53] Moreau et al. B17718/48.
[54] Cleghorn et al. B19125/48.
[55] Blalock B19948/40, Crile A32669/15, Gellhorn B27006/43, Roger A32642/16.

immobilizing an animal on a board (taking great care to avoid any physical injury), proved to be a suitable routine procedure for the production of a severe A-R.[56] Various emotions such as rage and fear elicit the A-R,[57] yet the functional integrity of the nervous system is not indispensable for the development of this reaction since it can also be produced by deep anesthesia.[58] Significantly, many of the manifestations of "nervous shock" in experimental animals have been ascribed to a "relative corticoid deficiency".[59]

In connection with our interpretation of certain types of hypertension as diseases of adaptation, it is interesting that exposure of rats to daily audiogenic stimulation causes great nervous irritation [60] and may persistently raise the blood-pressure, especially of older animals. It was concluded that this is "objective evidence for neurogenic influences in the etiology of hypertension".[61]

In another pertinent study rats were exposed to a complex type of nervous stimulation (intermittent ringing of a bell, air blasts and cage-vibration, once every hour). Here the weights of various endocrine organs were compared with those of normal controls and those of animals in which systemic stress was produced otherwise, e.g., by thyroid-overdosage. It was concluded that: "these results should be considered in relation to Selye's work on the alarm-reaction. Our experiments did not involve the extremes of stimulation characteristic of Selye's work, but some relationship is evident. In both the thyroid group and the disturbed group the adrenal weights are greater and testicular weights are less, which agrees with Selye's findings".[62]

Striking examples of G-A-S changes have also been noted in men under continuous, severe emotional stress; for instance, that incident to surgical interventions [63] or that to which men in the airforce were exposed during the war.[64] Comparisons of the reactions of normals and psychoneurotics to stress and non-stress interviews and other standard stress-situations suggest that they all respond with a rise in corticoid-production.[65] There is no doubt that the pain elicited by certain alarming stimuli (such as infections, trauma) greatly augments their alarming effect.[66] (See also: "Combined exposure to several systemic stressors" below.)

Data concerning the many interesting relationships between psychosomatic reactions and the G-A-S in man have been compiled by several investigators.[67]

It has been claimed that, in contradistinction to traumatic shock, there is blood-dilution in *spinal shock.*[68] Indeed, allegedly [69] "the only significance which the latter observation bears on the problem of traumatic shock is the additional evidence which it affords that traumatic and spinal shock are two totally distinct conditions." This conclusion has been refuted. Spinal shock was found to produce all the characteristic signs of the shock-phase, including hemoconcentration. The blood-dilution referred to above appears only during the counter-shock-phase. Thus spinal shock may also be regarded as an alarming stimulus.[70]

[56] Selye 36032/36, 38798/37, B1204/46.
[57] Selye 36032/36.
[58] Selye A8048/40, B1204/46.
[59] Riml 75159/39.
[60] Morin & Cain B38156/47, B38157/47.
[61] Medoff and Bongiovanni 91713/45.
[62] Herrington and Nelbach A37641/42.
[63] Crile 96642/36, Crile and Lower 97296/15.
[64] Grinker and Spiegel B18363/45.
[65] Cleghorn et al. B19125/48, Shands and Finesinger B31901/48.
[66] Judd B315/17.
[67] Alkan **B36275/30,** Clark B18538/48, Dunbar **B36276/35,** Wolf B26123/48.
[68] Mummery and Symes A32725/07.
[69] Henderson 47096/10.
[70] Selye 66551/36, B1204/46.

Transection of the upper thoracic spinal-cord proved to be one of the most effective, simple, routine procedures for the production of a typical and intense A-R in rats, especially if the animals are fasted during the experiment.[71] From an investigation in which this technique was used on rats kept at various room-temperatures, it was concluded that "these experiments in general confirmed Selye's contention that, among other procedures, transection of the spinal-cord is followed by a train of changes in the organism among which thymus-involution and adrenal-enlargement are the most prominent. But just as the procedure of cutting the cord is not to be thought of as a single causal agent, so the complex of the results observed cannot be considered a unitary reaction. Thus, although thymus and adrenal changes are quite clear even if the ordinary fall of temperature after spinal section is prevented, gastric hemorrhages are absent." The author concludes furthermore, however, that "stomach hemorrhages were seen almost invariably in animals which had been permitted to become chilled following transection of the cord, but never in those whose body temperature had been maintained".[72] As we shall see later, various factors can selectively condition certain organs to become more or less sensitive to one particular effect of the G-A-S. Hence, it is to be expected that under certain conditions a single manifestation (e.g., the gastric hemorrhages) could be prevented. It is also possible that the maintenance of the normal body-temperature merely diminished the systemic-stress effect of the cord-transection, so that the grave gastrointestinal changes were prevented, although less severe G-A-S manifestations still occurred. Another investigator [73] succeeded in preventing all the A-R changes in rats after spinal-cord-transection, by complete prevention of body-heat-loss. He concluded that heat-loss is the major cause of systemic stress after this operation.

The presence in the *hypothalamus* of important vegetative nervous centers may explain why lesions in this region are particularly prone to elicit G-A-S changes. Allegedly, the hypothalamus contains the effector mechanism regulating homeostasis.[74]

In dogs, lesions in the hypothalamic region (especially in the vicinity of the tuber cinereum) readily cause acute gastrointestinal erosions with hemorrhages into the alimentary tract.[75] Fibrin-clots are often formed in the cardiovascular system of dogs after injury to the base of the brain.[76] Such lesions are reminiscent of those seen in the experimental "hyalinoses".

The *vagus nerve* appears to play an important rôle in the production of gastric ulcers by systemic stressors in general and by hypothalamic lesions in particular. It has been possible to produce gastric ulcers in dogs by chronic stimulation of the vagus with an induction current.[77] Mild electrical irritation of the infundibulum produced hyperemic patches in the gastric mucosa as well as a pronounced increase in the tonus and peristalsis of the stomach. All these effects could be abolished by vagotomy.[78]

The observations cited above clearly indicate that nervous irritation is a particularly effective alarming stimulus. The hypothalamic vegetative centers

[71] Selye 36032/36, 38798/37.
[72] Frank A34171/40.
[73] Dalton A34566/40.
[74] Beattie 4685/32, Beattie et al. B19928/30, Cannon B19927/30.
[75] Burdenko and Mokilnitzky 2055/26, Keller et al. 15109/33, Skohlo 2056/30.
[76] Keller et al. 15109/33.
[77] Stahnke 21250/24.
[78] Beattie 4673/32.

play a prominent rôle in the G-A-S as co-ordinators of homeostatic mechanisms; through them emotional stimuli or localized nervous impulses may influence many organs, thus causing systemic stress. In comparison with the effects of other systemic stressors, the influence of nervous stimuli upon the gastric mucosa is especially prominent; this particular action appears to be mediated through the vagus nerve.

Muscular exercise.[79] — Excessive muscular work has extensively been used as a stressor in the earliest studies concerning the G-A-S.[80] In acute experiments. it is highly effective in producing thymico-lymphatic involution, gastrointestinal ulcers, adrenal-cortical enlargement and other A-R manifestations. We shall see later that in man this is accompanied by increased corticoid-elimination in the urine.[81]

The great similarity between the systemic effects of excessive muscular exercise and those of the A-R have been re-emphasized. The changes accompanying severe muscular fatigue have been ascribed to a "relative corticoid-deficiency" comparable to that produced by infections, irradiations, trauma, etc.[82] This is in accord with our concept of derangements due to hypo-adaptation.

In some respects, however, the systemic consequences of exercise differ from those produced by other alarming stimuli. Exercise causes remarkably little shock and very pronounced counter-shock phenomena. There is an especially intense and prolonged hyperchloremia and, after an initial fall in blood-sugar, there follows a marked hyperglycemia.[83] As judged by experiments in the rat, the transitory fat-deposition in the liver, which tends to occur during the A-R stage of the G-A-S, is also more pronounced after forced exercise than after most other types of stress.[84]

Rest. — Bed-rest alone can cause marked losses of nitrogen and potassium, a decrease in blood-volume and considerable vasomotor disturbances. The resemblance of these manifestations to those seen in various spontaneous diseases has been emphasized and the delay of recovery from disease caused by extensive "therapeutic" bed-rest has been illustrated by many examples.[85] Lack of exercise itself requires adaptive adjustments and since it represents a pronounced deviation from normalcy, it may perhaps act as an "alarming stimulus". This possibility has not yet been adequately studied, but observations on the rat suggest that forced restraint can produce G-A-S changes.[85a]

Anoxia and asphyxia.[86] — Experimental observations on rats exposed to greatly reduced atmospheric pressure for periods of 3 to 13 days revealed "... an increase in the absolute weight of the adrenal glands in association with a decrease in weight of the thymus and testes" ... "The pattern of change and the general condition of the animals were similar to that which may be produced by cold, injections of formaline or morphine, severe muscular work and other forms of stress (Alarm Reaction of Selye)".[87] Similar findings have been reported by others in rats, rabbits and dogs.[88] More recently, many invest-

[79] Herxheimer B23046/24, Ingle 75145/38, Jokl B19917/47, Steinhaus A8015/33.
[80] Selye 38798/37.
[81] Venning and Kazmin 93048/46.
[82] Riml 75159/39.
[83] Selye A15674/39.
[84] Selye A15667/39.
[85] Keys B23164/45.
[85a] Latta and Nelson B28667/48.
[86] Gellhorn B27006/43, Highman and Altland B43695/49, van Liere **B26199/42**, Monge **B27662/48**, Moon B19951/48, Thorn et al. B335/45.
[87] Dohan A37744/42.
[88] Thorn et al. A57759/42.

igators called attention to additional points of resemblance between the manifestations produced by anoxia and those of the G-A-S.[89]

It is especially important to realize that upon chronic exposure of rats to reduced atmospheric pressure a typical G-A-S develops, in the usual three stages, terminating in exhaustion.[90] Several subsequent investigators confirmed that following continued exposure to anoxia there is a decrement in altitude- tolerance in rabbits [91] and rats.[92] This "regression of adaptation" or "loss of adaptation" has been regarded as equivalent to the exhaustion-phase of the G-A-S.[93] It should not be confused with the phenomenon of "de-acclimatization" to anoxia, which occurs in animals (e.g., dogs) in which after inurement to anoxia, exposure to this stressor is temporarily discontinued. Anoxia causes hyperglycemia in not-adapted and "de-acclimatized" dogs but not in fully adapted animals during the stage of resistance.[94] In their excellent monograph on the rôle of the adrenal-cortex in adaptation to altitude, Sundstroem and Michaels [95] devoted a chapter to the possible relationship between such adaptive phenomena and the G-A-S. (Cf. especially the instructive table on page 390.)

Anoxia is certainly one of those stressors which, directly or indirectly, affect nearly all cells of the organism. It is now so generally accepted that this agent acts as a particularly effective alarming stimulus that it may be most profitable to insist upon those few points in which the response to reduced atmospheric pressure differs from the typical G-A-S. Most noteworthy among these differences are: (1) the great frequency of acute, hemorrhagic lung-edema,[96] (2) the pronounced stimulation of the hemopoietic organs,[97] (3) the striking increase in blood-sugar and liver-glycogen.[98] Allegedly the latter change is partly due to a decreased carbohydrate-utilization; [99] this can lead to an increase in the carbohydrate stores of the body if the gluco-corticoid production of the adrenal is simultaneously increased, as a result of systemic stress.[100]

Some investigators believe that anoxia is involved even in the response to many other systemic stressors. According to the concept of the *"histotoxic anoxia"*, various metabolites and drugs may so poison the cells that they impede their capacity to use oxygen, even if adequate amounts are present in the blood.[101]

Infections.[102] — It is common knowledge that various systemic infections and intoxications with bacterial toxins, produce changes which are independent of the specific nature of the pathogenic organism. Allegedly, hormones participate in the defense against infections [103] and, more specifically, the systemic stress caused by infections has been claimed to produce a condition of "relative corticoid-deficiency".[104] This view receives support from the extensive literature which shows that adrenalectomy decreases resistance to infection and that this

[89] Langley and Clarke 83179/42, Laugier and Leblond A72915/43, Smith and Oster 93055/46.
[90] Giragossintz and Sundstroem A6932/37.
[91] Armstrong and Heim B19926/38, A18224/38.
[92] Reynolds and Phillips B4516/47.
[93] Reynolds and Phillips B4516/47.
[94] van Liere et al. B17764/48.
[95] 83691/42.
[96] Laugier and Leblond A72915/43, Reynolds and Phillips B4516/47.
[97] Reynolds and Phillips B4516/47.
[98] Evans 30599/34, 56353/36, A36854/41.
[99] Langley and Clark 83179/42.
[100] Selye B1204/46.
[101] van Liere B26199/42.
[102] Judd B315/17, Lenti 95574/44, Moon B19951/48.
[103] Lenti 95574/44.
[104] Diaz-Rubio B30354/46, Riml 75159/39.

defect is corrected by adequate corticoid therapy.[105] (Cf. also "Systemic Infections" on pp. 67, 100.)

In guinea pigs and rabbits, severe intoxication with various **bacterial toxins** results in adrenal-hemorrhages, hypothermia and leucopenia, while treatment with small doses of the same toxins causes fever and a rise in total white-cell-count with polymorphonuclear leucocytosis and lymphopenia. This response is strikingly similar to that described as characteristic respectively of severe and mild alarm-reactions produced by other non-specific agents. The adrenal-hemorrhages are somewhat reminiscent of those seen in the Waterhouse-Friderichsen-syndrome.[106] Significantly, according to recent investigations, rabbits treated with bacterial toxins (diphtheria, meningococcic, staphylococcic, streptococcic) develop a syndrome of "toxic adrenal-insufficiency" characterized by adrenal-hemorrhages and necroses, skin-hemorrages, leucocytosis, rise in blood-N.P.N., hypothermia, hypotension, muscular weakness and finally cyanosis and death. It was especially pointed out that all these manifestations are qualitatively independent of the particular type of toxin used; hence, this experimental syndrome was considered to duplicate the clinical picture of the Waterhouse-Friderichsen-syndrome.[107]

Dysentery-intoxication tends to cause A-R changes, with especial prominence of the intestinal lesions, even if the toxin is given parenterally.[108] This may be due to the superimposition of a specific intestino-toxic effect upon the non-specific stress-action of the microbial toxin.

Parasites.[109] — In animals and man, helminthiasis, as well as intoxication with hydatid-fluid, the peri-enteric liquid of ascaris, various worm-extracts, etc., tend to cause a syndrome very similar to hypocorticoidism. There are prominent lesions in the adrenals, hypophysis and capillaries, all resembling those caused by other types of systemic stressors. The metabolites of many parasites appear to be eminently potent as alarming stimuli and often the resulting disease of adaptation to the parasite is much more serious than the direct damage caused by the parasite itself.

Anaphylactic reactions. — In guinea-pigs such antigens as horse serum cause disintegration of the thymico-lymphatic tissue, loss of chromaffin granules from the adrenal-medulla and proliferation of reticulo-endothelial cells. Curiously, these G-A-S changes appear both following the sensitizing injection (which elicits "adaptive" phenomena to the antigen) and after the second eliciting injection. From this it was concluded that "these changes are entirely comparable to those which Selye described in the course of the alarm-reaction".[110] Apparently not only the anaphylactogenic, but even the sensitizing injection causes marked A-R changes.

Drugs and other toxic compounds.[111] — Intoxication with various chemical compounds likewise causes systemic stress with manifestations of the G-A-S. (Cf. also radioactive elements, bacterial toxins and hormones, which are discussed elsewhere in this chapter.)

It would manifestly not be expedient to enumerate all publications concerning the production of G-A-S manifestations by drugs. Only a few partic-

[105] Selye 94572/47.
[106] Olitzki et al. 84474/42.
[107] Lithander 97243/45.
[108] Penner and Bernheim B37656/42.
[109] Simonin B12416/22.
[110] Simonin B23373/48.
[111] Riml 75159/39, Selye 38798/37.

ularly instructive examples of systemic-stress-producing chemicals will be surveyed here in alphabetic order.

Adrenergic blocking agents (see Adrenaline, under hormones, below).

Alloxan intoxication produces an immediate, pronounced hyperglycemia, followed by hypoglycemia before the blood-sugar permanently reaches diabetic levels. The initial biphasic glycemic response is independent of the pancreas and is accompanied by other typical manifestations of the A-R,[112] it may well be due to the systemic-stress caused by this drug.

Allylamine and allylformiate are especially conducive to systemic damage without causing any very specific organ-changes. They have been extensively used in the study of "serous inflammation".[113]

Atropin produces adrenal-enlargement, thymus-atrophy, gastrointestinal ulcers and other typical A-R changes in the rat.[114] The drug is particularly useful for the production of systemic stress, since in high doses it appears to affect a large number of tissues before causing death due to its specific effects upon vital organs.

Many *caryoclastic poisons* are discussed individually under the name of each compound (cf. also "caryoclastic crises" p. 20), and some of the recent reviews concerning their relation to the A-R.[114a]

Colchicine was considered to be one of the most potent "caryoclastic drugs" in that study of the "crise caryoclasique" which we mentioned in the historic introduction to this book.[115]

Experiments on the rat led several authors to conclude that colchicine causes a condition of relative corticoid-insufficiency[116] and is also one of the most active agents capable of producing an A-R.[117] Following colchicine-treatment typical G-A-S-changes appear in the thymus, spleen, lymph-nodes, adrenals and gastrointestinal tract. It was shown, furthermore, that, as with other alarming agents, adrenalectomy prevents the thymico-lymphatic involution normally caused by this drug.[118] Only in one experimental series[119] was there some indication of thymus-involution after adrenalectomy. Here colchicine was given more than four days after removal of the suprarenals and the possibility of hypertrophied accessory adrenals may have to be considered. Significantly the A-R-changes caused by colchicine (unlike those produced by adrenaline) are not prevented by adrenergic blocking agents (e.g., dibenamine). It was concluded that adrenaline-like compounds play no major part in the genesis of A-R-changes.[120] The development of allergic arteritis is allegedly prevented by colchicine-pretreatment, perhaps because this drug destroys the antibody-forming lymphocytes.[121]

The study of a woman who died after having taken 60 mg. of colchicine, led to the conclusion that "the endocrine glands show the picture of the "alarm syndrome" of Selye: hypertrophy and lipid discharge in the adrenal cortex, important degenerative changes in the pituitary with augmentation of the

[112] Arvy and Gabe B34748/48, B44853/49, Covian and de Oya B23023/47, Griffiths B23068/48.
[113] Eppinger B37085/49, Terbrüggen and Deneke B38040/47.
[114] Selye 38798/37.
[114a] Dustin **B38553/47**, Mascart B38797/49.
[115] Dustin 94304/46.
[116] Clark and Barnes A33441/40.
[117] Clark and Barnes A33441/40, Sentein B29896/48.
[118] Leblond et al. A18194/39, Leblond and Segal A50424/38.
[119] Leblond and Segal A17235/38.
[120] Seifter et al. B32930/49.
[121] Forman et al. B37491/48.

basophil cell count." There were also gastric erosions and hemorrhages, acute involution of the lymphatic organs, left-deviation of the Arneth count (with the appearance of immature and atypical forms of white and red cells), loss of zymogen granules from the exocrine pancreas with involution of the acinar parenchyme and great prominence of the Langerhans islets.[122] In another patient who recovered, the hematologic and gastrointestinal changes were quite similar.[122a]

Formaldehyde presumably elicits the G-A-S mainly due to its local action on tissues at the site of injection. It is because of its protein-precipitating power that "formalin" is commonly used as a fixative in histology and this same property manifests itself when subcutaneous or intraperitoneal injections of formaldehyde lead to local coagulation-necrosis in the tissues. The extent of this necrosis can be quite accurately gauged by the amount of substance injected. If comparatively small doses are administered at a time, the amount absorbed into the general circulation is not fatal and causes no important specific organ lesions. Even repeated formaldehyde injections fail to cause any specific changes apart from some respiratory embarrassment immediately following administration of comparatively large doses. This can be minimized by pretreatment with small doses. The only effects of such injections are those of pure, non-specific damage and hence the drug has been widely employed and proved extremely useful even in chronic experiments concerning the G-A-S.[123]

Glucokinin is a name which has been given to certain plant-extracts exhibiting insulin-like, hypoglycemic properties. Since this hypoglycemia is preceded by a rapid and marked rise in blood-sugar, it has been examined[124] whether these glycemic actions are merely G-A-S manifestations. The conclusion was reached that glucokinin, given in the form of plant-extracts, causes a more prolonged initial hyperglycemia than other alarming agents. However, certain bacteria, which also exhibit glucokinin-like properties, cause blood-sugar curves almost identical with those obtained by other stressors. For instance the blood-sugar-curve obtained by injecting killed bacillus aertrycke[125] can almost be superimposed upon the glycemic curve produced by chronic formaldehyde injections.[126]

Glucose, whether administered by mouth or parenterally, is an extremely innocuous substance. Yet, it can cause salt-depletion and peritoneal dialysis with isotonic glucose-solutions result in "a vascular collapse closely resembling that seen in traumatic shock". A comparable decrease in extracellular fluid, if produced by mere dehydration, does not have such an effect and intravenous administration of NaCl almost immediately cures this condition; hence the shock-like manifestations were ascribed to sodium-deficiency.[127] Since sodium is indispensable for many corticoid-actions and probably essential for the life of every cell, such sodium-depletion should be highly suitable for the production of truly non-specific stress, but the relationship between the acute-sodium-depletion-syndrome and the G-A-S has not yet been adequately studied. The intraperitoneal injection of hypertonic glucose has also been used to pro-

[122] Dustin 94160/41.
[122a] Layani et al. B38533/47.
[123] Leblond and Segal A50424/38, Selye 38798/37, 36038/37.
[124] Masson A15525/38.
[125] Delafield B19935/31-2.
[126] Masson A15525/38.
[127] Danowski et al. 93257/46, Elkinton et al. 93256/46.

duce standardized degrees of shock-like systemic damage in animals.[128] In man even mere oral administration of glucose (as in tolerance-tests) causes a fall in circulating lymphocytes and an increase in 17-KS-elimination.[129] These actions of glucose upon the blood-count have been repeatedly confirmed in man [130] and in the rat.[131] (Cf. also "water-intoxication" and "salt-depletion", below.)

Hemoglobin, even when given in relatively small amounts, elicits a typical "hemoclastic crisis", such as was also seen after administration of other macromolecular substances.[132] "This hematic reaction is characterized by a primary transitory leucopenia with relative lymphocytosis, a secondary leucocytosis with absolute neutrophilia, increased sedimentation-rate and lengthened coagulation-time".[133] Free hemoglobin may appear in the plasma as the result of various poisons, black-water fever, paroxysmal- and cold-hemoglobinemia, resorption of internal hemorrhages and transfusion with incompatible or hemolyzed blood; hence these observations may be of clinical significance. Spasms of the renal arterioles [134] and even histologically demonstrable degenerative changes in peripheral arteries [135] may occur after injection of hemoglobin-solutions in animals.

Histamine can also be used to produce the G-A-S [136] but there is no proof that its liberation from tissues plays an important rôle in the development of this syndrome.[137] It is particularly effective in producing gastric ulcers.

Iodoacetates are likewise very active in producing systemic stress, perhaps because of their ability to inhibit phosphorylations throughout the body; correspondingly they cause marked G-A-S-manifestations which have been interpreted as due to relative adrenal insufficiency.[138]

Menstrual toxin (whose identity has not yet been definitely established), administered to rats in the form of partially purified extracts, caused adrenal-changes which were described as "similar to those in the adrenals of animals during the last stage of the alarm-reaction as described by Selye, namely a picture of cortical exhaustion".[139] The discussion in the paper quoted above suggests that the stage of exhaustion and not the A-R-stage of the G-A-S is meant; however, this is of minor importance since the histologic changes during these two stages are essentially similar. That such extracts can cause a typical A-R has been further substantiated by experiments on rats. It was found that treatment with "menstrual toxin" not only causes adrenal-stimulation but also pituitary-changes indicative of corticotrophin discharge.[140] All this may well be due to the toxic fibrinolytic and other enzymatic effects of such extracts.

Morphine is also widely used as an alarming agent. It has been shown to cause adrenal-cortical-enlargement with loss of lipid-granules from the cortical cells, gastrointestinal ulcers, thymico-lymphatic involution and other changes

[128] Reiss et al. 85064/43.
[129] Freeman and Elmadjian B26580/47, Marks et al. B19152/48.
[130] Jailer et al. B30916/48.
[131] Elmadjian 95224/48.
[132] Hueper 91719/42.
[133] Hueper 91802/44.
[134] Hesse and Filatov B19936/33.
[135] Hueper 91802/44.
[136] Selye 36038/37.
[137] Selye B1204/46.
[138] Clark and Barnes A33441/40, Laszt B19999/39.
[139] Smith and Smith 81127/41.
[140] Smith and Smith 92761/46.

characteristic of the A-R.[141] Interestingly, here the G-A-S is elicited by an agent which depresses nervous functions.

Mustards (both the so-called sulphur and the nitrogen mustards) have been the object of considerable study in connection with their possible rôle in chemical warfare.[142] Systematic experiments on rats led to the conclusion that "the hypertrophy of the adrenals which occurs after injecting the β-chloroethyl vesicants does not appear to be a specific response to these agents, but rather a reaction typical of the general-adaptation-syndrome for non-specific stress. The results presented in this paper suggest that the enlargement of the adrenals is due chiefly to an increase in water content and to some extent to proteins and phospholipids".[143] An analysis of the changes in the total-lipid and cholesterol-content of the adrenals led the authors to conclude: "it is probable that the animals are at the end of the counter-shock phase of the alarm-reaction on the third day after injection of the mustards. It can be seen that the changes in the lipid content of the adrenals are not dependent on the cholesterol content during the first two days. The most marked and consistent decrease in the lipids are obtained on the third day for all groups", ... "animals injected with LD_{100} doses of the mustards become very ill on the 4th and 5th days and usually die at this time. This would correspond to the stage of exhaustion" of the G-A-S.[144] The rapid exhaustion of adaptability, after treatment with mustards, is somewhat reminiscent of the "telescoped" G-A-S, seen in adrenalectomized or hypophysectomized animals exposed to other stressors.

Many additional publications reveal that, in man and in experimental animals, sulphur-mustard (mustard gas) and nitrogen-mustard (ypérite) produce especially pronounced leucopenia, damage to the lymphoid organs, the bone-marrow and the intestinal mucosa,[145] with other typical A-R-changes.[146]

Pertinent experimental observations and a review of the literature led to the conclusion "... it appears that the lymphoid changes accompanying injections of compounds causing the "alarm reaction", roentgen irradiation, and other treatments interpreted as having been caused by changes occurring in the metabolism of the cells of the adrenal cortex, are paralleled by similar morphologic and physiologic changes in the adrenal glands of rats poisoned with vesicants".[147]

Unlike in the G-A-S produced by most alarming stimuli, adrenalectomy does not prevent the thymus-involution resulting from treatment with the mustard methyl-bis(2-chloroethyl)-amine.[148] Similar experiments with tris(2-chloroethyl)-amine revealed that here again adrenalectomy does not protect the thymus from involution and it was concluded "that the vesicants produce some of their intoxicating effects on the lymphatic organs directly, although they in part may be mediated by the adrenal cortex".[149]

[141] Selye 36038/37, 38798/37.
[142] Winternitz B19943/20.
[143] Ludewig and Chanutin B1348/46.
[144] Ludewig and Chanutin B1348/46.
[145] Hektoen and Corper B19940/21, Herman B19938/19, Krumbhaar and Krumbhaar B19937/19, Lynch B19941/19, Pappenheimer and Vance B19939/20, Warthin and Weller B19942/19, Winternitz B19943/20.
[146] Dekanski B37985/48, Heusghem et al. B31783/48, Philips et al. B29996/48.
[147] Kindred 99940/47.
[148] Karnofsky et al. B19945/46.
[149] Kindred 99940/47.

For a summary concerning the biologic actions of mustards, the reader is referred to the pertinent review articles.[150]

Papain increases the blood-coagulation-time, the eosinophil-count and the blood-sugar in guinea-pigs, while the total white-cell-count, the refractive index and the complement-fixation power of the blood diminish. This condition was designated as "papain-shock" to emphasize its similarity to anaphylactic or peptone shock.[151] Concerning its relation to the G-A-S (cf. peptone as a stressor, below).

Peptone produces a type of shock in the dog which greatly resembles anaphylactic shock.[152] As in the syndromes produced by ionizing radiations, incoagulability of the blood dominates the picture. The probable rôle of the white blood-elements (leucocytes and platelets), the accompanying discharge of histamine and heparin from the liver, as well as the fibrinolysis after peptone-injection, have been subjected to careful analysis.[153] The derangement in blood-coagulability is certainly more pronounced than could be expected during a typical A-R. Indeed it has been claimed that fibrinolysis actually participates in the production of peptone and anaphylactic shock.[154] However, abnormalities in blood-clotting, blood-fibrinogen concentration, etc., are also seen in more typical examples of the G-A-S, hence the experience with peptone shock — in which these are particularly prominent — may furnish valuable data concerning this aspect of the syndrome. In the rat — which is rather resistant to anaphylaxis — very large doses of peptone are required to produce "shock". When it occurs, it is characterized by adrenal and gastric hemorrhages as well as other typical manifestations of the A-R.[155]

Photodynamic substances sensitize the organism to the stressor effect of light and may thus induce typical A-R changes upon subsequent irradiation.[155a]

Protamine, given subcutaneously in toxic doses to rabbits, caused hemorrhages in the thymus, adrenals and kidneys; this is sometimes accompanied by degeneration of the renal tubules and the formation of hyalin casts. The changes are essentially non-specific and allegedly related to the A-R.[156]

In view of the great anti-rheumatic power of *salicylates*, special investigations have been carried out to determine whether they also produce an A-R. This was found to be the case,[157] but it is difficult to prove whether their anti-rheumatic effect depends upon this action, since so many drugs cause an A-R.

Even *sodium chloride* elicits A-R-changes if it is given parenterally in sufficiently large amounts to produce "dehydration shock".[158] (Cf. also "dehydration" and "salt depletion", below.)

Thiourea and its derivatives, likewise appear to be potent alarming stimuli if sufficiently large doses are given. In rats, marked enlargement of the suprarenal-cortex with loss of lipid granules, loss of liver glycogen and other A-R changes have been produced by toxic amounts of thiourea; significantly, the toxicity of these compounds was counteracted by suprarenal cortical extract.[159]

Tissue extracts, administered in toxic doses, are likewise very active in eliciting the G-A-S.[160]

Trypsin, as most proteolytic enzymes, causes marked systemic damage — with A-R changes — upon parenteral administration.[161]

Turpentine produces acute, sterile inflammation and abscesses at the site of injection; this is accompanied by typical G-A-S manifestations. In dogs it elicits very marked, acute body-protein breakdown, hence it has been used especially in studies concerning the "catabolic impulse".[162]

Urethane produces leucopenia and absolute lymphopenia both in intact and in adrenalectomized rats. It has been assumed therefore that its effect upon the lymphatic system is not mediated through the adrenal, although it is undoubtedly active in stimulating the latter. Thus urethane appears to be a "directly lympholytic" alarming stimulus like the ionizing radiations and the folliculoids. The adrenal enlargement itself "might be an alarm reaction to urethane secondarily, but directly, the result of the liberation of proteolytic products by this compound".[163]

It is noteworthy in connection with the theory of the "diseases of adaptation" that in certain, genetically predisposed, inbred mice, e.g., in strain "A" [164] and strain "NH",[165] urethane produces lesions in the renal glomeruli which resemble those caused by LAP or DCA.

Water given by stomach tube in increasing but non-toxic doses to rats, induces adaptation to subsequent water-intoxication. On the other hand, adaptation to intraperitoneal injections of glucose-solution (another stressor) provided slight if any protection against water-intoxication. The question arose whether this phenomenon is related to the G-A-S, but the authors concluded " . . . that while the acquired resistance to water administration may be in small part resistance to stress in general, it is largely a resistance to water (plus stomach tubing) in particular".[166] The "salt-depletion-shock", produced by forced water-administration [167] exhibits a manifest similarity to the A-R.

Conversely, *dehydration* is also a potent alarming stimulus. In this regard, it is immaterial whether dehydration is produced by a decreased water-intake or by an increased fluid-loss such as occurs in chronic diarrhea, vomiting, injection of hypertonic solutions, plasmapheresis, etc.[168] (Cf. also NaCl as a stressor.)

Hormones. — Corticotrophin, corticoids, R.P.S. and adrenaline ("sympathin") all play important parts in the defense-phenomena of the G-A-S. Therefore these hormones will be the subject of a detailed discussion in connection with the theory of hormonal interrelations during the G-A-S and need not be considered here. It would also be unnecessary to insist upon the

[150] Gilman and Phillips **B19944/46**, Graef et al. **B39006/48**, Kindred **99940/47**, B39175/49.
[151] Zacco and Biozzi B37976/47, Zacco and Pratesi B37560/47, B37559/47.
[152] Sonobe A8283/37.
[153] Jaques et al. 98542/47. Rocha e Silva B1280/46, Rocha e Silva and Teixeira B2058/46.
[154] Rocha e Silva B2174/47, Scroggie et al. B4341/47.
[155] Ingle 85588/44.
[155a] Eppinger **B37085/49**, Spiesz-Bertschinger B43955/47.
[156] Vartiainen and Marble 81118/41.
[157] Forman et al. B37491/48.
[158] Davis A37428/41.
[159] Glock B23056/45.
[160] Freud et al. 71309/38.
[161] Eppinger **B37085/49**, Mirsky and Freis B1167/44, Zeckwer B24198/47.
[162] Madden and Clay B2098/45, Menkin A57481/43.
[163] Dury and Robin B19209/48.
[164] Dunn and Larsen B15797/46.
[165] Kirschbaum and Bell B4294/47, 93955/47, Kirschbaum et al. B18282/48.
[166] Liling and Gaunt B495/44, 89147/45.
[167] Danowski et al. B38005/47, Elkinton et al. B38004/47, Marriott B38646/47.
[168] Broch 97241/45, Danowski et al. 93257/46, Elkinton et al. 93256/46.

fact that toxic doses of almost any hormone, e.g., thyroxin,[169] or parathyroid hormone [170] can cause such characteristic G-A-S-changes as gastric ulcers, thymico-lymphatic atrophy, adrenal-cortical stimulation, etc. However, a few hormone-effects deserve special consideration in connection with the G-A-S.

Posterior-pituitary-extracts cause very severe hemorrhagic erosions in the acid-bearing area of the stomach in various species.[171] In rare instances such ulcers may even become chronic. These changes are accompanied by the usual adrenal-cortical stimulation, thymico-lymphatic atrophy, etc., hence some relationship with the G-A-S, especially with the A-R-phase, has been suspected.[172]

The effect is due to the vasopressin-content of the crude extract.[173] Acute overdosage with vasopressin also causes pronounced vasoconstriction in other organs, especially in the kidney, so that renal infarcts may result.[174] These phenomena are frequently associated with marked leucocytosis and reticulocytosis; [175] such changes are reminiscent of those seen in response to non-specific systemic stress. Perhaps the great tendency of vasopressin to produce gastric ulcers and renal infarcts is merely due to particularly marked vasospasms in the stomach and kidneys; the reticulocytosis could be a simple compensatory response to the anemia caused by the gastric hemorrhages. In any case vasopressin produces much more pronounced gastric and renal lesions than other alarming stimuli of equal intensity. Still, because of the specific action of vasopressin upon the vascular system, its possible participation in the G-A-S and the cardiovascular diseases of adaptation deserves more attention than it received up to now. This is especially true since the incretion of this hormone has been shown to be influenced by emotional stress.[176]

Folliculoids ("estrogens") also produce typical G-A-S-manifestations in the rat. Here the adrenal-cortical lipid-discharge, the thymus-atrophy and the somatic-growth inhibition are disproportionately pronounced in comparison with the rather mild stress-effects of such compounds.[177] There seems to be considerable species-differences in the sensitivity to the alarming effect of folliculoids. Allegedly "mice undergo the alarm-reaction and respond with the general-adaptation-syndrome as described by Selye" while, "in rabbits there is a reduction of circulating lymphocytes but no increase in adrenal weights as a result of estrogen".[178] We are inclined to think that there is some adrenal enlargement, though very high doses of folliculoids are required to demonstrate it.

It is especially noteworthy that folliculoids belong to that limited group of agents which cause thymico-lymphatic involution even after adrenalectomy or hypophysectomy.[179] Perhaps the latter effect is due to some direct (not adrenal-mediated) action of the folliculoids upon the nuclear chromatin of the lymphatic cells. This action is comparable to that of ionizing radiations, mustards and corticoids.

A certain degree of inurement may occur upon continued treatment with folliculoids. However, this is an adaptation to the pharmacologic action itself,

[169] Kendall and Ingle 68707/37, Lowenstein and Zwemer A74481/43.
[170] Selye **94572/49.**
[171] Dodds and Noble 55669/34.
[172] Selye et al. 58020/36.
[173] Selye et al. 58020/36.
[174] Byrom A8247/37.
[175] Dodds and Noble 54523/35.
[176] Verney B18117/47.
[177] Gangitano B41887/48, Peczenik 85252/44. Selye A8610/37, A18206/39, Selye et al. 38815/36.
[178] Lurie et al. B31933/49.
[179] Selye et al. 38815/36.

not to the compounds which exhibit it, since pretreatment with stilbestrol produces resistance to natural (steroid) folliculoids and vice versa.[180]

Insulin is a potent alarming stimulus, since the hypoglycemia which it produces represents a stress for most tissues of the body and elicits violent autonomic and hormonal defense-reactions.[181] When given in repeated toxic doses to rats, insulin causes involution of the thymico-lymphatic apparatus, similar to that seen in the A-R. Investigations on adrenalectomized rats were designed to determine whether this effect of the hormone is mediated by the adrenal cortex. These experiments failed, however, because of the notoriously great insulin-sensitivity of animals deprived of their suprarenals.[182] (Cf. p. 29.)

Adrenaline (and sympathin) discharge is an integral part of the A-R and will be discussed later in connection with the hormonal interrelations during the G-A-S. Suffice it merely to mention here that toxic doses of adrenaline can evoke the G-A-S, but the hormone is no more active in this respect than any other compound which causes a comparable degree of systemic stress.[183] Thymico-lymphatic atrophy is produced by adrenaline in intact, but not adrenalectomized or hypophysectomized rats; hence this action is apparently mediated by the adrenal-cortex [184] The A-R changes caused by adrenaline are prevented by dibenamine,[185] but those elicited by other stressors are not. Since it had been claimed that corticotrophin discharge, in response to stress, depends upon an adrenergic mechanism it is especially noteworthy that, "in high concentrations" dibenamine itself was found to be an alarming stimulus".[185a]

Diet.[186] — Almost any severe quantitative or qualitative nutritional deficiency acts as a potent alarming stimulus.

Fasting must be regarded as a typical, though rather slowly acting, stressor agent since it elicits such characteristic symptoms as adrenal-enlargement, thymico-lymphatic atrophy, hypochloremia, hypoglycemia followed by hyperglycemia, hemoconcentration and gastrointestinal erosions.[187] Severe undernutrition on qualitatively normal diets produces a pronounced "shift of pituitary-hormone-production" in which increased corticotrophin secretion occurs at the cost of somatotrophin-, gonadotrophin- and prolactin-formation. This is indicated by the fact that in undernourished animals there is cortical hypertrophy but growth ceases and the sex-organs involute. Pertinent experiments in the rat revealed testicular atrophy with involution of the accessory sex-organs in males and atrophy of the ovaries with continuous diestrus or irregular estrus cycles in females. In lactating animals milk-production ceases.[188] As we shall see later, chronic undernourishment on low-protein diets fails to cause adrenal-stimulation, although otherwise it elicits typical G-A-S-changes.

The results of these animal-experiments are very reminiscent of the clinical "anorexia nervosa syndrome", which is interpreted by some as a "functional hypopituitarism".[189] G-A-S-changes are quite constantly manifest in man

[180] Selye A32153/40.
[181] Gellhorn B27006/43.
[182] Zeckwer B19293/48.
[183] Selye 36038/37.
[184] Selye 36032/36, 38798/37.
[185] Seifter et al. B32930/49.
[185a] Paschkis et al. B32805/49, B35916/49.
[186] Brozek et al. **B23241/46.** Lamy et al. **B26867/48.** Rondoni B23143/15, Uehlinger B24304/47, B27612/48.
[187] Leblond et al. A18194/39, Selye A15673/39.
[188] Selye A18343/39, 74721/39, A31127/40.
[189] Sunderman and Rose B25093/48.

subjected to severe starvation.[190] Observations on gravely undernourished prisoners of war revealed the frequent occurrence of what has been termed the "castration syndrome". There was impotence with loss of axillary and pubic hair. In those individuals who previously suffered from acne and seborrheic dermatitis these changes (which are presumably due to testoids) vanished during starvation but reappeared after refeeding. Immediately upon return to a normal diet, many of the undernourished males developed a transitory gynecomastia which was attributed to liver-damage.[191] Severe undernourishment may also cause marked testis-involution in man.[192] Among undernourished boys cryptorchidism, and sometimes even orchitis, are claimed to occur quite frequently.[193] During the prolonged siege of Leningrad (1941-42) essentially similar changes were noted in a large portion of the population, as a result of undernutrition and psychologic stress. In pertinent reports, special emphasis is placed upon: decreased resistance to infection, loss of fat and muscle tissue, hypothermia, bradycardia, dryness of hair and skin, psychologic disturbances and amenorrhea.[194]

Overfeeding, if acute, may produce "food-shock". This is a condition of acute gastric dilatation and marked hyperemia of the central nervous system. It is a common cause of sudden death, for instance among rats receiving excessive amounts of food by stomach-tube. If the amount of nutrient is gradually increased over a period of many days, the development of food-shock can be prevented due to adaptation. The pathogenesis of this syndrome is not yet clear but its possible relationship to the A-R has been considered.[195]

Chronic overfeeding; e.g., in geese and ducks forced-fed to fatten them for table use, leads to marked atrophy of the testes.[196] Similar observations have been made on overfed mice.[197] In the rat, forced feeding with high carbohydrate diets by stomach tube caused not only testis atrophy with involution of the seminal vesicles, but also enlargement of the adrenals (which were dark-red in color) and atrophy of the thymus, that is, typical manifestations of the G-A-S.[198]

High-fat-diets (e.g., "pernicon") which are often poorly tolerated, allegedly cause salt depletion with hypochloremia, ketonuria and abnormalities in the glucose-tolerance curve; all these are rather typical G-A-S changes.[199] In the rat, diets very rich in fats cause extraordinarily pronounced adrenal-enlargement.[200]

High-protein diets have also been claimed to cause adrenal-enlargement in the rat similar to that seen during the G-A-S; it was assumed that the protein-catabolites themselves stimulate corticotrophin-production.[201] However, subsequent experiments revealed that a definite increase in adrenal-weight is not obtained under such conditions in the rat unless about 80% (!) of the dietary

190 Keys **B37797/48,** Selberg B37871/47, B38019/47, Sendrail and Lasserre B37450/48, Taylor et al. B23191/45, Uehlinger **B27612/48.**
191 Jacobs B25095/48.
192 Lamy et al. B26867/48.
193 Offergeld 7388/32, 7388b/32, Stefko 21104/27.
194 Anonymous B27050/43, B27051/44, Brozek et al. B23241/46.
195 Ingle B1361/46, B23235/48.
196 Patzelt 17670/23.
197 Stieve 16659/23.
198 Ingle B1361/46, Ingle and Nezamis 98817/47.
199 Consolazio et al. B19796/46.
200 Selye 35935/ND.
201 Tepperman and Engel 83735/42, Tepperman et al. A58184/43.

calories are derived from protein.[202] Probably the positive results of the earlier investigators were due to the use of unusually high-protein-diets, which represented a severe stress in themselves. This is all the more likely since — as we shall see later — both stress and pronounced protein-catabolism are necessary to elicit the usual adrenal-hypertrophy during the G-A-S.

Our observations, gathered over a period of several years, consistently failed to show any significant effect of dietary protein upon adrenal-size in the rat, as long as the protein-concentration was kept within near-physiologic limits (12-30%); on the other hand, if animals kept on low- or high-protein-diets (within the above range) were exposed to systemic stressor agents (e.g., cold) then the adrenal-enlargement was much more pronounced on the higher protein-intake.[203] It was concluded that, for intense adrenal-cortex-stimulation, both stress and a high protein-catabolism are required.

Multiple dietary deficiencies, such as occur in guinea-pigs fed exclusively on corn, have long been known to produce changes now recognized as typical of the G-A-S, for instance adrenal enlargement, thymico-lymphatic atrophy, gastric erosions, involution of the sex-organs and proliferation of the reticulo-endothelial system.[204]

Pantothenic-acid-deficiency can cause adrenal hemorrhages and necroses, accompanied by thymic atrophy and sometimes purpura. The similarity of these morphologic changes to those of the Waterhouse-Friderichsen-syndrome [205] and the A-R [206] has been emphasized by several authors. According to a slightly different interpretation "One could also look upon adrenal hemorrhage and adrenal necrosis as the "stage of exhaustion" during the course of an alarm reaction".[207] In any event it was concluded that the change is not merely due to decreased food-intake, since no comparable degree of thymus-atrophy occurred in paired-fed controls.[208] Nevertheless, the adrenal stimulation and thymic involution observed in these experiments could not be regarded as specific for pantothenic-acid-deficiency, for similar, though less marked, changes were noted in *thiamine* [209] or *riboflavin-deficient* rats [210] and after many other types of systemic damage. Indeed it has been stated that the changes in riboflavin-deficient rats correspond to those of the A-R during the early phases and to the stage of exhaustion towards the end before the animals die.[210a]

Choline deficiency causes marked adrenal-enlargement and thymus-involution, in addition to the typical hemorrhagic lesions in the kidneys of immature rats.[211] Despite continued deficiency the adrenal-cortex returned to normal within 19 days. At this time it even recovered its normal lipid and "ketosteroid" droplets which had originally disappeared. Here again "the increased fasciculata activity and thymus involution probably results from the alarming stimulus of inanition".[212]

202 Ingle B360/45, Tuchmann-Duplessis et al. B24538/48.
203 Selye B1204/46.
204 Rondoni & Montagnani B23143/15.
205 György B19250/48.
206 Ashburn 96043/40, Deane and McKibbin B1349/46.
207 György B19250/48.
208 McQueeney et al. B4907/47.
209 Deane and Shaw B30043/47, Eppinger B37085/49. Skelton B41300/50.
210 Deane and Shaw B30043/47, McQueeney et al. B4907/47.
210a Reade and Morgan B32976/49.
211 Bellows and Chinn B25557/41, Christensen 77229/40. B25555/42, Engel and Salmon B25556/41, György and Goldblatt B25553/40, Jervis A55990/42.
212 Deane and Olson B18259/48.

Desoxypyridoxine (a pyridoxine-antagonist) produces marked atrophy of normal and neoplastic lymphoid tissue as well as impairment of the "anamnestic response" in rats and mice. These changes did not occur when pyridoxine-HCl was administered together with desoxypyridoxine. "The loss of lymphoid tissue was not mediated by adrenal cortical hyperactivity, since adrenalectomy did not modify the extent of lymphoid atrophy in acute pyridoxine deficiency".[213] Thus it appears that pyridoxine-deficiency likewise belongs to that small group of systemic stressor agents which cause direct thymico-lymphatic atrophy without mediation through the adrenal-cortex.

Gravity-shock.[214] — Rabbits suspended head up, without anesthesia, become unconscious within 1-2 hours and may actually die within 24 hours. This condition has been described as "gravity shock". It is accompanied by: anuria, acidosis, decreased blood-pressure, blood-CO_2 and plasma-chlorides, increased plasma-lactate, phosphate, potassium, pyruvate and NPN.[215] The blood-sugar rises at first, but then falls below normal and the glycogen-stores are depleted.[216] The relationship of gravity-shock to the G-A-S has not yet been much studied, but some of the above manifestations are strongly reminiscent of those seen in the A-R.

Diurnal variations. — The urinary elimination of 17-KS and of neutral reducing lipids (mainly corticoids) shows regular variations during the course of the day. Most subjects show minimal excretion of both types of steroids during sleep and maximal output in the morning. These changes have been ascribed to a diurnal rhythm in adrenal-cortical activity in response to the stress and strain of normal daily activity.[217] Such observations give added support to the view that even mild, physiologic stimuli suffice to mobilize the hormonal defense-mechanism of the G-A-S. Although the diurnal pattern of 17-KS- and neutral-reducing-lipid-excretion is similar, the lack of a significant correlation between them implies that they can vary independently. These considerations lead to the conclusion "that in the human subject different adrenocorticotropins may be involved. The pituitary seems to be essential for an increase of adrenocortical secretion in the alarm reaction and if we consider these diurnal changes as responses to the stresses of daily life a differential evocation of pituitary corticotropin is suggested".[218] We shall see later, however, that different corticotrophic actions do not necessarily imply the existence of different corticotrophic hormones. Conditioning factors may qualitatively alter the adrenal-response to the same corticotrophic preparation.

Climatic conditions. — In "weather sensitive" individuals even moderate changes in atmospheric conditions can act as "stressor agents" and produce A-R changes.[219]

Parabiosis. — If two rats are united by parabiosis, fatalities tend to occur during the second week. It was concluded that "at some time during the process of healing (1 to 2 weeks) or somewhat later, the parabiotic animal may go through a critical period. In this stage the animal may present one or all the

[213] Stoerk B18187/48.
[214] Allison et al. B26108/43, Cole et al. 85357/43, Terbrüggen and Deneke B38040/47.
[215] Allison and Cole B20411/44, Cole et al. 84978/44.
[216] Nastuk B26184/47.
[217] Pincus 98426/47, Pincus et al. B25094/48.
[218] Pincus et al. B25094/48.
[219] Klotz B36440/49, Peterson A34994/40.

symptoms described by Selye under the term alarm-reaction".[220] The mechanism of this reaction has not yet been elucidated.

Combined exposure to several systemic stressors. — We have seen, early in the course of our work on the G-A-S, that the systemic-stress-effect of various alarming stimuli can be summated. For instance, after determining the alarming dose of three noxious agents — such as *histamine, cold and formaldehyde* — it was found that in the event of combined treatment with all three agents, one third of the dose of each suffices to produce a G-A-S equal in severity to that elicited by the full dose of any one of the three agents.[221] This was interpreted as evidence supporting the view that the non-specific stress-effect of the agents, and not their specific pharmacologic actions, are responsible for the production of the G-A-S.

Fasting proved to be a particularly effective means of increasing the alarming effect of any stressor agent. Hence starvation was regularly used in the early experiments on the A-R to render animals more sensitive to non-specific stress.[222]

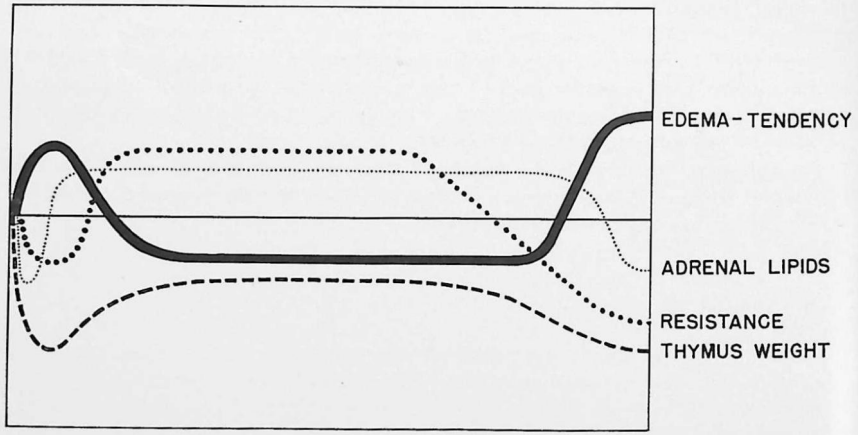
An increase in the alarming effect of two simultaneously applied agents has subsequently been confirmed for numerous combinations of stresses, notably for: *protein-intoxication with fasting,*[223] *anoxia with fasting,*[224] *anoxia with emotional stimuli,*[225] *spinal-cord-transection with cold,*[226] *muscular exercise with anoxia,*[227] *hemorrhage with nerve-stimulation,*[228] *hemorrhage with* cold [229] and *histamine with burns.*[230] In the latter instance only the production of gastric ulcers was facilitated by simultaneous administration of histamine in beeswax to rabbits injured by superficial skin-burns.

An apparent exception is the increased tolerance to anoxia of rats following prolonged fasting,[231] but this may be due merely to a reduction in the B.M.R. which diminishes oxygen-requirements.

[220] Cutuly and Cutuly 72076/38.
[221] Selye A15800/38.
[222] Selye 38798/37, A15673/39.
[223] Delaunay and Lebrun B3182/47.
[224] Laugier and Leblond A72915/43.
[225] Pincus 98426/47.
[226] Frank A34171/40.
[227] Jokl B19917/47.
[228] Gregersen B19252/48.
[229] Dosne 94398/46.
[230] Friesen and Wangensteen 95355/46.
[231] Laugier and Leblond A72915/43.

SPECIAL PHYSIOLOGY AND PATHOLOGY OF SYSTEMIC STRESS

In previous sections of this book we first presented a synoptic outline of the G-A-S, in which we merely sketched its most important features to give a bird's-eye view of its course. Special emphasis was placed upon new observations which played a fundamental part in the evolution of the G-A-S-concept. Some of these findings were the roots from which the theory developed. Others were the fruits of investigations inspired by it. Then, after defining the principal new terms used in connection with such studies, we devoted a chapter to the "alarming stimuli", the "stressor agents" which, upon short exposure, are particularly suited to produce an A-R and, upon more prolonged treatment, an entire G-A-S.



Schematic graph illustrating the overlap between the three stages of the G-A-S. Note that edema-tendency, adrenal lipids, resistance to stress and thymus weight (given here as illustrative examples) do not traverse simultaneously from the A-R to the resistant stage and subsequently to the stage of exhaustion. This has been ascribed to different degrees of "inertia" in the various targets affected by the G-A-S.

Subsequent sections will be devoted to a more detailed, systematic study of the course of the G-A-S; we shall separately consider the metabolic, morphologic and physiologic changes which occur during the various stages of the response to systemic stress. Some degree of overlap between chapters is unavoidable, but this will be minimized by cross-references to that part of the book in which the subject is discussed in the greatest detail. Occasional repetition of the cardinal points was considered permissible, however, wherever it facilitates the comprehension of our subject.

It is essential in describing a complex and hitherto neglected syndrome, such as the G-A-S, to integrate pertinent data and to co-ordinate the facts with the theories proposed to explain them. But what is the best order of

presentation? It is obviously impractical to study an alarming stimulus without considering the changes it produces, and vice versa, or to enumerate observations without an attempt of interpretation. An additional complication is created by the triphasic nature of the G-A-S. It would be artificial to enumerate separately all observations concerning each of the three stages. The transition between them is not sharp and often there is some dissociation of the manifestations, with certain signs of two stages simultaneously in evidence. Therefore, we felt that it would be most instructive to *follow each change through the three stages,* rather than to describe all the manifestations of each stage separately. Consequently our material is classified according to targets. A separate chapter is devoted to each target (e.g., protein-metabolism, cardiovascular system) and the changes occurring in it during the three stages of the G-A-S are discussed conjointly. This is immediately followed by the "diseases of adaptation" affecting this target and subsequently by a theoretic evaluation of all pertinent data.

RESISTANCE

The present chapter is devoted to the first, and most important "target" of the G-A-S, to resistance itself. In it we propose to discuss what little we know about factors which influence the ability of the organism to withstand systemic stress. Since many of these factors have not yet been elucidated it is expedient to deal with the complex phenomenon of resistance as if it were a single target.

It may be well to re-emphasize first of all that almost all the changes caused by systemic stressors follow a characteristic **triphasic course** in which the direction of the deviation from the norm is the same in stage I (A-R) and III (stage of exhaustion), but is reversed in stage II (stage of resistance). For instance, the adrenals lose their lipids in stages I and III, but store lipids in stage II; the thymus discharges thymocytes in stages I and III, but stores them in stage II; there is hypoglycemia and hypochloremia in stages I and III, but hyperglycemia and hyperchloremia in stage II. This explains many of the apparently contradictory findings reported in the literature concerning the effects of exposure to systemic stressor agents. Strange as it may seem at first sight, it is equally correct to assert that a stressor causes hyperglycemia and alkalosis, as it is to say that it produces hypoglycemia and acidosis. Hence, the changes produced by stressors in the various targets cannot be discussed without consideration of the time-relations, as outlined above. This greatly complicates the study of systemic-stress effects in comparison with other pharmacologic actions. Most biologic agents influence their targets only, or at least predominantly in one direction: insulin causes hypoglycemia, thyrotrophic hormone stimulates the thyroid-cells, excitation of a motor nerve causes muscular contraction. Hence, it was somewhat unexpected to find that **the same stressor agent causes diametrically opposed effects depending upon the previous history of the experimental subject;** that is, the type and duration of pretreatment if any.

Until quite recently the triphasic nature of the response to systemic stressors had not been recognized. This was probably the greatest obstacle to research in this field, since diametrically opposed actions produced by the same agent have generally been regarded as random variations devoid of significance. Yet this triphasic type of reaction is apparently a fundamental characteristic

of the body's response during prolonged, systemic stress. It has been found to occur in all targets (biochemical, morphologic and physiologic), which have been examined throughout the course of the G-A-S.

These facts were established by animal experiments,[1] but there is good reason to believe that they are applicable to clinical problems as well. Thus the three stages of the G-A-S have been shown to occur with all their typical features in chronically undernourished concentration-camp inmates.[2]

Before we begin to discuss our first target let us also remind the reader that various **systemic stressors** (e.g., anoxia, cold, trauma, x-rays), **anterior-pituitary-preparations** (e.g., LAP), **corticoids** (e.g., DCA) and **RPS** (e.g., those produced by the "endocrine kidney") **have many actions in common.** We believe that this similarity of action is important for the understanding of the underlying pathogenic mechanisms. We shall therefore discuss the effects of systemic stressors, on each target, conjointly with those of pituitary, adrenal-cortical and renal hormones, a procedure designed to emphasize both the similarities and the discrepancies between them. These hormonal factors, as well as other stimuli presumably involved in the genesis of the G-A-S, will be given special consideration under the heading: "Stimuli Influencing the Response During the G-A-S", in connection with each target.

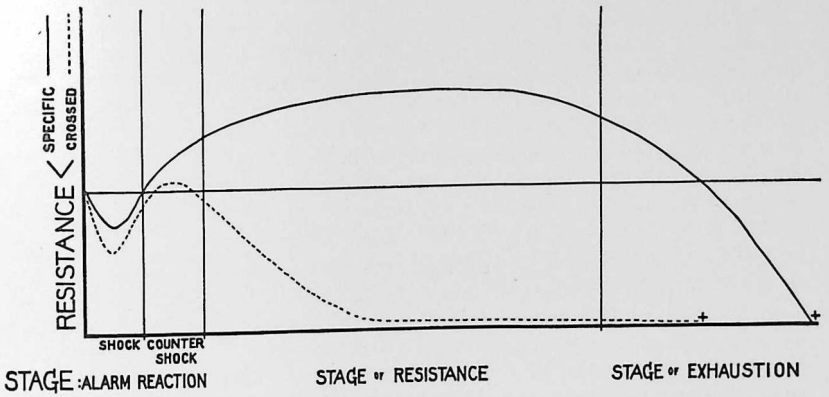
Systemic Stress

If an animal is continuously treated with the same, sublethal, daily dose of one alarming stimulus, its resistance to an additional minimum lethal dose of that same stimulus decreases during the shock phase and gradually returns to or above normal in the counter-shock phase of the ensuing A-R. During the subsequent stage of resistance, a considerable amount of **specific resistance** to this same systemic stressor becomes evident; yet, if exposure is continued over a period of many weeks or months, eventually this acquired adaptation breaks down. Apparently, even a fully inured organism cannot indefinitely maintain its adaptation when continuously exposed to a potent systemic stressor agent. It is this observation which led to the concept of *"adaptation energy"*.[3] The impression is gained that under the influence of continuous adaptive work, the adaptability or "adaptation energy" of the organism is eventually exhausted. The time at which this breakdown of adaptation occurs is usually referred to as the *"stage of exhaustion"*.[4] Even unicellular organisms (e.g., sea-urchin eggs) gradually lose their ability to recover from exposure to non-specific damaging agents.[5]

There are few, if any, systemic stressors to which the organism can not acquire some degree of adaptation. Ionizing radiations were thought to be an example in point, but experiments with internally administered radioactive isotopes show that animals may acquire a certain radio-resistance. Thus after some time hemopoiesis is resumed despite the presence of large quantities of radioactive materials in the tissues.[6] Repeated traumatic injuries may allegedly

[1] Selye 38798/37, B1204/46, Sundstroem and Michaels 83691/42.
[2] Uehlinger B27612/48.
[3] Karády et al. 74590/39, A31125/39, Masson A38380/40, A36632/41, Selye A8049/38, Selye and Masson A17983/39.
[4] Selye A8049/38.
[5] Brock et al. 81455/39.
[6] Bloom B31225/48.

even induce a certain degree of resistance to trauma [7] and prolonged under-nutrition to fasting,[8] although these are admittedly stressors to which it is especially difficult to acquire adaptation.



Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during the three stages of the general-adaptation-syndrome. The progress of time is indicated along the abscissa and the degree of resistance along the ordinate. Note that specific resistance to the agent with which the animal is treated decreases during the shock phase of the alarm reaction and increases during the counter-shock phase, reaching its maximum during the stage of resistance; in the stage of exhaustion, it falls below normal and finally, death ensues. Crossed resistance, to agents other than that with which pretreatment occurred, falls even lower than the specific resistance during the shock phase, rises but slightly during the counter-shock phase and is definitely subnormal in the stage of resistance. This indicates that while resistance to one agent (specific) is acquired by pretreatment with this same agent, resistance to other stimuli (crossed resistance) falls below the normal level (horizontal line). (After H. Selye: J. Clin. Endocrinol. 6, 117, 1946.)

Non-specific resistance is also characteristically influenced by the G-A-S. While an organism becomes adapted to one systemic stressor, its resistance to other agents is also altered. During the shock-phase, the non-specific resistance decreases even more than the specific resistance. In the counter-shock-phase, however, there is an increase in the animal's ability to withstand various systemic stressors, not only that to which it had been previously exposed. Yet, this "non-specific resistance" or **"crossed resistance"** is not nearly as great as the specific resistance to the particular agent with which the A-R had been produced.[9]

There are many observations which could be cited as examples of such a "crossed resistance". They will be discussed in detail under each of the targets affected, but let us give a few examples here.

The *appendicitis-like changes* elicited by intravenous histamine injections and certain other very acute systemic stressors, can be prevented by pretreatment with the same or different stimuli.[10]

The *lung-edema,* normally produced by high doses of adrenaline, is prevented in rats in which an A-R had been previously elicited either by adrenaline or by

[7] Noble A56868/43, Noble and Toby B38835/47, Ungar A57983/43.
[8] Hottinger B31235/48, Lamy et al. B26867/48.
[9] Selye 36038/37, 38798/37, A8049/38.
[10] Selye 66642/36, 68819/37.

other systemic stressors (e.g., exercise, cold, surgical trauma, formaldehyde injections).[11] Even the pulmonary edema which normally occurs in nephrectomized rats receiving intravenous infusions of saline solution, fails to develop in rats during the A-R.[12] More recent experiments led to the conclusion that "the alarm reaction, as produced in rats by exposure to cold and subcutaneous injections of formalin, rendered most of the animals resistant to ammonium pulmonary edema. The explanation for this is not apparent. The animals were in a state of shock of some degree and it is possible that the altered hemodynamics retarded the absorption of ammonium ion. However, the appearance of other signs of ammonium intoxication speaks against this explanation." [13] In our experiments concerning the prevention of adrenaline-lung-edema by the A-R, the adreline was given intravenously in order to exclude the possibility of an inhibition due merely to delayed absorption.[14]

A considerable amount of work has been done in connection with the effect of the A-R upon the course of *anaphylactic shock*.[15] Experiments on guinea-pigs, in which an A-R was produced by formaldehyde, cold or forced muscular exercise lead to the conclusion "that a relatively mild alarm reaction, followed by an interval of 18 to 24 hours rest, decreases the anaphylactic response of sensitized guinea pigs to the subsequent re-injection with the antigen (egg-white)." This observation gives further support to the conception that the alarm reaction increases the non-specific resistance of the organism against various nocuous agents. If, on the other hand, the alarm reaction is particularly severe and the interval between the treatment with the alarming agent and the re-injection of the antigen is short, such pretreatment may have an inverse effect and may actually increase the severity of the anaphylactic shock. It has long been known that fever exerts a favorable action on certain apparently unrelated diseases of man, which are thought to be allergic (e.g., chorea and other manifestations of the rheumatic state, intractable asthma of the allergic type, dermatitis following injection of arsenicals, etc.).[16] In serum-sensitive guinea-pigs there is transitory desensitization during hyperthermia, induced by short-waves [17] or by exposure to the high temperature of a heated "fever box".[18]

The prevention of anaphylactic shock by salicylates in the rabbit, is allegedly due to a decrease in circulating antibodies, induced by the drug at the time of the challenging dose.[19] It will be recalled that salicylates produce a typical A-R with lympholysis, and their ability to prevent allergic arteritis has been ascribed to the destruction of antibody-forming lymphocytes.[20]

The so-called anaphylactoid edema of the face and paws, in rats injected with egg-white, is likewise readily prevented by various systemic stressors during the ensuing A-R.[21]

Numerous experimental studies have been performed with the aim of finding an explanation for the desensitization of allergic patients by histamine. It was noted that in animals, anaphylactic reactions can be inhibited only if highly toxic doses of histamine are previously administered. It was concluded that

[11] Selye A8050/38, A7154/38.
[12] Selye A8050/38.
[13] Kœnig B25562/in press.
[14] Selye A7154/38.
[15] Karády et al. A9071/38, A9072/38.
[16] De Kruif and Simpson B25563/40.
[17] Gernez and Eloire B25564/37.
[18] Goldman B25565/39, Gottschall et al. B656/44.
[19] Campbell B23927/48.
[20] Forman et al. B37491/48.
[21] Léger B25567/48, B25569/48, Léger and Masson B4327/48, Léger et al. 95943/47, Selye 38798/37.

this type of resistance has nothing in common with clinical desensitization induced by minute doses of the compound and that "the positive results which have been reported, should probably be attributed to the alarm reaction".[22]

All these observations are interesting not only as examples of crossed resistance but also because they suggest close relations between non-specific resistance and serologic defense reactions. (Cf. also G-A-S → "anamnestic reaction" and G-A-S → serum-proteins.)

Experiments on *water intoxication* led to the conclusion that upon repeated exposure, some specific resistance may also be acquired to this type of stress.[23] Experiments performed to study the changes concerning water-metabolism during the G-A-S led to the conclusion that "if during the course of an alarm reaction produced by any stimulus, the same or any other stimulus is given, then the second stimulus not only fails to cause water retention, but actually increases urine output". These findings were likewise interpreted as indications of some "crossed resistance".[24]

Preteatment with *folliculoids* greatly augments resistance to *x-irradiation* in mice and since these hormones cause enlargement of the adrenals the possible participation of the latter in this instance of crossed resistance has been considered.[25]

It has been found that in rabbits a typical A-R is produced by *nitrogen-mustards* or by *bleeding* and that a previous hemorrhage protects against subsequent intoxication with this vesicant.[26] However, exposure to *heat* does not appear to exert any marked influence upon resistance or "de-acclimatization" to *cold* in man [27] or vice versa.[28]

It is also instructive to note in this connection that the amount of mercapturic-acid-sulphur excreted by the rabbit following oral administration of *monobrombenzene* is increased in the presence of a *sterile abscess*. Due to tissue-breakdown, such an abscess makes more neutral sulphur available which might be utilized in forming mercapturic acid. These findings may help to explain the mechanism through which sterile abscesses protect against certain drugs.[29]

A *sterile abscess* also affords protection against hepatic damage due to *chloroform-poisoning*.[30] Chemical analysis revealed increased quantities of protein, and particularly of purines, in the livers of rats bearing an abscess or anesthetized with chloroform. It has been suggested that this change in hepatic composition may explain the "crossed resistance" in this instance, especially since the disproportionately large increment in nucleic-acid content is considered to be characteristic of tissues actively forming new protein.[31]

These biochemical findings are consonant with the earlier histologic observations which led to the conclusion that "a severe injury of the liver from *uranium nitrate* may lead to the development, through a process of metaplasia and as a reaction of repair, to the formation of an atypical kind of hepatic epithelium which is resistant to *chloroform*".[32]

[22] Wells et al. A37472/41.
[23] Liling and Gaunt 89147/45.
[24] Karády et al. A8194/38.
[25] Patt et al. B32806/49, Straube et al. B33113/48.
[26] Heusghem et al. B31783/48.
[27] Stein et al. B33477/48.
[28] Eliot et al. B33097/48.
[29] Schultz B18183/48.
[30] Ravdin et al. B25566/39.
[31] Schultz and Vars B2500/47.
[32] MacNider 81174/37.

Numerous *other instances of crossed resistance* between various damaging agents have been described,[33] but of course there is no reason to believe that every type of agent would give crossed resistance with every other type. Indeed, during the stage of resistance to one agent, tolerance to other stimuli usually falls below normal (see below). Hence, it is not surprising if one author [34] found no crossed resistance between formalin and adrenaline under the particular experimental conditions which he used. He states " . . . the animals pretreated with formalin showed only a local resistance, whether they were subjected to a lethal dose of formalin or one of adrenaline. Although no general resistance was observed, the formalin treatment produced the principal anatomical signs of Selye's alarm reaction". From this the author concludes that perhaps the phenomenon of crossed resistance in the G-A-S may be due to a diminished absorption-rate from the damaged skin of formalin-treated animals. This could only explain increased resistance to a drug injected into the area damaged by formalin. It would obviously not account for crossed resistance in our experiments (cf. above) which were performed under conditions specifically designed to exclude this possibility (e.g., by intravenous administration of the drugs).

It should be emphasized that in any particular instance it is extremely difficult to prove that "crossed resistance" is a direct result of the G-A-S rather than due to some specific protective mechanism. The concept of crossed resistance should obviously not be extended to such specific instances of protection as, for instance, that afforded by glucose against insulin or by an antihormone against a corresponding hormone. The term "non-specific resistance" must only be applied to increased tolerance due directly to systemic stress, no matter how produced.

The *mechanism* through which systemic stress can thus raise resistance is not yet known. The stimulation of corticoid-production, the catabolic impulse, which provides protein-decomposition-products, the glycogenolysis and gluconeogenesis, which renders glucose available for repair and regeneration, as well as the profound change in the hemodynamic equilibrium and in the blood-proteins involved in serological defense reactions, probably all participate in these phenomena.

For centuries, various types of *non-specific therapy, protein-therapy, shock-therapy, bloodletting, etc.*, have empirically been used in the treatment of what we would now consider to be "diseases of adaptation". However, here the mechanism of action may be somewhat different from that involved in the protection of a healthy animal by the A-R against the action of a subsequently applied agent. It must be realized that most of the diseases of adaptation correspond to derailments of the resistant stage of the G-A-S and not of the A-R. In the resistant stage there is a great deal of specific adaptation to one type of agent to the detriment of resistance to other stimuli. Furthermore, there is evidence of continuously hyperactive defense-mechanisms, e.g., increased production of pituitary-hormones and corticoids. At this time, systemic stress induced by non-specific therapy could act by merely "utilizing" the excessive adaptive adjustments, for instance, by causing a relative corticoid-deficiency which would tend to counteract hypercorticoidism.

[33] Locke A6829/37, 74998/39, Perla and Marmorston 32161/35, Selye 36038/37.
[34] Gasic B17561/47.

The possibility must also be kept in mind that it may be advantageous for the organism to "defocus" highly selective adaptative reactions in individuals in which adaptation has become too specific. Even among the animal experiments cited above as examples of crossed resistance, the best protection was usually obtained against rather selective actions (e.g., lung-edema, anaphylactic and anphylactoid responses). It is as though crossed resistance were most readily obtained by a non-specific systemic stressor against the highly specific, organotropic actions of other agents, not against their general stress-effect. Indeed perhaps the mere stress-effects of various stimuli are always additive. This could explain why for instance a mild A-R desensitizes while a severe A-R sensitizes to anaphylaxis. In the former instance the crossed-resistance-effect (protection against selective overreaction of the shock-organ) would prevail, while with a severe A-R the animal would die in spite of this protection, due to the summation of the systemic stress-effects of the two agents.

All these considerations are, of course purely speculative; our only excuse for this digression is to emphasize the essential difference between non-specific and specific "crossed resistance" phenomena.

The counterpart to crossed resistance — a decrease in tolerance to one agent produced by pretreatment with another agent — might be designated as **"crossed sensitization"**. Numerous examples of this phenomenon have been described during the stage of resistance of the G-A-S.

After pretreatment with morphine, resistance to cold or atropine treatment is diminished, while intense muscular training was found to decrease atropine or cold resistance.[35] Mice kept in a cold environment become unusually x-ray sensitive.[36] Morphine addicts, who have acquired great resistance to this drug, proved to be hyperreactors in the "cold-pressor test".[37] Chronic undernourishment during famines (wars, concentration camps) endows the body with the ability to subsist on a minimum of food, but this occurs at the expense of resistance to other stressors, for instance infections. Hence epidemics (typhus, tuberculosis, etc.) are common, and especially lethal, among the undernourished.[38] The same is true in animals; thus rats kept on inadequate diets become unusually sensitive to Salmonella typhi murium.[38a]

Occasionally an artificially induced attack of fever (e.g., by injection of gonococcus vaccine) can precipitate the development of typhus fever. The view was expressed that the shock may diminish host resistance against a latent typhus infection and thus precipitate a clinical outbreak of the disease. If this explanation proves to be valid, the conservation of the virus between typhus epidemics would become more readily understandable.[38b] In mice a number of substances used for the production of experimental shock enhance the lethal effects of anthrax spores.[38c]

[35] Masson and Selye A17983/39, Selye A8049/38.
[36] Smith et al. B37748/49.
[37] Himmelsbach A37140/41.
[38] Brozek et al. B23241/46, Gell et al. B38934/48, Gsell B27611/48, Gsell and Hottinger B27610/48, Jones B37603/48, Labhart B27613/48, Lamy et al. B26867/48, Salzmann and Hottinger B27609/48. B27608/48, Uehlinger B24304/48, B27612/48.
[38a] Guggenheim and Buechler B38537/47.
[38b] Jude and Brumpt B45434/47.
[38c] Howie and Cruickshank B40948/47.

The notorious decrease in resistance to infection which occurs after exposure to ionizing radiation [39] may represent another pertinent example.

Systemic stress may even sensitize to allergens. "Thus during difficult life-situations productive of conflict, typical hay fever attacks followed pollen-inhalation" in otherwise insensitive individuals.[40] It was also found for example, that mice, when optimally adapted to ultraviolet irradiation, lose their resistance to acetonitril.[41] In this latter instance, the crossed sensitization was ascribed to an activation of the thyroid by the ultraviolet rays, as it is known that hyperthyroidism raises sensitivity to acetonitril. As in the case of "crossed resistance", many instances of "crossed sensitization" may well be due to the specific actions of the agents. It is curious, however, that all types of prolonged, intense, systemic stress appear to cause some degree of crossed sensitization at the height of inurement to the agent to which adaptation occurs. This non-specificity suggests that the phenomenon is an integral part of the G-A-S.

Stimuli Influencing Resistance During the G-A-S.

Systemic stress. — Previous exposure to stressor agents considerably influences the development of the G-A-S but since this factor has already been dealt with in connection with changes in specific and non-specific resistance (see above) we need not discuss it here.

Hypophysectomy. — The great diminution in resistance to non-specific stress occasioned by hypophysectomy in the animal, or by destructive pituitary-diseases in man, is one of the salient features of anterior-lobe insufficiency.[42] Hypophysectomized rats become so sensitive that they die if treated with minute doses of **x-rays,**[43] **insulin** [44] or even comparatively small amounts of the otherwise so innocuous **folliculoids.**[45] Experiments specifically designed to study the influence of hypophysectomy upon the course of the G-A-S in the rat revealed that the decrease in stress-resistance — though very severe — is not quite as pronounced as after adrenalectomy. Probably some cortical function persists even in the absence of hypophyseal corticotrophin since adrenalectomy causes death, while hypophysectomy is compatible with the prolonged maintenance of life as long as the organism is not exposed to any unusual stress-situation.[46]

Hypophyseal extracts. — **Anterior-pituitary extracts,** though notoriously effective in restoring stress-resistance after hypophysectomy, are comparatively ineffective in intact animals.[47] Nevertheless, some increase in stress-resistance has been observed with crude corticotrophic preparations.[48] In rats suffering from traumatic shock the effect of corticotrophin was slight and approximately the same as that of cortical extract.[49] Resistance to the damage caused by intraperitoneal administration of hypertonic glucose-solutions is also somewhat increased by corticotrophin, but in hypophysectomized animals this improvement is much more considerable.[50] (Cf. also "Serologic reactions".)

Vasopressor **posterior-pituitary extracts** are comparatively ineffective in raising resistance to systemic stress although some beneficial results have allegedly been obtained in the treatment of traumatic and hemorrhagic shock.[51] Vasopressin has also been recommended as a prophylactic in clinical surgery, especially following severe abdominal interventions.[52] Perhaps the pressor action, the stimulation of intestinal contractility (as a prophylaxis against postoperative ileus) and the influence upon water and electrolyte balance, are responsible for these effects.

Adrenalectomy. — Adrenalectomy considerably decreases resistance to all types of systemic stressors (infections, intoxications, malnutrition, trauma, extremes of temperature, anoxia, etc.). This is mainly due to cortical insufficiency, since transplantation of adrenal-cortical tissue, or administration of corticoids, restores the resistance of adrenalectomized animals towards normal, while adrenaline is comparatively ineffective. These fundamental facts of adrenal physiology are now so well established that the reader may be referred to standard textbooks for relevant data.[53]

In connection with the G-A-S it is particularly noteworthy that adrenalectomy markedly decreases resistance to *emotional stressors.* Thus the excitement incident to electro-shocks is frequently fatal to the adrenalectomized rat. DCA-therapy is beneficial, but much larger doses are required for life-maintenance, during such stimulation, by the emotional, wild strains, than by the placid laboratory rat.[54]

It is especially interesting to note the close *parallelism between the amount of corticoid given and the degree of stress which an adrenalectomized animal can tolerate.* This relationship is so close that a sensitive bioassay-method for corticoids has been based upon the determination of the amount of material (solution containing unknown quantities of corticoids) required to maintain adrenalectomized rats during exposure to the systemic stress caused by cold.[55]

It is very difficult to *raise the resistance of adrenalectomized animals above that of intact controls.* This has been accomplished for instance with DCA against potassium-intoxication,[56] but in such instances, specific hormone-actions (e.g., upon blood-potassium) are probably involved and not a mere non-specific increase in stress-resistance.

The great *similarity between the manifestations of the A-R* (especially the shock-phase) *and those of adrenal insufficiency,* is rather striking. Both these conditions cause hypotension, hemoconcentration, hypoglycemia, hyponatremia, hypochloremia, hyperpotassemia, hypothermia, muscular weakness, gastric and intestinal ulcers, etc. It had been variously claimed that the main function of the adrenal is the maintenance of body-temperature, the prevention of muscular fatigue, the detoxification of harmful metabolites, the maintenance of the normal blood-sugar concentration, and so forth. The earliest experiments on the A-R revealed however "that *animals previously adapted to such stimuli as muscular exercise, cold or toxic doses of drugs will tolerate exposure to these*

[39] Cronkite B24051/48. Liebow et al. B41902/49. Tullis B27010/48, B41901/49, Tullis and Warren B41776/47.
[40] Holmes et al. B33418/49.
[41] Ellinger 78163/38.
[42] Selye 94572/47.
[43] Tyree et al. B33116/48.
[44] Swann and Fitzgerald A15712/38.
[45] Selye et al. 38815/36.
[46] Selye B1204/46, **94572/49,** Selye and Collip 66617/36.
[47] Selye **94572/49.**
[48] Locke A6829/37.
[49] Noble and Collip A56107/42.
[50] Reiss et al. 85064/43.
[51] Best and Solandt A33635/40.
[52] Adams B10543/37.
[53] Selye **94572/49,** Turner **B19831/49.**
[54] Covian B35960/49.
[55] Selye and Schenker A15353/38.
[56] Truszkowski and Duszynska A33160/40.

same stimuli very well, even after the adrenals have been removed, while exposure to the same stimuli invariably kills not-adapted, adrenalectomized controls, with symptoms characteristic of adrenal insufficiency and of the alarm reaction".[57] Subsequently it was noted that "adrenalectomized animals may even acquire resistance to new stimuli if they are protected against their immediate damaging effects, by sodium chloride treatment, during the process of adaptation. After salt treatment is discontinued, such pretreated adrenalectomized animals proved more resistant to the stimulus to which they adapted themselves than non-adapted adrenalectomized controls".[58] Using cold and forced muscular exercise as stressors, it has been confirmed that a previously acquired adaptation is not abolished by adrenalectomy in the rat. Although the adapted-adrenalectomized animal is, of course, not necessarily more resistant than the not adapted-intact, it is always more resistant than the not-adapted-adrenalectomized control.[59]

Normally adrenalectomized animals are ill equipped to acquire or maintain a state of adaptation. Yet, if the stress is not lethal during the A-R stage, the characteristic three-stage G-A-S occurs even in the absence of the adrenals, although the resistant stage is much shorter than in the intact animal. Thus the G-A-S was found to be "telescoped" into a period of a few days while normally it may last weeks or months. It was concluded that "these experiments are in agreement with the conception that the primary cause of the adrenal insufficiency syndrome is a disturbance in the mechanism of adaptation and more particularly a decrease in the ability to maintain adaptation once it is acquired".[60]

Subsequently it was found [61] that adrenalectomized dogs, which are extremely sensitive to dietary administration of *potassium,* tolerate considerable amounts of it if the potassium-concentration of the diet is raised gradually.

Pretreatment with DCA protects the adrenalectomized rat against otherwise lethal *burns.*[61a]

The survival of *x-irradiated* adrenalectomized mice is but slightly prolonged by DCA or adreno-cortical extract. "The adrenals are apparently involved only secondarily as part of the organism's buffer response to the stress of irradiation.[61b] The loss of adrenal-lipids in atomic bomb victims has been ascribed to the A-R. Yet if the adrenal region is protected, the resistance of rats to total-body x-irradiation rises.[61c]

If adrenalectomized rats are exposed to *anoxia* their corticoid requirement is extremely high, but drops close to normal maintenance-levels after adaptation has been acquired. Rats adrenalectomized after adaptation to anoxia do well on comparatively little cortical extract.[62]

Experiments concerning the resistance to *water intoxication* of adrenalectomized rats (some of which were, while others were not previously adapted) likewise suggested a somewhat greater resistance in the adapted series. It was concluded that "the suggestion of the positive results is reminiscent of the carrying-over of resistance to other stresses after adrenalectomy as reported

[57] Selye 67153/37.
[58] Selye 36038/37.
[59] DesMarais B32732/49, DesMarais and Dugal B33123/48.
[60] Selye A9210/38.
[61] Kendall and Ingle 68707/37.
[61a] You and Sellers B46218/50.
[61b] Straube et al. B39082/49.
[61c] Craver B42673/48.
[62] Langley 83877/43.

by Selye".[63] It should be mentioned in this connection that the adrenals enhance resistance to water-intoxication only through cortical activity; the medulla does not appear to be essential for this.[64] DCA and the rapidly absorbable, water-soluble desoxycorticosterone glucoside are about equally effective in protecting the adrenalectomized rat against water-intoxication.[64a]

Intact rats readily adapt themselves to the shock-producing effect of intraperitoneal injections of *hypertonic (40%) glucose-solutions,* while adrenalectomized animals allegedly fail to acquire such resistance.[65] As judged by the previously cited observations, it is very probable, however, that if smaller doses of glucose-solution had been used, some degree of adaptation could have been demonstrated even after ablation of the suprarenals.

Morphine is a drug to which an extraordinarily high degree of adaptation may be acquired by intact animals. In one experimental series non-pretreated and morphine pre-treated rats were adrenalectomized and subsequently treated with the same dose of morphine; 75% of the pretreated animals survived while all the non-pretreated succumbed.[66]

In connection with the concept of the diseases of adaptation, it is of special interest that a high *sodium*-intake prolongs the survival of adrenalectomized animals, presumably because it diminishes mineralo-corticoid requirements.[67] Curiously *ammonium-chloride* — which causes Na-depletion — does not abolish the life-maintaining action of DCA in the adrenalectomized rat. This is all the more remarkable since the hyalinosis-producing action of DCA is very effectively combatted by NH_4Cl.[68] Such observations suggest that the therapeutic administration of NH_4Cl against clinical hyalinosis would not necessarily impede the "defense-actions" of corticoids.

The rôle of the adrenals in the acquisition of resistance to *steroid hormones* is of particular interest. Most of the steroid hormones and their immediate derivatives are extremely well tolerated by the rat even if very large doses are given. As previously mentioned, however, overdosage with certain steroids, especially folliculoids, can produce manifestations reminiscent of the G-A-S, particularly adrenal-cortical enlargement, involution of the gonads, thymico-lymphatic atrophy and growth-inhibition. It has also been emphasized that continued treatment with large doses of folliculoids leads to a typical triphasic response. There is an initial, marked loss of weight and pronounced adrenal enlargement, followed by a resumption of growth and some decrease in adrenal size, while eventually exhaustion and secondary adrenal enlargement with weight loss ensue.[69]

Unlike normal controls, adrenalectomized rats are especially sensitive to the toxic effects of various steroid hormones, especially the folliculoids. They respond with extremely severe A-R (shock-phase) changes resulting in death. While, even after adrenalectomy, hormonally inactive steroids (e.g., pregnanediol, cholestenone) are practically non-toxic, testoids are definitely damaging, although not quite as much as the folliculoids. Since testoids possess a considerable amount of folliculoid potency, it has been concluded that the toxicity of various steroid hormones, in adrenalectomized animals, is dependent

[63] Liling and Gaunt 89147/45.
[64] Eversole et al. 78679/40.
[64a] Cosmos et al. B46483/50.
[65] Reiss et al. 85064/43.
[66] Selye 38798/37.
[67] Selye **94572/49.**
[68] Selye and Stone A96818/45.
[69] Selye A8610/37, A18206/39, A32153/40.

upon their folliculoid action.[70] Diethylstilbestrol proved to be as toxic as the natural folliculoids, hence the damaging effect of these compounds apparently depends upon their folliculoid potency and not upon their steroid structure.[71]

The fact that high-carbohydrate *diets* and Na-supplements prolong the survival, and increase the stress-resistance of adrenalectomized animals, is too familiar to deserve special consideration.[71a] Interestingly, however, pantothenic acid supplements proved especially effective in this respect.[71b]

Adrenaline. — Administration of adrenergic substances such as adrenaline, gives little protection against the systemic stress effect of various non-specific agents. This is probably due to the fact that an absolute or even a relative deficiency in adrenergic substances is rarely a limiting factor in resistance. The pronounced beneficial action of adrenaline and its derivatives in combatting certain special types of damage such as histamine-shock, anaphylactic shock or insulin hypoglycemia, is presumably due to specific actions of adrenergic hormones (e.g., upon the bronchial musculature, the cardiovascular system or the blood-sugar), not to a systemic effect upon resistance in general.[72] These effects will be discussed in greater detail in the section concerned with the individual targets affected (e.g., cardiovascular system, lung). Because of its special implications upon the stress problem, let us merely mention here that the anaphylactoid edema, produced by parenteral administration of egg-white in the rat, is also effectively prevented by pretreatment with adrenaline. Since a variety of stressors inhibit this response, while adrenalectomy aggravates it, this observation deserves special mention. It has been considered to indicate that, in the case of anaphylactoid edema, the "protective effect of alarming stimuli might be interpreted as a result of the release of epinephrine from the adrenal medulla".[73]

Corticoids. — As stated above, the extraordinarily low stress resistance of adrenalectomized animals can readily be raised towards normal by corticoids. In animals with intact adrenals, on the other hand, these hormones are comparatively ineffective in augmenting non-specific resistance above normal. Apparently, the mechanism for the excess production of corticoids during stress-situations is nearly optimal, so that additional administration of exogenous hormones does not appreciably change stress tolerance, except under certain conditions. Thus, in patients with pre-existent, latent hypocorticoidism ("Addisonism") and in those with extensive adrenal necrosis, such as occasionally develops in acute fulminant infections, the lack of corticoids may become a crucial weak point in the defense-mechanism against systemic stress; in these cases, corticoid-therapy is usually effective.

The extraordinary efficiency of desoxycorticosterone in combatting potassium-intoxication, or that of 11-oxygenated corticoids in counteracting insulin hypoglycemia (see below), can hardly be regarded as indicative of their value in non-specific stress-situations. These actions are due to the specific mineralo- and gluco-corticoid effects of the compounds respectively.

It is not within the scope of this monograph to present a detailed discussion of the voluminous literature concerned with the effects of corticoids in the

[70] Schacher et al. A231/37, Selye et al. 38815/36, Selye and Masson A18204/39.
[71] Selye and Masson A18204/39.
[71a] Selye **94572/49.**
[71b] Dumm and Ralli **B39044/49.**
[72] Selye **94572/49.**
[73] Clark and MacKay B36925/49.

prophylaxis and treatment of shock-like conditions. The following condensed survey is presented merely as a guide to this field which offers such interesting possibilities for the practical application of the G-A-S-concept. From the papers quoted, it will be seen that the corticoid therapy of systemic stress appears to hold promise. However, the optimal quantities of hormone are probably far above those in general use and much further work is needed to establish the best conditions of dosage, route of administration, type of corticoid to be given, conditioning factors (e.g., diet), kind of "supportive therapy" (blood-transfusion, glucose, saline, ascorbic acid), etc.

Considerable work has been done concerning the value of corticoids in the prophylaxis and therapy of **traumatic shock** due to surgical interventions or crushing injuries in *man*. The pertinent reports are quite contradictory and difficult to evaluate.[74] Nevertheless, a study of these publications leaves one with the impression that cortical extracts and gluco-corticoid compounds can be effective in the treatment of systemic stress due to trauma if very high doses are given before the development of irreversible shock. The value of DCA is much more questionable; prolonged pretreatment with this steroid may even be detrimental by causing "compensatory atrophy" of the adrenal cortex and thus inhibiting the normal function of the cortex. If corticoid-therapy is instituted in traumatic shock, it should always be supported by the usual prophylactic and therapeutic procedures (e.g., transfusions, maintenance of body temperature).

The literature concerning the efficacy of corticoid therapy in the various types of experimental traumatic shock in *animals* (crushing injuries, tourniquet, Collip-Noble drum, temporary blood-vessel ligatures, etc.) is likewise contradictory. Some investigators reported excellent results, proven to be statistically significant, while others found little or no improvement.[75] Careful scrutiny of the pertinent literature did not enable us to single out any particular circumstances in the experimental procedures used, which could explain the conflicting nature of apparently reliable observations. As with the clinical data, it appears that gluco-corticoids are most likely to be effective while desoxycorticosterone acetate possesses little, if any, beneficial action.[76] The rôle of the compensatory adrenal-cortical atrophy in the prophylactic administration of corticoids has been studied especially in the rat. It was found that pretreatment with various corticoids causes pronounced adrenal-cortical involution and thus interferes with the normal stress-response of the cortex. This "compensatory atrophy"

[74] Anonymous A32943/40, A34297/40, A57085/43, Beiglböck A39860/41, Besser A37728/41, Brodin A38184/41, Browne B25561/42, Clermonthe A57129/41, Corrado A63584/41, d'Harcourt and Pi A38248/40, Harrower A37916/41, Honan B28042/45, Hügin B24201/47, Keating et al. 80833/41, 81842/42, A37500/42, A55839/42, Koster and Kasman 83511/42, Larget and Lamare A38155/41, Larget et al. A57032/41, Léger A38192/41, de Luca A54791/42, Meakins A34669/40, Menten and Smith A58080/36, Pollak A32944/40, Ragan et al. A31233/39, Reed A19354/38, Stähli B29541/46, Tarantino 95868/42, Thygesen and Moller-Christensen B29544/46.
[75] Bourque et al. A57912/43, 84560/44, Cleghorn B2571/47, Fine et al. A56268/42, Helfrich et al. A37774/42, Ingle A59854/43, Katz et al. 82049/42, A55777/42, Noble and Collip 81405/41, A56107/42, Noble and Toby B38835/47, Root and Mann A57542/42, Shleser and Asher A56711/42, Swingle et al. A61337/43, Wegria et al. A56861/43, Weil et al. 78692/40.
[76] Selye et al. A32768/40, Selye and Dosne A33299/40.

is particularly detrimental if it is produced with DCA, since the latter, being a mineralo-corticoid, has little, if any, shock-preventing effect, but seriously impedes the endogenous production of more useful gluco-corticoids. Thus rats pretreated with DCA and then submitted to the systemic stress of trauma, develop signs of severe cortical insufficiency much more readily than non-pretreated controls.[77]

In **fetal shock** (infants born in shock), treatment with DCA was allegedly beneficial when administered in combination with saline infusions,[78] but these observations still await confirmation.

The sudden **collapse in cases of infantile eczema** apparently responds very well to treatment with adreno-cortical extract.[78a] (Cf. also "Infantile diarrhoea" p. 101 and "Premature infants" p. 70).

Similar therapeutic trials in **obstetric shock** led to the conclusion that "the use of adrenal cortex extract may be of value as a preventive. This is of unquestionable value when cortical function is known to be deficient".[79] In the prophylactic administration of corticoids, the pretreatment period must be brief to permit optimal hormone saturation of the organism without incurring the danger of compensatory adrenal-atrophy.

The shock-like condition produced by **intestinal obstruction** in the dog, has been claimed to be partly relieved by intravenous administration of DCA.[80] On the basis of animal-experiments some investigators recommend the use of cortical extracts in the treatment of intestinal strangulation.[81]

Efforts to relieve **hemorrhagic shock** by corticoids have been rather uniformly discouraging.[82]

In patients and experimental animals who suffered from the systemic stress of severe **burns**, corticoid-therapy yielded conflicting results in the hands of different investigators.[83] Simultaneous administration of large doses of ascorbic acid has occasionally been recommended.[84] Curiously some experiments on intact rats suggest that DCA gives more protection against burns than cortical extracts.[84a]

Since exposure to **cold** is a particularly effective alarming agent, numerous investigators examined the value of corticoids in combatting the systemic stress caused by low temperatures. Beneficial effects have allegedly been obtained in some clinical cases.[85] Animal experiments with cortical extracts and gluco-corticoids were much less encouraging. Indeed, following chronic DCA-pretreatment, resistance to cold was found to be subnormal as a result of the compensatory-atrophy-phenomenon.[86]

[77] Dosne A34564/40, Dosne and Selye 81963/42, Selye and Dosne A37249/42.
[78] Berlind A37586/41.
[78a] Marsden B40887/47.
[79] Matthews A30867/39.
[80] Fine et al. A32224/40.
[81] Laufman and Freed 88861/43.
[82] Fine et al. A56268/42, Huizenga et al. A59447/43, A54816/43, Viale 16495/33, Wiggers 96828/43.
[83] Bergman et al. B2009/45, Goetze A38591/40, Harkins 82895/42, Heni A50877/40, Houot 95984/42, 95985/43, B28043/45, Hügin B24201/47, Ingle and Kuizenga 96155/45, Osswald A39035/39, Rhoads et al. A37675/41, B20641/43, Wilson and Stewart 94458/38-39, Wilson et al. A34942/36.
[84] Einhauser A31896/39, Ovnbol 96139/43.
[84a] You and Sellers B46218/50.
[85] Goldhahn A67992/43, Killian A67991/43.
[86] Dosne A34564/40, Selye and Dosne A37249/42.

In patients suffering from **heat**-stroke favorable results have been reported by various authors who used either cortical extracts or DCA.[87] In subjects in whom fever-therapy was instituted for syphilis of the central nervous system, it was found that "this extract decidedly reduced the degree of fatigue and accelerated the rate of recovery after one or two treatments. The frequency and intensity of other symptoms were also favorably affected. Desoxycorticosterone acetate produced no beneficial effects." Although the extract caused a fall in plasma-sodium and diminished the loss of sodium through perspiration, it was concluded that "the retention of sodium, when adrenal extract was given, was insufficient to account for the amelioration of the unfavorable clinical reactions to fever therapy".[88] In rabbits, cortical extract also appears to have raised resistance to artificially produced fever.[89]

In patients with systemic stress due to **x-ray damage**, DCA treatment has been claimed to give marked protection.[90] In experiments on mice, the liver-damage normally seen after x-irradiation was allegedly strikingly reduced and the survival slightly improved by DCA-treatment.[91] However, certain strains of mice do not appear to benefit from such therapy.[91a]

In various types of **nervous diseases**, especially in chronically fatigued neurotics,[92] and in "acute confusional states",[93] treatment with cortical extracts has been claimed to be beneficial. Excellent results have also been reported in DCA-treated epileptics (grand mal). In the latter instance, the beneficial results were ascribed to the changes in water- and electrolyte-metabolism which DCA could induce in the brain.[94] (Cf. also: Nervous system.)

The mortality rate of rats in which **forced exercise** led to severe exhaustion, is claimed to be diminished by adrenal-cortical extracts [95] and even by DCA.[96] These beneficial results were manifest although the adrenal hypertrophy, normally produced by exercise, was inhibited by the corticoids. However, after prolonged and intense DCA-pretreatment, the mortality from forced exercise is greatly increased in the rat, presumably because the compensatory adrenal-atrophy prevents the elaboration of more useful (gluco ?) corticoids.[97]

In combatting the systemic stress of **anoxia and reduced atmospheric pressure**, strikingly favorable results have been obtained with various types of corticoids,[98] but in one experimental series, in which cortical extract was highly effective, DCA and 17-hydroxycorticosterone proved to be without value.[99]

Many investigators examined the possible value of corticoids in raising resistance to spontaneous and experimental **infections**,[100] or intoxications with

[87] Böttner and Schlegel A39672/41, Schlegel A56984/41, Schlegel and Böttner A54893/41.
[88] Edelman et al. A56665/43.
[89] Maddaloni A18244/38.
[90] Ellinger et al. B44439/49, Weichert A56943/42.
[91] Ellinger 93367/46, 93953/47, B24015/48.
[91a] Straube et al. B39082/49.
[92] Gorrell A36385/40, Huddleson and McFarland A30745/39.
[93] Hoff and Shaby A32900/40.
[94] McQuarrie B37369/46, McQuarrie et al. A55652/42.
[95] Korényi and Hajdu A56945/42.
[96] Beznak and Korényi A57235/41.
[97] Dosne A34564/40.
[98] Armstrong and Heim A18224/38, Britton and Kline 93980/45, Giragossintz and Sundstroen A6932/37, Johnson et al. 96626/43, Kottke et al. B25989/48.
[99] Thorn et al. B335/45.
[100] Argentina 94842/28, Baccarani 92386/30, Biro B34001/46, Brodin A38184/41, Malato A58330/36, Weinstein B15029/39, Whitehead and Smith 3194/32, Zwemer and Truszkowski 35802/36.

bacterial toxins; [101] the results were often far from spectacular, but perhaps in some cases such therapy has been useful. Combined administration of ascorbic acid and corticoids is recommended by some authors.[102]

Particularly favorable results have been reported in very acute infections, which cause a great deal of systemic stress, with a marked adrenal response; for instance in *malaria,*[103] *pneumonia,*[104] meningococcemia with *Waterhouse-Friderichsen syndrome,*[105] and in *typhoid fever.*[106] In intact mice, treated with typhoid endotoxine, cortical extracts are rather ineffective, although the extremely low endotoxin-tolerance of the adrenalectomized animal is considerably increased by such treatment.[107] Beneficial results have also been obtained in *diphtheria* and after *diphtheria-toxin administration.*[108] In the latter instance, many authors stressed the value of simultaneous ascorbic acid administration.[109] Several of the investigators who employed corticoid-therapy in these acute, infectious diseases, claim to have obtained very satisfactory results even with DCA.

In clinical and experimental *gas gangrene* due to infection with Cl.Welchii, favorable results were again allegedly obtained, not only with cortical extracts but also with DCA.[101] In any case, the corticoids tend to prevent only the manifestations of shock and not the progress of the local infection itself.

During an epidemic of *whooping cough,* a small group of patients were given injections of adrenal-cortical extract; it was concluded that "the severity and duration of whooping cough in these patients was notably diminished".[111] In a *cholera*-epidemic cortical extracts were found useful but the number of cases treated was too small to draw definite conclusions.[112]

The experimental *poliomyelitis* of Swiss mice was not influenced by DCA treatment.[113]

It has been claimed that the resistance of mice to *streptococcus,* and of guinea-pigs to *spotted fever* infection is raised by cortical extracts,[114] but the figures given are not very convincing. The resistance of rats to *trypanosoma equiperdum* [115] and that of mice to *pneumococcus* [116] were not influenced by cortical extract.

In chronic infections corticoid therapy is even less likely to be of value. Only in *tuberculosis* has it been seriously recommended, mainly because this infection is so frequently accompanied by actual adrenal-cortical failure.[117] However, recent observations with cortisone suggest that, by enhancing the absorption of delimiting connective-tissue barricades, the spread of tuberculous lesions is promoted by gluco-corticoids.

In view of the great resemblance between hypocorticoidism and **celiac disease** (idiopathic steatorrhea, non-tropical sprue) several investigators attempted corticoid therapy in the latter condition. The results so far reported, both with cortical extracts and with DCA, have been equally encouraging.[118] Of course corticoids should merely be employed as an adjunct to the usual nutritional and liver therapy. (Cf. also p. 101.)

The use of cortical extracts or DCA in the treatment of **eclampsia** and other **pregnancy-toxicoses** has had many advocates,[119] but it is not always effective; indeed it may even aggravate the condition.[120]

In the pregnancy-toxicoses, manifestations of hypocorticoidism (gastro-intestinal disturbances, increased tendency for pigmentation, muscular weakness, etc.) are often associated with signs of hypercorticoidism (hypertension, renal lesions, sodium- and water-retention, hyalinosis, etc.). The adrenal cortex tends to enlarge even in normal pregnancy. It is not impossible therefore that many of the manifestations of pregnancy-toxicoses are due to inappropriate (hypo-, hyper- or dysfunctional) responses of the adrenal cortex during a condition of greatly increased corticoid-requirement. If this be the case, corticoids may have either beneficial or detrimental effects depending upon the circumstances. (Cf. "Pregnancy diseases of Adaptation".)

In various **allergic conditions** — especially in asthma, serum-sickness, herpes zoster, urticaria and dermatitis venenata — treatment with cortical extracts or DCA has allegedly given excellent results.[121] It has also been claimed that cortical-extract or DCA-pretreated guinea-pigs sensitized to horse-serum or egg-white, show unusually mild anaphylactic phenomena upon re-injection with the same antigen.[122] (Cf. also "Serologic reactions".)

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[101] Diller B1967/46, Ingle B42751/47.
[102] de Candia B32082/42, Cosentino 94421/39, Floris A55355/40, Traxel A57313/42.
[103] Bahtiyar B26539/47.
[104] Perla and Marmorston A34156/40, Traxel A57313/42.
[105] Albahary 93962/46, Bickel A39967/40, Greene A71705/44, Grubschmidt et al. B3985/47, Harrell B2189/47, Jacobi and Harris B2026/45, Mores B24203/47, Peabody 96810/43, Potter and Bronstein B658/44, Strick B676/44, Wasserman B1926/43.
[106] de Candia B32082/42, Fiorentini 33774/35, Galli and Sabatelli A39613/40, Hoff and Shaby B32900/40, Turner and Dent B44802/49, Wahl A54635/41, A72348/43.
[107] Delaunay and Lebrun B3140/47.
[108] Dieckhoff 93813/43, Dieckhoff and Schulze B10185/37, Doskocil A58309/36, Grenet et al. A57405/42, A63747/43, Hansen-Ymker 96288/46, Heni A50877/40, Hoffmann-Wülfing 95047/37, Hügin B24201ü47, Maly A72170/42, Marquézy and Ladet A38186/41, Marquézy et al. A63748/43, Pesch and Strelow 16742/23, Steinhardt and Türk 94673/37.
[109] Aicham and Bock A58298/36, Bamberger and Wendt 55736/35, Bamberger and Zell A58302/36, Berger 95075/37, Behr A39758/41, Bernhardt A58304/36, A72013/42, Dieckhoff 94423/39, Dieckhoff and Schüler 90943/38, Galeotti-Flori 94659/39, de Marchi A30837/38, Messer A58333/36, Schmidt 94670/37, Sedallian et al. B30410/47, Siegl A39931/40.
[110] Kepl et al. A56633/43, Niedner A72792/43, Singer B316/40.
[111] Jacobs A59436/43.
[112] Lahiri B28052/45.
[113] Anderson and Bolin 92825/46.
[114] Langecker and Singer 15034/33.
[115] Scott et al. 15446/33.
[116] Scott et al. 15446/33, Tobian and Strauss B28613/48, Vollmer and Samsell B34718/49.
[117] Bernhardt A72013/42, Chiray et al. A38188/41, A72116/42, Cozutti and Bekdemirian 95813/41, Fabiani 90395/29, Lafontaine 99506/46, Pottenger and Pottenger A71234/37, Scotti A57139/40.
[118] Aguirre et al. 83100/41, Alvarez et al. A33405/40, Gigon A50865/41, van Nieuwenhuizen A72150/41, Oettel and Thaddea A67906/41, Parade A50851/41, Pock-Steen A39387/39, Schwartzer A32946/39.
[119] Bottiroli 93807/43, 96074/43, 93808/44, Elert A55079/42, de Gennes and Mahoudeau A38185/41, Hart A56858/43, Kemp A71173/32, Kotz and Kaufman A32559/40, Lange-Sundermann A38799/40, Laubscher 99140/46, Navratil A63833/43, Posatti A57267/41, A57348/41, Smith and Smith 81127/41, Spitzer 94623/38, Thaddea A54761/42, A72540/43, Wagner A32111/39.
[120] Brandstrup A34210/39.
[121] Eiselsberg A39684/40, Harding 83634/41, Harrower A62572/35, Hipple A33587/39, Hofmann A54723/42, Ludy and Applestein 90998/39, Moll A35996/41, Pottenger A6275/37.
[122] Gros A66862/41, Gros and Benoit A39781/41, Wolfram and Zwemer 30809/35.

In **premature infants** DCA-treatment has also been recommended,[123] mainly because during the first weeks of life they may present a syndrome resembling hypocorticoidism (anorexia, failure to gain weight, dehydration, hypoglycemia).

Corticoid-therapy has likewise been suggested for various **other diseases** [124] including the *habitual vomiting of infants,*[125] *dehydration of infancy,*[126] *various types of marasmus,*[127] ill-defined *gastrointestinal disturbances,*[128] etc., but most of these findings are greatly in need of confirmation.

The efficacy of corticoids in augmenting the resistance of not-adrenalectomized animals to toxic doses of **various drugs and hormones** has been the subject of particularly numerous studies.[129] In adrenalectomized animals corticoids are always very effective in raising resistance to drugs so that this literature need not be discussed here. In the intact animal, however, the results are less clear-cut. As applied to *bacterial toxins* we have already mentioned this above (see: Infections).

The resistance of rats to *acetonitril* was considerably raised by intraperitoneal implantation of adreno-cortical tissue, but since a cortical extract did not show this effect [130] it is doubtful whether the implants owed their activity to corticoids.

DCA was claimed to raise the resistance of intact animals to *bromide*-intoxication,[131] but this requires confirmation.

Adreno-cortical extracts allegedly possess a considerable protective action against the toxicity of *colchicine,* a drug known to be a particularly powerful alarming stimulus.[132]

The life-span of rabbits in which a considerable NaCl-depletion was induced by the intraperitoneal administration of hypertonic *glucose*-solution has not been significantly prolonged by cortical extracts.[133]

Observations concerning the ability of corticoids to prevent *histamine*-shock led to somewhat contradictory results.[134] However, the extraordinarily low histamine-resistance of adrenalectomized animals is very effectively raised by corticoids. This is noteworthy because the liberation of histamine or similar substances from tissues has often been postulated as playing a prominent rôle in the production of shock and of various allergic phenomena.

The shock-like condition induced by *insulin* in experimental animals [135] as well as the systemic stress occasioned by insulin-shock therapy in man [136] are effectively counteracted by gluco-corticoids, but not by DCA. This effect cannot be ascribed exclusively to a rise in non-specific resistance; it is due mainly to the prevention of insulin-hypoglycemia by the increased amounts of carbohydrate rendered available through the action of gluco-corticoids.

123 Archimede A33701/40, Jaudon 99655/46.
124 Lapin et al. 96634/43.
125 Buoncore B25609/47, Gambaro B26538/47, Jaudon B36572/48.
126 Heni A50877/40.
127 Hislop 90968/38.
128 Chiray et al. A38187/41.
129 Zwemer 95960/41.
130 Dessau 34845/35.
131 Wohl and Robertson 93480/42, 93481/44.
132 Clark and Barnes A33441/40.
133 Loreto A30833/38.
134 Binet A38193/41, A39122/42, Perla et al. A31863/40, Wittich A99080/43.
135 Jensen and Grattan 77887/40, Levene and Swann 80483/41.
136 Goldman A33782/40, Saito A56946/40.

Iodoacetate tends to cause a very severe A-R, hence it is noteworthy that its non-specific stressor effects are but slightly [137] or not at all [138] inhibited by cortical extracts.

The alleged beneficial effect of corticoids in *lead-poisoning* [139] requires further confirmation.

Resistance to the so-called *menstrual toxin* is purportedly raised in intact rabbits by treatment with adreno-cortical extract.[140]

Since *mustard gas* is a very powerful alarming stimulus, it is interesting that corticoid-therapy has been found of some value in combatting its systemic stress effect.[141]

Experiments on rats, which developed shock after intraperitoneal injection of large amounts of *peptone,* led to the conclusion that "injection of large doses of adrenal cortical extracts increased the incidence of survival over that of untreated animals. Extracts derived from hog adrenals were superior to extracts of beef adrenal glands. The administration of 11-desoxycorticosterone acetate and of small doses of adrenal cortical extract was ineffective".[142]

Resistance to *potassium*-intoxication is consistently raised both by cortical extracts,[143] and by DCA [144] in various species. However, it was noted that although "desoxycorticosterone acetate protects the normal rat from KCl poisoning, repeated 2-mg. doses of desoxycorticosterone acetate resulted in the physiological atrophy of the adrenal cortex. This atrophy was manifested in the decreased resistance to KCl poisoning if enough time was allowed for the protective concentration of the drug itself to disappear from the body".[145] Apparently, here, we are dealing with another instance of induced hypocorticoidism because DCA was given for a sufficiently long time to cause compensatory atrophy of the animal's own cortex. Comparative studies in the rat revealed that while cortical extract afforded immediate protection against potassium poisoning, DCA had to be given for several days as a pretreatment. This is noteworthy since DCA is more active in depressing serum-potassium than impure cortical extracts.[146]

Severe intoxication with *thiourea* or its derivatives, may cause a syndrome reminiscent of acute adrenal insufficiency in the rat. In such animals treatment with cortical extract diminished mortality.[147]

Thyroid hormone is extraordinarily injurious in hypocorticoid patients or animals. It causes an intense catabolic response accompanied by marked hypertrophy of the adrenal-cortex with other manifestations of the G-A-S.[148] It is especially interesting, therefore, that the toxicity of thyroxine is most effectively counteracted by DCA even in intact guinea-pigs and mice.[149]

The toxicity of certain *tissue extracts* is allegedly also reduced by cortical extracts.[150] In view of the probable rôle played by toxic tissue-catabolites in the G-A-S, this observation would well deserve further study.

137 Laszt and Verzar 34843/35.
138 Clark and Barnes A33441/40.
139 Benko 95966/42.
140 Smith and Smith A32972/40.
141 Kucharik and Telbisz 96165/45.
142 Ingle 85588/44.
143 Mullins et al. 83885/43, Zwemer and Truszkowski 35802/36, A2330/37.
144 Robertson B32963/49.
145 Lowenstein and Zwemer A74481/43.
146 Thatcher and Radike B4515/47.
147 Glock B23056/45.
148 Rogoff 85421/43.
149 Kinsell et al. A37369/42, 80834/41.
150 Laufman and Freed 88861/43.

Trichlorethylene-intoxication tends to cause very pronounced adrenal changes; hence it has been tried to raise resistance to this drug with corticoids. Apparently favorable results were obtained in the guinea-pig, especially if ascorbic-acid was also given.[151]

The shock-like condition caused by *veronal*-poisoning is allegedly also improved by cortical extracts.[152]

Experiments concerning the toxicity of excess *water* led to the conclusion that "large doses of adrenal cortical extract or desoxycorticosterone acetate will protect normal rats from doses of water which otherwise produce lethal water-intoxication".[153]

DCA-pretreatment delays death after complete **nephrectomy** in the mouse and rat.[154] Since this corticoid decreases the potassium-content of the body, the prolongation of life which it occasions has been ascribed to a mere delay in the rise of the serum-K to the toxic levels characteristic of uremia.[155] In dogs with anuria following ureter ligation, the post-operative administration of DCA failed to yield beneficial results. This was also interpreted as showing that the steroid acts by previously depleting the body of K.[156] In dogs, pretreated with DCA, the rise in blood-K was delayed and the life-span prolonged after subsequent complete nephrectomy. It was again concluded that the steroid acts by delaying the attainment of toxic serum-K levels.[157] It has been shown, however, that in rats pretreated with DCA, not only are the hyperpotassemia and death delayed following subsequent complete nephrectomy, but even the rise in N.P.N. is greatly inhibited,[158] though apparently on certain diets only.[158a]

A delay in the rise of blood-K and blood-N.P.N. undoubtedly plays an important rôle in the anti-uremic effect of DCA, but it is very doubtful whether one should ascribe these effects to an increased stress resistance rather than to specific hormone-actions.

In fasting **partially hepatectomized** rats the usual hemoconcentration, hypochloremia and hypoglycemia are inhibited by cortical extract. After complete hepatectomy, however, the hypoglycemia is not delayed by such treatment. Apparently the cortical hormone does not inhibit the utilization of circulating sugar but acts mainly by increasing hepatic gluconeogenesis. Here again the beneficial effect of the corticoid cannot be ascribed merely to a rise in non-specific resistance, but rather to its specific influence upon sugar metabolism which is always deranged after partial hepatectomy.[159] The resistance of the rat to burns is greatly diminished by partial hepatectomy.[159a]

In **summarizing** the large number of publications cited above, a few of the most striking facts should be re-emphasized. There is no doubt about the possibility of raising resistance to various damaging agents, in adrenalectomized animals and frankly hypocorticoid patients with cortical extracts, DCA and other purified cortical steroids. Yet, in comparison with the adrenal-deficient, the benefit derived from corticoid-therapy by intact animals

[151] De Dominicis B3412/42.
[152] Einhauser A19483/39.
[153] Gaunt A63323/43, 84567/44.
[154] Dosne A35924/41, Nylén 94793/46, Selye A34190/40, A35626/41.
[155] Durlacher and Darrow A55533/42.
[156] Winkler et al. A55742/42.
[157] Rodbard B22509/45, 82148/42.
[158] Selye and Nielsen A35723/41.
[158a] Masson et al. B43628/49, B40204/49.
[159] Selye and Dosne A30702/40.
[159a] DesMarais B46032/49.

and man is very small. In numerous types of stress no benefit could be detected. The literature contains many most encouraging reports, but this is deceiving since negative findings are often not reported so that mere statistical evaluation of the published facts would give an erroneously favourable impression. Our experiments convinced us that under certain circumstances at least, gluco-corticoids can be beneficial in raising the resistance of intact animals to trauma, cold and drugs, but the improvement so obtained is rather slight.

The hormones of the adrenal cortex are undoubtedly most important for resistance to systemic stress. This is clearly shown by the great stress-sensitivity of adrenalectomized animals and the facility with which their resistance is restored — proportionately to the dose — by corticoids. On the other hand, the adrenal-cortex appears to be very effective in producing as much corticoid as is desirable; hence, lack of corticoids is perhaps rarely an important, limiting factor of resistance in conditions of grave systemic stress. The most consistently beneficial results of corticoid therapy have been seen in those conditions in which an overwhelming systemic stress led to hemorrhages or necrosis of the adrenals (e.g., diphtheria, Waterhouse-Friderichsen syndrome). Here the endogenous production of corticoids was probably no longer maintained on the high level necessary for optimal stress-resistance.

Finally, it must be pointed out that not all types of protection afforded by cortical hormones are necessarily the result of an increase in non-specific resistance. Thus the beneficial effect of corticoids in uremia, potassium-intoxication, insulin-shock, and perhaps also in water-intoxication, are probably — in part or entirely — due to the specific actions of these steroids upon electrolyte-, water- and carbohydrate metabolism respectively.

Kidney. — It has been claimed that "the renal pressor system has no influence on either mortality or survival time in burn shock". Nephrectomized dogs proved less resistant to scalds than intact animals, but dogs with bilateral ureter ligatures were no more resistant than the nephrectomized. Hence, their diminished resistance was ascribed to uremia.[160] It must be remembered, however, that occlusion of the ureters damages both the excretory and the endocrine activities of the kidney.

In dogs, complete ligature of both renal arteries causes a more rapid rise in blood-N.P.N., resulting in death, than bilateral nephrectomy. This difference was ascribed to the liberation, from the anoxemic kidney, of substances (RPS?) which allegedly stimulate protein-catabolism. Accordingly, pretreatment with low-protein diets prolonged the survival-time and delayed death from uremia. This was noted both after complete nephrectomy and after ligature of the renal arteries.[161] It will be recalled that the damaging effect of the "endocrine kidney" operation is not influenced by the protein content of the diet,[162] but perhaps here, the production of RPS is so great that dietary factors fail to mitigate its toxic actions.

Spleen. — Much has been written about the rôle of splenic hormone-production and other functions of the spleen in systemic defense-reactions.[163]

[160] Hechter et al. B2007/45.
[161] Mylon and Goldstein B28280/48.
[162] Selye and Stone B18527/48.
[163] Perla and Marmorston-Gottesman **32161/35.**

Undoubtedly this organ plays an important rôle in the resistance to certain infections (e.g., bartonella muris), but its possible participation in the non-specific defense phenomena of the G-A-S has not yet been elucidated.

Interestingly the survival of mice subjected to intense x-irradiation is improved if their spleens are exteriorized and placed in a protective lead box during exposure.[164] However, here we are probably dealing with a rather specific action, since x-rays exhibit a particularly pronounced detrimental effect upon the blood-clotting mechanism and hemopoiesis, both of which are largely under splenic control (cf. chapter: Hemopoietic system).

Other hormones. — **Testosterone**-propionate has been recommended in shock due to intestinal obstruction [165] or burns [166] but its efficacy is rather limited and perhaps largely due to the anabolic properties of this compound. Its alleged utility in the uremic form of cholera has been ascribed to the specific renotrophic action of this testoid.[167]

Pretreatment with **folliculoids** improves the survival rate of mice subsequently subjected to x-irradiation.[167a] This beneficial effect — like the lympholytic action of folliculoids — is independent of the adrenals. Perhaps the folliculoids render hemopoietic tissues more resistant to x-rays, because their initial disintegration is followed by a proliferation which counteracts the toxicity of the radiation.[167b]

Thyroid-hormone-pretreatment greatly facilitates the production of traumatic and hemorrhagic shock in dogs,[168] probably because the hormone increases the metabolic level and hence augments tissue-breakdown during the catabolic stage.

It is presumably for similar reasons that thyroid-hormone increases, while the thioureas decrease resistance to cold.[169] To withstand this particular stressor, a high B.M.R. and an increased heat-production are advantageous. However, the fact that goitrogens (or thyroidectomy) usually cause some degree of adreno-cortical involution may also be involved in this diminished resistance to cold.

The often fatal convulsions produced by the ringing of a bell in the so-called "sonogenic" strains of mice, are inhibited by thiouracil.[170] This may be due to a depression of nervous functions, which diminishes the stressor effect of sound.

All these observations suggest that effects of hyper- and hypothyroidism upon the G-A-S differ depending upon the alarming stimulus used to elicit it.

Temperature. — The surrounding temperature has an important influence upon the course of the G-A-S. We have already mentioned that extreme cold or heat can in itself act as potent systemic stressors. We also learned that, in the event of simultaneous application, the systemic stress-effect of different alarming stimuli is summated. It is understandable therefore that exposure to cold is very detrimental, especially during the period of shock when thermo-regulation is defective. It is for this reason that patients in

[164] Jacobson B33422/49.
[165] Bassett B356/43.
[166] Abbott et al. B29501/46.
[167] Henderson et al. B23880/48.
[167a] Treadwell et al. A56593/43.
[167b] Patt et al. B43570/49.
[168] Schachter and Huntingdon A32970/40, Schachter B929/45.
[169] Lange et al. B23962/48, Zarrow and Money B27880/49.
[170] Vicari B33080/49.

shock must be kept warm. Overheating, by excessive application of blankets, etc., should be avoided, however, since heat likewise causes additional systemic stress, especially when temperature-regulation is impaired.[171]

These recommendations are mainly based upon clinical experience, but they have been confirmed in many animal experiments. In pertinent investigations specifically designed to study the A-R, it was pointed out that the maintenance of a normal body-temperature is especially effective in preventing manifestations of systemic stress following high spinal-cord transection, which tends to cause an unusually pronounced hypothermia. The A-R-changes elicited by formaldehyde-injections — though also accompanied by some hypothermia — are not effectively prevented by raising the room temperature.[172]

Nervous system. — The importance of the nervous-system in the etiology of traumatic shock has long been recognized.[173] Convincing evidence shows that afferent nervous impulses from a traumatized limb play an important rôle in the causation of shock.[174] For instance, following trauma to an extremity disconnected from the body except for the main nerve-trunks, shock can still occur.[175] Conversely the severe drop in blood-pressure caused by trauma to the hind-limbs can be prevented by preliminary transection of the lumbar spinal-cord.[176] Survival following trauma is improved in dogs by previous deafferentation of the injured limbs.[176a] The shock caused by burns is likewise greatly diminished after spinal-cord transection.[177] Spinal anesthesia has therefore been recommended as a means of preventing shock following trauma to the lower limbs in man.[178] The utility of morphine [179] in severely injured patients is probably also due to the elimination of excessive afferent impulses. The entire concept of "anoci-association" [180] (cf. Glossary) is based upon the observation that surgical operations are much better tolerated if the accompanying nerve-damage is minimized. As we have stated before, nervous and emotional stimuli are in themselves very potent systemic stressors, hence it is understandable that, whatever other agent is operative in causing systemic stress (trauma, hemorrhage, etc.), additional, intense nervous stimuli can aggravate the condition. (Cf. also p. 92.)

Conversely, the nervous system also plays a prominent rôle in the defense against alarming stimuli. The importance of adrenaline [181] and sympathin-discharge during systemic stress has already been mentioned.[182] It is also noteworthy in this connection that complete sympathectomy greatly decreases the resistance of dogs to such alarming stimuli as histamine, acetylcholine or peptone.[183] Sympathectomized cats readily succumb to heat or cold [184] and are abnormally sensitive to the damaging actions of excessive muscular exercise,[185] hemorrhage,[186] and anoxia.[187] Some of the most striking man-

[171] Blalock B19948/40, Moon A16304/38, Scudder A32530/40.
[172] Dalton 79110/40-41, A34566/40, Frank A34171/40.
[173] Crile B25572/899.
[174] O'Shaughnessy and Slome B25573/35.
[175] Lorber et al. A36146/40.
[176] Freedman and Kabat A35187/40, Kabat and Hedin A56063/42.
[176a] Wang A95926/46, B4725/47. Wang and Overman B39013/49.
[177] Kabat and Hedin A56063/42.
[178] Reader A31351/39.
[179] Adams B10543/37. Reader A31351/39.
[180] Crile and Lower 97296/15.
[181] Cannon 57873/14.
[182] Cannon **B14905/39.**
[183] Bennati and Baco B23242/47.
[184] Cannon B14905/39.
[185] Freeman and Rosenblueth 9605/31.
[186] Schlossberg and Sawyer 7161/33. Freeman et al. B27052/38, B27053/36.
[187] Sawyer et al. 7159/33.

ifestations of hemorrhagic shock may actually be inhibited by total sympathectomy because the usual preferential blood-shift to the vital organs (heart, brain) no longer occurs so that other organs are not as severely deprived of blood; yet death occurs sooner than in intact animals.[188] (Cf. also: Cardiovascular system.)

Cocainization of one carotid sinus allegedly raises resistance against primary traumatic shock,[188a] presumably due to inhibition of the depressor mechanism.

Drugs. — Only few pharmacologic agents exert such a pronounced effect upon the course of the G-A-S that they deserve special consideration:

Intravenous **fluid administration** has become a routine procedure in the prophylaxis and treatment of shock [189] and numerous investigators discussed the relative merits of blood- or serum-transfusion and the intravenous injection of solutions containing osmotically active colloids (such as isinglass, acacia, polyvinylpyrrolidone, gelatin), sodium chloride, glucose, etc.[190] The efficacy of this therapy is mainly based upon the maintenance of a normal blood-volume by raising the fluid-content and the osmotic pressure within the vascular bed. However, glucose, as a source of readily available energy, and sodium, because of its specific pharmacologic properties appear to have special functions in this connection, apart from their osmotic effects. The therapeutic value of blood or plasma is so much greater than that of most other transfusion-fluids that it can hardly be explained entirely by its colloid-osmotic effect. Some workers believe that during stress the blood may become depleted in certain labile substances and that only blood- or plasma-transfusions can restore these.[191] (Cf. also deficiency-theory of shock: p. 93.)

Sodium salts administered intravenously or even orally, suitably diluted in water, have also given considerably better protection against various types of stress (e.g., trauma, heat, burns, hemorrhage) than could be accounted for merely by their osmotic pressure. Whenever possible, it is best to administer Na in the form of slowly dissolving non-irritating salt-tablets, specially prepared for this purpose.[192] Apparently here the Na-ion plays a specific effect.[193] NaCl also proved beneficial in protecting rats against such typical alarming stimuli as colchicine and iodoacetate.[194] Perhaps the corticoids help to make sodium available to those structures that require it during stress.

Sodium **succinate** injected intravenously is claimed to bring about considerable improvement in the condition of dogs in tourniquet-shock. "This may

[188] Freeman et al. B27052/38, B27053/36.
[188a] Jourdan et al. B45997/49.
[189] Allen A18905/39, Harkins 82895/42, Moon A16304/38.
[190] Allen A18905/39, Anonymous B26226/40, B26225/43, B26869/44, Bovet et al. B3181/47, Cleghorn B2571/47, Davidson 55943/26, Elman and Brown B26231/43, Freeman A32609/35, Hayden B26224/43, Heyl and Janeway B26223/42, Legueu et al. A32661/33, Meyer et al. 88840/45, Mylon et al. A59010/43, Olitzki et al. 84474/42, Robineau A32662/33, Roscher B25560/33, Scudder and Elliott B26227/42, Sonobe A8283/37, White et al. B41506/41, Winkler et al. 93261/46.
[191] Mylon et al. A59010/43.
[192] Consolazio et al. B37554/47.
[193] Cullumbine B41625/48, Fox B18169/44, Frank et al. B26188/45, Harkins 99836/47, Levine et al. B26185/44, Mylon A59010/43, Rosenthal B26228/43, B26229/43, Tabor and Rosenthal B26187/47, Wiggers and Ingraham 95649/46.
[194] Clark and Barnes A33441/40.

indicate a definite disturbance in the earlier stages of carbohydrate breakdown" since glucose is not equally effective.[195] Sodium **lactate** proved to be beneficial in burn-shock.[195a]

Antipyretic drugs (e.g., quinine) have been highly recommended as adjuvants in the treatment of various diseases causing pronounced catabolism (e.g., typhoid fever, tuberculosis). Although these compounds diminish phagocytosis and the antibody-titer, they are allegedly beneficial because they decrease the metabolic rate and impede exaggerated defense-reactions against the causative pathogenic agents.[195b]

Certain **autonomic drugs,** for instance, adrenergic blocking agents, such as *dibenamine,* shorten the survival of rats in tourniquet-shock,[196] while the same drug allegedly exerts a marked protective effect in mice in which an A-R is produced by colchicine.[197]

Since endogenous adrenaline discharge was believed to play an important rôle in the response of the adrenals and the thymico-lymphatic apparatus during the A-R, it is noteworthy that in these latter experiments "the histological changes of the alarm reaction in the thymus and the adrenals provoked by epinephrine were reversed by dibenamine but those provoked by colchicine were not".[198]

Allegedly, in the dog, dibenamine decreases the incidence of irreversible shock after extensive hemorrhage or trauma. This is apparently due to inhibition of excessive vasoconstriction during the later stages of shock.[199] Conversely, experiments with the sympathetic-blocking agent ergotamine, showed that the resistance of cats to hemorrhage is just as markedly diminished by this drug as by total sympathectomy.[200] Apparently, in the early stages of the shock-phase, adrenergic peripheral vasoconstriction is useful because it helps to shift blood to vital organs (brain, heart, lung); later, however, when tissue-anoxia becomes severe, this excessive vasoconstriction may expedite the onset of the "irreversible shock" due to the general, anoxic tissue-damage. Thus sympathectomy and sympatholytics may be helpful or detrimental, depending upon experimental conditions (cf. p. 75).

Attempts to increase the resistance of rats during tourniquet-shock and of dogs after severe burns, by pretreatment with *benadryl* yielded no definitely conclusive results.[201] Under certain experimental conditions *TEA* appears to improve the prognosis in dogs subjected to hemorrhagic shock,[202] but the underlying mechanism is not quite clear.

Remarkable beneficial results were allegedly obtained in the treatment of experimental shock, in dogs, by *cholinesterase.* Unfortunately, in this series, no recovery experiments were done, all animals being killed after about six hours. However, it would be very desirable to repeat and extend these observations, since they not only hold therapeutic promise, but are also likely to shed light upon the participation of the vegetative nervous system in various systemic stress-phenomena.[203]

[195] Mylon et al. A59010/43, B419/44.
[195a] Fox B18169/44.
[195b] Albert-Weil **99366/34.**
[196] Wiedeman and Lewis B37752/49.
[197] Seifter et al. B32930/49.
[198] Seifter et al. B32930/49.
[199] Ingraham et al. B17694/48, Remington et al. B27054/48, Wiggers et al. B27055/47, B23362/48.
[200] Schlossberg and Sawyer 7161/33.
[201] Ederstrom et al. B33096/48.
[202] Glasser and Page B28222/48.
[203] Schachter B929/45.

Inhalation of **oxygen** in dogs damaged by trauma, hemorrhage or histamine-injections, exerted a beneficial effect, especially if concomitantly the CO_2-tension of the air was also raised. This has been ascribed to the increased amount of oxygen made available to tissues which had been rendered anoxic by the peripheral circulatory failure characteristic of the shock-phase.[204] On the other hand the claim that **cytochrome C** mitigates the effects of anoxia could not be substantiated.[204a]

Diet. — The diet also plays a very important rôle in determining the course of the G-A-S. This will be discussed in more detail when we describe those organ-changes (nephrosclerosis, periarteritis nodosa, adrenal cortical hypertrophy, myocarditis, etc.) whose development, under the influence of systemic stress, is conditional upon dietary factors, especially protein and sodium (cf. Hypophysis, Adrenal, Kidney, Cardiovascular system). Here we shall review only those nutritional influences which may affect resistance in general.

We have repeatedly emphasized that **fasting** greatly increases the stressor effect of most alarming stimuli.[205] This is presumably due to the aggravation of tissue-catabolism during the G-A-S by withholding exogenous sources of energy. Anoxia appears to be an exception to this rule, inasmuch as prolonged starvation tends to raise resistance to the stress of oxygen want in the rat.[206] However, after a short fast (12 to 24 hours) resistance to anoxia is markedly decreased; starvation must be prolonged to 48-96 hours before a rise in resistance is obtained. Since starvation in itself is an effective alarming stimulus and within 48-96 hours produces pronounced counter-shock phenomena with hyperglycemia, the rise in resistance to anoxia at this time might well be an example of "crossed resistance".[207] In the guinea-pig papain-shock and anaphylactic-shock are also attenuated by fasting.[208] This is apparently in agreement with the above interpretation since anaphylactic and anaphylactoid reactions are known to be particularly well inhibited by "crossed resistance" elicited by any alarming stimulus (cf. p. 55).

Experiments concerning the influence of the dietary **fat** and **carbohydrate** upon the ability of rats to adapt themselves to extremes of temperature led to the following conclusion: "a diet rich in fats is decidedly superior to one rich in carbohydrates (both diets being equicaloric and equivitaminic) for adaptation and resistance to cold on the part of the animals, and that a diet rich in carbohydrates and poor in fats is much more favorable than one rich in fats for conferring resistance to heat".[209]

It certainly depends upon the quality of the stressor whether high- or low-carbohydrate-diets will best help resistance against it. Some stressors are predominantly "glucoclastic" (e.g., acute starvation, exercise, insulin, phloridzin), others "proteoclastic" (e.g., chronic starvation, ionizing radiations, hemorrhage, vesicants) and the diet should be adapted to special requirements. In general a very acute demand for energy is met by carbohydrate combustion and certain readily utilizable high-carbohydrate foods, e.g., "energetikum" (30 gm. dextrose, 30 gm. levulose and 20 gm. ethyl alcohol), have been recommended to combat the stress of acute muscular fatigue, sepsis, hepatic insufficiency, etc.[210]

[204] Frank and Fine A26173/43, Wood et al. A34379/40.
[204a] Michel and Scheinberg B38096/47.
[205] Selye 36032/36, 38798/37, B1204/46.
[206] Laugier and Leblond A72915/43, Smith and Oster 93055/46.
[207] Laugier and Leblond A72915/43.
[208] Zacco and Pratesi B37560/47.
[209] Dugal et al. 93308/45.

Observations in rats in which traumatic shock was produced by the Noble-Collip drum showed that **protein**-deficient diets decrease resistance to this type of stress, while the addition of gelatin to such diets exerts a definite protective action.[211] The importance of adequate nitrogen intake during recovery from trauma is one of the principal indications for the use of parenteral alimentation in surgery.[212] However, extensive clinical studies led to the conclusion that diets rich in calories and protein do "... not seem advantageous during the catabolic phase following a burn, even though the nitrogen deficit can, at times, be minimized. In fact, such therapy seems to be harmful when given during the first week or two".[213]

Systematic experiments on rats suggest that certain amino-acids, particularly **methionine**, exert a highly beneficial effect in combatting burn-shock in rats, but only if treatment is begun before the thermal injury.[214] (Cf. Protein Metabolism.)

Special attention has been given to the possible rôle of **ascorbic-acid** in adaptation and the development of the G-A-S. Experiments on the rat (a species not dependent upon exogenous ascorbic-acid since it can synthetize this vitamin) revealed that during exposure to cold the ascorbic-acid content of the tissues (liver, kidney, testes) increases by about 50%. This was regarded as a physiologic response during adaptation to cold, especially since rats which failed to resist, and died in the cold, had a very low ascorbic-acid content.[215] Accordingly, the length of survival, in rats chronically exposed to cold, could be markedly prolonged by ascorbic-acid-treatment.[216]

In guinea-pigs (which depend upon exogenous ascorbic-acid since they cannot synthetize it) cold-tolerance is actually proportional to the daily intake of ascorbic-acid. Furthermore, excessive amounts of ascorbic-acid are retained in the tissues of guinea-pigs exposed to low temperatures and the resulting ascorbic-acid-level in various tissues — especially in the adrenals — parallels the degree of their adaptability to cold.[217]

In man, however, administration of excess ascorbic-acid failed to raise the ability to withstand repeated exposures to cold.[218]

Resistance of guinea-pigs to hemorrhagic shock can be raised by ascorbic-acid [219] especially upon intravenous or intraperitoneal administration, if the vitamin is given before irreversibility to transfusion had been established. Curiously, oral administration of this vitamin proved ineffective.[220]

It has also been claimed that ascorbic-acid increases the resistance of guinea-pigs to anaphylactic shock [221] and of guinea-pigs, rats and mice to traumatic shock.[222] In clinical medicine, ascorbic-acid has been recommended for the prophylaxis of surgical shock.[222a]

[210] Gremels B37632/48.
[211] Noble and Toby B3012/45, Toby and Noble B41749/47, B41750/47.
[212] Elman **B23376/48.**
[213] Abbott et al. B29501/46.
[214] Hazan and Treadwell B23897/48, McCarthy and Bodkin B38224/46.
[215] Dugal and Thérien B2210/47, B2569/47, Thérien and Dugal B4624/45.
[216] Dugal and Thérien B23325/48.
[217] Dugal and Thérien B2569/47, B2210/47, B36429/49, Thérien and Dugal B3157/47.
[218] Glickman et al. 93060/46.
[219] Stewart et al. B26866/41.
[220] Dosne B17586/47.
[221] Ogawa B33790/40, Takemoto B33789/40.
[222] Ungar A57983/43.
[222a] Holmes B40756/46.

Acrodynia, a sign of **pyridoxine** deficiency, appears in rats earlier at 40°F. than at comfortable temperatures. Since acrodynia resembles chilblains, it was suggested that susceptibility to the latter may depend upon the pyridoxine-reserves in the body and that pyridoxine could be of value in the prevention of chilblains.[223] Significantly, the x-ray resistance of mice allegedly rises after pyridoxine administration.[224]

It has been stated that **thiamine** deficiency in pigeons hastens the appearance of edema and sciatic-nerve degeneration after immersion of the feet in cold water.[225] The data in this report do not show whether the more rapid appearance of deficiency symptoms was caused directly, by exposure to cold, or indirectly, through increased consumption of the deficient diet. Other observations indicate that the minimum requirement of thiamine tends to increase parallel with the surrounding temperature.[226]

Observations in man failed to reveal any improvement in cold tolerance following excessive administration of thiamine, **riboflavin** and **nicotinic-acid.**[227] On the other hand, the resistance of rats to anoxia is allegedly much increased by nicotinic-acid or its amide.[228]

Considerable attention has been given to the effect of **"vitamin-P substances"** of the flavonoid series in combatting the damage caused by ionizing radiations, especially because these compounds diminish capillary fragility. In dogs to which the flavonol-glucoside "rutin" was given, it not only reduced the hemorrhagic diathesis, normally produced by single-dose total-body-irradiation, but also considerably decreased mortality. Since here the control of purpura was achieved in spite of thrombocytopenia and other typical manifestations of x-ray damage, it has been suggested that rutin either decreases vascular disintegration or promotes its repair.[229] Essentially similar, beneficial results were obtained in guinea-pigs with a flavonoid preparation derived from lemons.[230]. However, other experiments led to the conclusion that " . . . rutin in the doses used was of no value in improving the survival of mice. The data presented suggest that rutin may have been harmful inasmuch as all rutin-treated groups died at a significantly faster rate".[231]

Perhaps some of the apparent contradictions in these reports are due to the use of different animal-species and variable experimental conditions. The activity of "vitamin-P substances" largely depends upon the simultaneous availability of vitamin-C, which only some species can synthesize. Subsequent systematic studies, with a large group of flavonoids, showed that resistance to single-dose, total-body x-irradiation is significantly increased by rutin, hesperidin, epimerized d-catachin, homoeriodictyol and morin. These substances exhibit increasing activity in the order mentioned. Several other flavonoids proved to be inert. However, ascorbic-acid, which in itself was of no value, endowed certain inactive flavonoids (e.g., quercitin) with a protective effect. It is suggested that "previous misunderstanding of the nature of vitamin-P has arisen from both the failure to recognize that several flavonone analogues possess very similar anti-hemorrhagic activity and that ascorbic acid has the capacity to potentiate activity in other flavonones".

223 György B26002/38.
224 Goldfeder et al. B25104/48.
225 Champy and Coujard B26001/40.
226 Robinson B26003/43.
227 Glickman et al 93060/46.
228 Calder B23890/48.
229 Field and Rekers B38225/49, Rekers and Field B33764/48.
230 Clark et al. B28231/48.
231 Cronkite et al. B31726/49.

Incidentally, this same study revealed that potent hyaluronidase inhibitors, such as dopa and sodium-gentisate, fail to influence the course of irradiation-disease in dogs. Hence, it was assumed, in contradiction to some earlier workers, that hyaluronidase "plays little or no rôle in the evolution of this disorder".[232]

"Vitamin-P-substances" have also been claimed to increase resistance against anoxia in mice. This is due to the fact that they inhibit the hemorrhagic lung-edema which is usually the cause of death from acute, intense oxygen lack. This inhibitory effect has actually been used as a basis for the bioassay of "vitamin-P",[233] but a number of other substances, not known to have any specific effect upon capillary fragility (e.g., propylene-glycol, ethylene-glycol, ethyl-alcohol, glucose), give similar results. Hence, the test cannot be regarded as specific for "vitamin-P".[234] As we shall see later, it is a typical characteristic of the A-R to inhibit acute, hemorrhagic pulmonary edema produced in various ways. This appears to be one example of the "defocusing" of highly specific reactions by systemic stress. It is possible that the above substances which give a positive reaction in this test also do so because they produce an A-R (cf. also: Lung, Cardiovascular system).

The x-ray-tolerance of mice is allegedly increased by **folic acid,**[235] but this requires confirmation.

Available data, concerning the possibility of raising resistance to systemic stress by vitamins, in amounts exceeding the minimum daily maintenance dose, failed to give any clear-cut and uniform results. However, some experiments — especially those with ascorbic-acid — are sufficiently encouraging to warrant further work along these lines.

Other factors. — The important influence which **weather** and **climate** exert upon the response of the body to stress, has been the subject of much study. The possibility has been considered that climatic factors may themselves act as alarming stimuli and thus influence adaptability through the G-A-S and particularly the adrenals.[236] Since climate and weather are very complex stimuli, their objective, scientific analysis is difficult, but this should not discourage our efforts to elucidate their, certainly far-reaching, influence upon physiologic and pathologic life.

The **sex** of the individual likewise influences the course of the G-A-S. In most animal species, the male has a smaller adrenal than the female and testoids decrease, while folliculoids increase, adrenal-size.[237] Correspondingly, during exposure to systemic stress, adrenal enlargement and thymico-lymphatic involution are more pronounced than in the female.[238] Furthermore, testoid-administration inhibits the adrenal response during the G-A-S (cf. chapter on adrenals, below). The importance of these sex-differences has not been fully elucidated, but perhaps many of the examples of low resistance, hitherto vaguely ascribed to "maleness"[239] could profitably be reconsidered from this point of view.

The **age** of the animal has a most important bearing upon the manner in which it develops a G-A-S. During the first few days of life the rat adrenal

232 Field and Rekers B37300/49.
233 Majovski et al. 84778/44.
234 Raiman and Necheles B33739/47.
235 Goldfeder et al. B25104/48.
236 Petersen A34994/40.
237 Selye **94572/49.**
238 Selye 38798/37.
239 Hamilton B29329/49.

responds poorly to stress although it is normally sensitive to ACTH.[239a] After the first two weeks of age, however, young, growing animals, exposed to systemic stress, develop an A-R very readily and exhibit particularly marked catabolic phenomena and adrenal-cortical enlargement.[240] Perhaps the change from anabolism to catabolism, occasioned by systemic stressor agents, is especially damaging at an age when the growth-impulse of the body is normally maximal. Conversely, young animals are more efficient than old in acquiring adaptation to new types of stressors and in maintaining it for a long time. This may be due to the gradual loss of "adaptation energy" in the course of aging. Interestingly, rats continuously exposed to various stressor agents (continuous nervous irritation, heat, thyroid-extract) "all had aortae with low tensility, resembling that of older animals".[241]

Whatever the explanation, these experimental observations are singularly reminiscent of the excessive responses to stress (e.g., high fever, hallucinations, weight-loss, dehydration) during acute infections and intoxications in infants as compared to adults. We have repeatedly emphasized the many similarities between the stages of alarm, resistance and exhaustion, on the one hand, and infancy, adulthood and senility on the other.

All the pertinent observations can perhaps best be expressed as follows: The very young organism is still unadapted to most things it meets with in life and hence reacts violently to them, but it rapidly acquires and maintains adaptation to almost any change. Conversely, the adult has already acquired adaptation to most of the stimuli he is likely to encounter and has become resistant to them, but gradually the power of learning how to meet new situations or to withstand fatigue during long-continued stress is lost. Then, in senility, all types of adaptive reactions break down.

In retrospect, it is remarkable how generally these rules, derived from animal-experimentation, are applicable to various aspects of human life, including both physical (trauma, infections, intoxications, etc.) and psychic (intellectual and emotional) stress-situations.

Resistance Diseases of Adaptation

This chapter will deal with diseases apparently due to derangements of the adaptive mechanism, whose principal manifestation is a failure of resistance in general. We shall not attempt to make the list complete — this would be futile since any stressor can eventually cause exhaustion with a breakdown of resistance — it will suffice to select a few particularly striking examples of this group to illustrate how they fit into the G-A-S concept.

Shock. — In the following paragraphs it will be our task to consider shock as a disease of adaptation. But what is shock? This fundamental question has been asked by so many investigators, so often and in so many different ways, that the very volume of the resulting literature became a major handicap to progress. Today, no investigator can expect to acquire an adequate familiarity with all the intricate aspects of the shock-problem which have been raised in pertinent papers and, hence, their complete integration into a single concept has actually never been attempted. It throws a truly devastating

[239a] Jailer B44799/49.
[240] Selye 38798/37, B1204/46.
[241] Herrington and Nelbach A37641/42.

light upon the lack of common sense with which certain medical problems are approached, to realize that so many workers attempted to "explain" shock without attempting to crystallize in their minds what they meant by this term.

As we said in the introductory section (cf. Definitions), usually one or the other sign of the shock-syndrome was singled out as its basic feature and then the condition was defined as being characterized by this manifestation (e.g. prostration, hypotension, hemoconcentration). Yet, it is admitted that any one of these signs may be manifest although there is no shock, and conversely, that shock may develop in the absence of one or the other of these signs. It has also been claimed that shock is due to the failure of a certain organ (e.g., the liver, adrenals, heart, vessels, kidney) yet, a condition which according to current concepts qualifies as shock can develop in a heart-lung preparation, the perfused hind legs of a frog, an isolated blood-vessel strip, or even a single cell.

A loss of the selective permeability of capillary and cell-membranes in the sense of a "serous inflammation", is certainly a characteristic feature, probably the most characteristic feature of shock, but it is only one manifestation of the phenomenon, not its cause. The membranes lose their ability to maintain the characteristic individuality of the biologic units which they delimit (e.g., the cells of tissues or the circulating blood from intercellular fluid), because they are no longer able to retain or absorb certain substances selectively. However, to state this is merely another way to say that partial death, "necrobiosis", has set in.

We therefore prefer to consider shock merely as a condition of *suddenly developing intense systemic damage,* in other words an acute, generalized "necrobiosis". For the rational of this formulation, we refer the reader to the section "definitions". Let us merely add here that the word "systemic" should in the present instance be interpreted as generalized to whatever system is under consideration . This is not necessarily the organism as a whole but may be a perfused organ or even a single cell. It has empirically become an inherent part of the shock-concept that it must involve the whole of a biologic unit; injuries strictly localized to one part of an organism, a single organ or a single cell, are not so designated unless they secondarily lead to generalized damage involving the entire unit.

The most important conclusions to be derived from such considerations are: (1) that any number of qualitatively quite distinct derangements can lead to shock, hence it would be futile to search for a single pathogenic mechanism; (2) shock is a phenomenon of generalized necrobiosis always involving a biologic unit in its entirety; (3) empirically we have come to consider only acute damage as shock, slowly progressing impairments (wasting, exhaustion) are not so designated.

We realize that our definition of shock is rather broad and non-specific but this must be so, since shock is a non-specific phenomenon.

Nevertheless, we feel that it will be instructive to review briefly the most important observations which led to the formulation of the current more specific shock-theories. This will help us to outline the major features of shock; at the same time, it gives us an opportunity to verify to what extent various theories are compatible with the observed facts. It would be futile to review all these theories in detail, but our summary will serve as a key to the relevant literature.

While reading the following paragraphs, keep in mind that the two greatest problems in interpreting the manifestations of shock are: why do so many different agents lead to essentially the same syndrome and how does injury to a limited part of the body affect the entire organism.

Some of the older theories of shock need not be discussed, since they have been almost unanimously rejected by modern investigators. Suffice it to mention that, among other factors *acapnia*,[242] *acidosis*,[243] *fat embolism* [244] and *contraction of the hepatic vessels* [245] have been considered, more or less seriously, as being of pathogenic importance. Here we shall concentrate our attention only upon those shock-theories which in our opinion deserve serious consideration.

(1) *Impaired circulation.* — It is undoubtedly true that during shock there is usually a grave impairment of circulation. The patient is pale because the arterioles of the skin and mucous membranes are constricted, but there develops an atony of the capillaries in internal organs which causes sequestration of much blood in the viscera and hence the circulating blood-volume and the blood-pressure drop.[245a] "As a result of decreased filling of the heart, the cardiac output is lowered to a level at which cardio-acceleration and vasoconstrictor reflex no longer compensate and the blood-pressure falls. This classical concept still holds true but as a result of much research, it has undergone modification .. .".[246] Indeed, one of the much quoted definitions of shock claims it to be "a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood-volume, decreased cardiac output (reduced volume flow) and by increased concentration of the blood.".[247] Yet, this definition is hardly valid in every case; for instance, it excludes spinal shock, which is generally considered to result from vasomotor paralysis and yet leads to the typical morphologic and chemical changes characteristic of shock.[248] It also fails to account for shock resulting from excessive muscular exercise, which is often accompanied by hemodilution.[249]

In experiments with the "heart-lung-dog preparation", venous flow and cardiac output are controlled and the total peripheral resistance can be calculated under these conditions, "shock can develop without progressive reduction or even with a rise of venous pressure or cardiac output and it cannot be prevented or cured by increasing venous inflow or cardiac output". In this preparation a fulminant, irreversible shock develops spontaneously due to "a pronounced decrease in total peripheral resistance, which enabled the animal to store, over and above its own blood-volume, quantities of blood equal to 25% of its body-weight or four times its own blood-volume. Autopsies revealed no storage depots other than the mucosa of the upper intestine, which was always edematous, intensely congested and often hemorrhagic." Although cardiac output at equivalent venous pressures also decreased, indicating that depression of the myocardium occurred; this was not an initiating

[242] Fortier B24848/49, B26249/48, Henderson 47096/10, Henderson and Scarbrough 47097/10.
[243] Beznak et al. A39634/40, Guthrie 59493/17, 59496/18, Koehler et al. A32691/23, MacLeod A32690/21, McEllroy A32689/18.
[244] Bissel A32688/17, Groeninqen A32683/885, Porter A32686/17, A32687/19, Warthin A32684/13.
[245] Mautner and Pick 13044/22.
[245a] Selkurt et al. B38544/47.
[246] McMichael 89888/45.
[247] Moon **A16304/38**, 78336/40.
[248] Selye 38798/37.
[249] Selye A15674/39.

factor nor was it necessary to produce an irreversible state.[250] Observations on dogs in which shock was induced by burns also showed that capillary atony, especially in the visceral organs, occurs rapidly (within one minute) and it was stated that "this is therefore the primary disturbance and is not secondary to anoxia, nor is it terminal".[251] There may also be very severe cardiac lesions in burn-shock, but the claim that these play an important rôle in the resulting systemic stress [252] is yet to be proven.

As shock progresses, the initially accelerated pulse tends to become extremely slow and the blood-pressure, which at first was maintained, suddenly falls; simultaneously, there is vasodilatation in the arterioles of the skeletal musculature. These changes were ascribed to a "vaso-vagal reaction", especially since the peripheral vasodilatation can be abolished in the forearm muscles by blocking the main nerves at the bend of the elbow, which suggests that it is mediated by autonomic nerves.[253]

Eventually shock becomes irreversible because the vessels no longer respond to vasopressor agents or any other therapeutic procedure.[254] In cases of severe experimental shock "transfusions of blood or plasma no longer suffice to save life, even though the corpuscle count is kept at a normal or reduced level and all indications point to normal or increased blood-volume together with adequate propulsion of the blood. Theories which regard these as the determining factors in shock are thus invalidated".[255] However, it must be kept in mind that even when shock reaches this otherwise "irreversible" stage, for instance in dogs with hemorrhage, recovery can still be accomplished, by separate vivi-perfusion of the liver through cross circulation with a healthy donor dog. From such observations it has been concluded: "(1) that liver damage is intimately related to the collapse of the peripheral vascular mechanism in advanced hemorrhagic shock, (2) that restoration of the integrity of the liver is necessary for recovery of function of the peripheral vascular system in advanced hemorrhagic shock, and (3) that restoration of this aspect of liver function can be accomplished by providing adequate blood-flow from a donor dog to the liver, even after 'irreversibility' to transfusion has been demonstrated".[255a]

(2) *Dehydration and hemoconcentration.* — This theory is closely related to that mentioned above. It is based on the assumption that the symptoms of shock are primarily due to dehydration. This allegedly results from increased capillary permeability with consequent loss of plasma, especially into the directly damaged area.[256] Indeed a decrease in blood-volume was considered to be so obviously the basic feature that it has been proposed to substitute the term "exemia" for shock.[257] However, this conclusion was largely based upon investigations with methods for the measurement of blood-volume and capillary permeability which have since been found to be unreliable. A recent review criticized the errors involved in the old techniques and after surveying

[250] Wégria et al. A56861/43.
[251] Prinzmetal and Bergman B3109/45.
[252] Fain 75452/39.
[253] McMichael 89888/45.
[254] Richards B19251/48.
[255] Allen A18905/39.
[255a] Seligman et al. B40998/47.
[256] Allen A18905/39, Bell et al. A15746/38, Blalock 9290/31. 9291/31, Blalock and Beard 8726/32, Blalock and Cressman A33060/39, Davis A31851/40, A31852/40, Harris and Blalock 9294/31, Hepler and Simonds A15174/38, Moon A16304/38, Sloan and Klaus 82174/42.
[257] Cannon A32617/23.

the observations made with allegedly unassailable methods stated that there is "overwhelming evidence against the concept of generalized capillary leakage" during shock.[258]

On the other hand, there is no doubt that increased capillary leakage is always demonstrable at the site of injury. Sometimes the reduction in blood-volume can be accounted for by such fluid-loss into the directly damaged tissue. Elsewhere in the body, fluid may be even simultaneously absorbed into the blood. Of course, if the damaging agent directly affects large parts of the body (e.g., peritoneal injuries, septicemias) widespread capillary injury and leakage will ensue but this is not a prerequisite for the development of shock, since it does not occur in other cases.[259] Although the local fluid-loss at the site of injury is usually not of sufficient magnitude to account for all the changes observed,[260] in certain conditions it can be a major factor, for instance in extensive burns, where plasma-leakage from the wound surface is considerable.[261] The same is true of "dehydration-shock", which is produced in experimental animals by subcutaneous injections of hypertonic NaCl-solution. Since here the local fluid-accumulation is poor in protein, the protein-loss in itself is not of major importance.[262]

Certain investigators do not entirely subscribe either to the dehydration or to the toxic theory of shock and assume that both fluid-loss and the toxic factor are probably involved.[263] While this is true, there is no doubt that in certain instances many more factors play equally important rôles in the pathogenesis of shock.

The categorical denial of a generalized capillary leakage during shock — though accepted by some of the most prominent authorities in this field [264] — should be qualified. What the observations actually showed was merely that following a local damage, in man and certain shock-sensitive animals, the clinical manifestations of the shock-syndrome can develop without there being generalized capillary leakage. Even death from shock may ensue before capillary permeability is noticeably augmented at a distance from the direct injury. Our observations on relatively shock-insensitive animals (e.g., the rat) showed, however, that localized lesions (circumscribed trauma, spinal-cord transection) or stressors not involving any local tissue injury at all (e.g., nervous stimuli, cold) can cause widespread and pronounced capillary leakage during the ensuing A-R. This is manifested by the formation of edema, and sometimes even leucocytic infiltration or capillary hemorrhages in internal organs, especially the thymus, lymph-nodes, adrenals, hibernating gland and upper gastrointestinal tract. It will be noted that these are the organs most acutely affected by the A-R; hence, in a modified sense, we may still speak of the capillary damage as due to local injury, but it must be understood that the latter occurs as a result of humoral or nervous mediation at a distance from the primary insult. There are other examples of increased capillary permeability at sites not directly affected by the stressor agents, e.g., the formation of transudates in the large serous cavities, the tendency

[258] Gregersen **96515/46.**
[259] Gregersen **96515/46.**
Koletsky and Gustafson **93288/46.**
McMichael **89888/45.**
[260] Hamilton and Haist 93309/45.
[261] Gregersen **96515/46.**
[262] Davis A31852/40.
[263] Ashworth and Haist 97325/47, Cleghorn B2573/46.
[264] Gregersen 96515/46,
McMichael 89888/45.

towards the development of lung and brain edema. All these changes occur not only in experimental animals but even in man during the A-R, though they are not necessary prerequisites for the development of shock in the surgeons' sense of this term.

A very slow and comparatively circumscribed capillary leakage at a distance from the direct injury is not detectable with current (e.g., dye methods or radioactive protein) techniques. Nevertheless it could have a most important influence upon the course of disease, for instance, in the case of slowly progressing brain- or lung-edema. We insist upon this point particularly because it has been the subject of so much controversy in the literature and caused considerable confusion.

To express our own opinion most succinctly, we may say that any systemic stressor can cause capillary leakage even in tissues which are not directly exposed to it. Indeed such capillary leakage is a characteristic feature of the shock-phase of the A-R, yet, it is not always manifest since shock and even death may ensue before such capillary leakage could assume detectable proportions.

(3) *Endogenous intoxication.* — The possibility has been discussed extensively that shock may be due to a systemic intoxication by endogenous metabolites formed in the traumatized tissues themselves; [265] indeed the existence of such an auto-intoxication during secondary shock has been considered to be so characteristic as to justify the renaming of this condition as "histotoxicosis".[266]

In general the evidence for or against this theory was derived from observations made with three types of techniques:

(A) It was noted that if the blood-circulation of a limb is temporarily obstructed (for instance in man, by heavy debris during a bombardment or in animals by temporary vessel-ligatures or tourniquets) shock develops only after *release of the vessel-occlusion.*[267] This was taken to mean that during obstruction of the circulation, toxic metabolites accumulate in the limb, but these do not cause shock until they are allowed to enter the systemic circulation. The much discussed crush syndrome is also especially common among individuals who were partly buried under falling debris. Such patients remain in comparatively good condition until their compressed limbs are freed and circulation re-established (see below).

This basic observation is definitely established; however, its interpretation in favor of the toxemia theory is debatable. It has been claimed that after release of the occlusion the pronounced loss of fluid into the damaged limb (due to a local increase in capillary permeability) causes hemoconcentration and a decrease in blood-volume, which in themselves suffice to cause shock. Another possibility

[265] Allen A18905/39,
Andrews and Hrdina 85723/30,
Beznak et al. A57371/42,
Bottin 78625/39,
Freeman and Schecter A55985/42,
Green et al. 85844/45,
Hilgenfeldt 38008/36,
Katsenstein et al. A59009/43,
Manzini 76996/39,
McIver and Haggert 14025/23,
Milhorat et al. A58525/43,
Muirhead and Hill B724/44,
Takeda 67165/36,
Toby and Noble 85303/44,
Wilhelmi **B18793/48.**
Wilson et al. A32678/37.
[266] Allen A18905/39.
[267] Cannon A32617/23,
Debie et al. B38222/46,
Friedberg and Katz 88843/45,
Tabor and Rosenthal A96000/46.

is that the tissues of the temporarily anoxemic limb consume some vitally important metabolite and thus induce shock due to deficiency (cf. deficiency theory below). Much emphasis has been placed upon the observation that if, immediately after release of the occlusion, the damaged limb is mildly compressed (by bandage or a tightfitting cast) the onset of shock is delayed or even prevented. This has also been taken to signify that loss of fluid into the limb is normally the cause of post-occlusion shock, since mild compression does not abolish circulation through the limb and hence could not eliminate an endogenous intoxication. However, compression diminishes free circulation through the damaged tissue, especially since some capillary leakage still occurs and the resulting edema further impedes the flow of blood. This could of course also interfere with the effective discharge of hypothetical shock-toxins, or impede the excessive utilization of blood-borne principles needed elsewhere in the body.

(B) Considerable work has also been done with various types of *cross-circulation experiments*. In these, either the entire shocked animal, or merely a circumscribed directly injured part of the body, are connected by cross-circulation with an otherwise intact recipient animal.[268] Here the traumatized tissue of the donor is connected with the recipient only through the blood-stream; hence, the development of shock in the latter was again ascribed to blood-borne toxic substances. In experiments of this type the possibility of blood- or plasma-loss into the donor preparation can be checked, but it is not possible to exclude the utilization of vitally important substances by the traumatized tissue. Thus, here again, positive results are equally compatible with the intoxication- and the deficiency-theories.

(C) Probably the least assailable techniques used in the search for auto-intoxication-products are those in which the *toxicity of tissues or blood taken from a shocked animal* is assayed by injection into other animals.[269] However, experiments with this technique gave extremely variable and contradictory results.

Adrenalectomized animals are notoriously sensitive to all types of toxic substances and unusually subject to shock. Hence, we tested the venous blood of a directly damaged extremity by injecting it into adrenalectomized mice. It was no more toxic than that coming from an intact limb.[270] This observation makes it highly improbable that toxic substances produced by the directly injured tissue itself could play a major rôle in the pathogenesis of traumatic shock.

In most of the above-mentioned investigations, no specific attempt was made to identify the nature of the hypothetical "shock-toxins", since even their very existence appeared to be highly dubious. Nevertheless, many data in the literature tend to incriminate certain metabolites as being mainly responsible for the development of the shock-syndrome. Among these, special attention has been given to *histamine and histamine-like compounds* in connection with

[268] Giraldi et al. B4037/47, Green et al. A95850/46, B40751/47, Mylon and Winternitz 93053/46.
[269] Eggleton B692/44, Fanconi A32021/39, Heilbrunn A95857/46, Hiestand and Fuller B17686/48, Mason and Richardson B2170/47, B40971/47, Mason et al. B38530/47, Prinzmetal and Bergman B3109/45, Prinzmetal et al. B4493/46, 93536/46, Ramsey and Adler A95901/46, Roome and Wilson 30672/34, Selye 68414/37.
[270] Selye and Dosne A35802/41.

the pathogenesis of shock caused by trauma,[271] burns,[272] cold,[273] peptone,[274] incompatible blood transfusion,[274a] snake-venoms,[275] bee venom,[276] microbial toxins,[277] intestinal occlusion,[278] allergy,[279] and numerous other stressors.[280]

Under certain circumstances there appears to be an actual decrease in the histamine content of the blood during shock.[281] Yet, some investigators [282] believe that in the final analysis it is nevertheless histamine liberation that initiates the A-R-syndrome although, under certain circumstances, increased histamine destruction may overcompensate for increased formation. We have also considered this possibility,[283] but took care to emphasize that there is no irrefutable evidence to support it and that numerous other metabolites might be invoked with almost equal justification. Among these are the energy-yielding adenosine-derivatives, such as *ADP* and *ATP*,[284] *acetylcholine*,[285] various toxic *by-products of blood-clotting*,[286] *thromboplastic metabolites*,[287] certain incompletely identified vasoconstrictor substances,[288] the *leucotaxin* and *necrosin* of Menkin,[289] etc. (Cf. literature on these metabolites under: Metabolism.)

Some investigators rejected the histamine theory of the A-R, favoring the concept that *potassium* may be the shock-producing metabolite,[289a] since "in all conditions given by Selye as suitable to produce the alarm-reaction, there is a rise in the concentration of potassium in the serum".[290] Yet, it is possible to raise the serum-K without eliciting an A-R. Furthermore, animals with hypopotassemia due to DCA-overdosage, are especially prone to develop shock.[291]

Although the blood-potassium rises during shock, according to a critical reviewer of the pertinent literature "recent evidence fails to support earlier

[271] Allen A18905/39, Barsoum and Smirk A32676/36, A44/36, Cannon 13119/22, Chambon et al. B36392/43, Cicardo B23263/47, Csaiky and Magyary-Kossa B38615/47, Dale 11743/20, 9055/32, Hoet 23875/29, Johnson and Blalock 9990/31, Schneider 8972/32, Sierra A32675/35, Urabe 35816/36.
[272] Barsoum and Gaddum A32677/36, Bennett and Drury 9569/31, Feldberg 71340/37, Gaddum 38471/36, 33164/36, Harris 25198/27, Hoet 23875/29, Nagamitu 35299/35, Wilson et al. A32678/37.
[273] Horton and Roth A31817/39, Shimada 39090/35.
[274] Dale 15875/29, Feldberg 71340/37. Feldberg and O'Connor A8289/37, Hayashida A32701/35-36.
[274a] Cicardo B39944/48.
[275] Essex and Markowitz A32681/30, A32682/30, Feldberg 71340/37, Feldberg and Kellaway A7966/37, Kellaway A32679/29, Kellaway and Le Messurier A32680/36.
[276] Feldberg 71340/37.
[277] Feldberg 71340/37, Kellaway and Trethewie A36936/41.
[278] Alberti A54780/41.
[279] Williams B1187/45, B1184/45.
[280] Kellaway B38694/47, Reding 39925/35, Ungar A15416/37, 85462/44, B4934/47, Zacco and Ferrara B39574/49, Zipf 9952/31.
[281] Rose and Browne A32980/40.
[282] Karady and Kovacs B40495/48, MacKay and Clark A15541/38, Ungar 85462/44, Zacco B39571/48,
[283] Selye 36030/36, 38798/37, 68414/37, Selye et al. 38815/36.
[284] Cullumbine B38022/47, Green 89887/45, Green and Stoner B40524/44, B38502/47, Selye et al. 38815/36, Stoner and Green B38479/49, Zipf 8904/32.
[285] Danieloopolu B45612/47, Selye 38798/37.
[286] Freund 12058/20.
[287] Green and Stoner B38502/47, Moreau B29447/48. Moreau et al. B17718/48, B23919/48, Stoner and Green B38571/47.
[288] Page A31299/39, 83887/43.
[289] Cullumbine B38022/47, Cullumbine et al. B38021/47, Menkin B1166/45.
[289a] Cicardo B23263/47, Roos et al. B38603/47.
[290] Kendall and Ingle 68707/37.
[291] Selye 35935/ND.

claims that shock can be attributed to a rise in the blood-potassium level. This is clearly a terminal event".[292]

It would not be profitable to discuss the pertinent literature in detail, since the evidence concerning all these theories is extremely controversial; indeed, as we have said above, the very existence of a shock-toxin is yet to be proven. The above enumeration was meant only to remind the reader of the compounds which have been considered to be shock-mediating metabolites. Additional references will be found in the papers quoted here, as well as in another section ("Metabolism", below) in which we shall examine the effect of the G-A-S upon the metabolism of these compounds quite apart from their possible shock-mediating rôle.

A slightly different formulation of the "endogenous intoxication theory" postulates that the shock-mediators are endogenously produced during acute systemic stress, but not in the directly damaged region. Thus, it has been assumed that toxic substances, and perhaps even live micro-organisms (which are normally retained in the intestine by the lining epithelium which is impermeable to them) may enter the circulation during the A-R. To defend this theory of *enterogenic intoxication,* it was pointed out that orally administered histamine and adrenaline are highly toxic to animals during the A-R, presumably because they are absorbed from the gastrointestinal ulcer surfaces.[293] Interestingly, anoxia is also claimed to increase the permeability of the gastrointestinal tract, thus predisposing, for instance, to food allergy.[294] In the dog, the rapid development of clostridial infection during shock may also be due to invasion of the blood from the damaged gastrointestinal tract.[295]

Absorption of toxic, digestive secretions from the intestine could likewise be involved. Thus, at least the shock due to intestinal obstruction is greatly alleviated if free elimination of pancreatic juice is insured by transplantation of the pancreatic ducts into a non-obstructed intestinal segment.[296]

Another form of endogenous intoxication, by metabolites produced at a distance from the original site of injury, ascribes shock to a derangement of the VEM-VDM system. Allegedly during shock the production of VDM (which originates mainly in the liver) greatly exceeds the secretion of VEM (by the kidney); since VDM renders the blood-vessels insensitive to vasoconstrictor stimuli, hypotension and shock ensues.[297]

All these factors may play a rôle in the pathogenesis of shock, but they are certainly not indispensable for its development. Obviously no substance originating from a tissue other than that directly exposed to injury could be the initiating factor. For example, even if we did accept that the gastrointestinal tract, or the liver, produce toxic metabolites we would still have to account for the mechanism that induces these organs to do so during shock following a limited injury, let us say, to a limb. The gastrointestinal or hepatic derangements might, in such cases, be due to impaired circulation and not to humoral mediation, but this still cannot explain why the circulation in these organs would be impaired by a limited injury to a distant part of the body.

[292] Gregersen **96515/46.**
[293] Selye A8052/38.
[294] Baker B659/44.
[295] Aub B38226/44, B38227/44, Aub et al. B38228/47, Prinzmetal et al. B38230/44.
[296] Bottin B37926/47.
[297] Shorr et al. 89011/45, B19255/48, Zweifach et al. B15859/45.

The most conclusive evidence, against the universal applicability of any among the above-mentioned theories, is that typical shock ensues in completely eviscerated rats, which are deprived of their entire gastrointestinal tract including the liver.[298] Here, we can certainly not ascribe shock to principles coming either from the gastrointestinal tract or the hepatic tissue.

Despite our inability to furnish any definite proof in favor of the intoxication-theory, it must be admitted that the latter is rather attractive. Undoubtedly, many potentially toxic substances can be liberated from injured cells and perhaps our inability to demonstrate toxic concentrations of them in the blood was due to the use of inappropriate techniques. There is one formulation of the toxic theory which has not yet been considered to our knowledge. Perhaps during shock there is *not only an excess production of toxic metabolites, but also an inability to detoxify them.* If this were correct, it would be understandable that neither the tissues nor the blood of shocked animals proves to possess a demonstrable toxicity if assayed on intact recipients. Indeed, even our experiments on adrenalectomized animals may not have been conclusive, since it is possible that adrenal insufficiency does not impede the detoxification of these particular metabolites, while shock does. The toxic metabolites produced by tissue injury may be so readily inactivated that they could only be demonstrated on animals who are already in shock at the time of the experiment. Here they might manifest themselves by aggravating and accelerating the development of a pre-existent shock.

Of course this is a purely hypothetic possibility. We mentioned it here merely because it has not yet been explored and all other efforts to implicate toxic metabolites in the pathogenesis of shock gave inconclusive or negative results.

(4) *Nervous disturbances.* — There is a great deal of evidence suggesting that the nervous system plays an important rôle in the pathogenesis of shock.[299] This is particularly true of the so-called *"primary shock"* (cf. p. 10), that is the shock-like collapse of the circulation which develops almost immediately upon exposure to severe damage. Even authors who believe in the toxic theory of secondary shock postulate that the initial or "primary shock" period is of neurogenic origin.[300]

The terms "syncope" or "collapse" have often been used as synonyms for primary shock, but it is debatable whether this condition should be designated by a special name, suggesting that it is fundamentally different from secondary shock. One of the most outstanding authorities in this field summarized the question as follows: "Collapse designates a sudden failure of the circulation. When this presents, as it usually does, the features embodied in the definition of shock, the terms should be regarded as interchangeable".[301] Yet, others believe that primary and secondary shock are two entirely different conditions, mainly because the changes in the blood-count characteristic of the latter, are usually not found in the former. Hence, it has been stated that "it is questionable whether the name shock should continue to be applied to both".[302] In our opinion the irregularities in the blood-count, which occur during the first hour of the shock-phase in the A-R (cf. also: "Blood-count") are not sufficiently

[298] Selye A8052/38, 35935/ND.
[299] Crile 12245/21, Hilgenfeldt 38008/36.
[300] Gaujard 97306/46, Laflaquière 97307/42.
[301] Moon A16304/38.
[302] Allen A18905/39.

constant and important to justify the distinction between two different types of shock. In any case, such terms as "collapse" [303] and "syncope" [304] have never been clearly defined and in common parlance they are used as more or less synonymous with "primary shock".

The fact that strong *nervous stimuli can act as systemic stressor agents* has repeatedly been mentioned (cf. "Alarming Stimuli" above). As such they not only cause "primary shock", but also secondary shock and if they are sufficiently prolonged, they can produce all three stages of the G-A-S. Among the nervous stressors, strong emotions (e.g., rage, fear), spinal-cord transection and audiogenic stimuli were most commonly used in studies concerned with the G-A-S.[305] Even shock caused by intestinal obstruction has been considered to depend largely upon nervous irritation.[306] However, preliminary exclusion of the gastrointestinal tract's extrinsic nerve supply does not influence the survival time of cats in which shock is produced by intestinal obstruction.[307] (Cf. also p. 75.)

Since burns cause a great deal of pain, it has been assumed that nervous stimuli probably play a particularly important part in the pathogenesis of shock produced by them. Nevertheless spinal-cord transection fails to prevent the onset of shock produced by burning the de-afferented part of the body in rats.[308] As we have stated in connection with the toxic theory, shock is also produced in animals which are connected with traumatized tissue only by way of blood-vessel anastomoses.

All these observations clearly show that shock can develop in the absence of nervous stimuli, although the latter may act as systemic stressors and hence, like so many other agents, they are also capable of producing shock.

The elimination of unnecessary fear and pain during operations greatly diminishes the incidence and severity of shock in man,[309] presumably because this reduces the number of stressors which affect a patient who undergoes a surgical operation. Experiments planned to prove that anesthesia alleviates shock, have yielded contradictory results, perhaps because deep narcosis is in itself a potent alarming stimulus.[310] To make anesthesia a useful shock-preventing agent, care must be taken that its own alarming effect be less pronounced than that of the nervous stimulus which it is supposed to counteract.[311]

We know very little concerning the *mechanism through which nervous stimuli influence the development of the G-A-S* in general and the shock-phase in particular. It has been claimed, with more or less justification, that overstimulation of the sympathetic nervous system can cause shock,[312] but this did not remain uncontested.[313] Fear in particular, may induce hemoconcentration and a secondary hypotension which are allegedly the direct results of an initial adrenaline discharge, adrenergic vasoconstriction and a consequently increased capillary permeability in tissues thus deprived of blood.[314]

[303] Meessen 96334/47, Moon A16304/38.
[304] Jokl B19917/47, Palmer 95299/46.
[305] Selye **B1204/46.**
[306] Fine et al. 78126/39, Herrin and Meek 59776/33, Taylor et al. 44916/33.
[307] Fine et al. 78126/39.
[308] Prinzmetal and Bergman B3109/45.
[309] Crile and Lower 97296/15.
[310] Blalock and Cressman A33060/39.
[311] Loeber et al. A36146/40, Moon et al. A31861/40, Reader A31351/39, Selye 35935/ND, B1204/46.
[312] Freeman 44351/33, Tomb B313/37, A36165/41.
[313] Fine et al. 78126/39.
[314] Cannon A49772/34, Freeman 44351/33, B314/39.

Neurogenic shock has also been produced in animals (even in the anesthetized dog) by carotid-sinus stimulation, but this hardly has much bearing upon clinical shock, since comparable conditions would rarely arise in man.[315]

Nervous stimuli, also play an important rôle in *mediating certain specific manifestations of the A-R.* Sympathectomy interferes with many adaptive reactions and prevents adrenaline liberation in emergencies,[316] while vagotomy tends to inhibit the formation of gastrointestinal ulcers during the A-R (Cf. Gastrointestinal Tract). Furthermore, vagotomy, adrenal-denervation and spinal-cord transection, greatly influence the glycemic response to stressors.[317]

It may incidentally be mentioned that there is some evidence suggesting that many, if not all the manifestations of the G-A-S, are due to *conditioned reflexes.*[318] Thus the tachycardia elicited by adrenaline in the dog can be subsequently produced even by the injection of saline solution after a conditioned reflex to injection has been established.[319] This example is perhaps somewhat far fetched, but it illustrates how certain manifestations of the G-A-S, which are dependent upon pretreatment or training, could be based upon the development of conditioned reflexes.

In *summary,* it may be said that nervous stimuli undoubtedly can produce not only shock but also the later stages of the G-A-S. They probably play a prominent rôle in the so-called primary shock or collapse. In the event of exposure to various stressors, incidental pain, fear, rage and other nervous stimuli can be superimposed upon the effect of the main alarming stimulus and thus aggravate its systemic stress effect. Hence, incidental nervous irritation should be eliminated as much as possible in clinical medicine. Many of the individual reactions which compose the shock syndrome can be mediated by nerves. Nevertheless, the production of shock is not dependent upon the integrity of the nervous system.

(5) *Disturbed thermo-regulation.* — It is a characteristic feature of severe shock that the mechanism of thermo-regulation is disturbed and the body-temperature falls. Furthermore, exposure to excessive cold can elicit shock-like symptoms by depressing the body-temperature.[320] The A-R-symptoms produced by transection of the spinal cord, are diminished by maintaining the body-temperature.[321] On the other hand exposure to excessive heat may also lead to shock-like symptoms, although the body-temperature rises,[322] and it is common clinical experience that in patients, suffering from trauma or burns, shock is not necessarily prevented by maintaining the body temperature at a normal level. Hence, we must reject the theory that a disturbed thermo-regulation is always the primary derangement in shock.[323]

(6) *The deficiency theory.* — As we have seen, the various previously mentioned interpretations of the shock-syndrome may explain certain instances of shock, but none of them is applicable to all cases. This led us to consider the possibility that shock may not always be caused by the same mechanism. For instance, under certain circumstances, it may be caused by deficiency in certain vitally important metabolites rather than by excessive production of toxic

[315] Phemister and Schachter A56310/42.
[316] Cannon B14905/39.
[317] Gellhorn and Feldman A36776/41, Gellhorn et al. 80365/41, 81846/41.
[318] Selye B1204/46.
[319] Subkov and Zilov A15671/37.
[320] Selye 38798/37.
[321] Dalton A34566/40, 79110/40-41.
[322] Selye 36032/36.
[323] Selye B1204/46.

substances. Let us not forget that the data obtained with all the classical experimental arrangements, designed to prove the toxic theory, are equally compatible with the deficiency-theory. For instance, the fact that occlusion of a vascular territory produces shock only after re-establishment of the circulation, has always been ascribed to an intoxication by metabolites coming from the damaged tissues, but actually it could just as well be due to the drainage of vitally important substances from the general circulation into the area of damage.[324]

In some instances, it is undoubtedly a deficiency that causes shock-like symptoms. Thus, shock was produced by *partial hepatectomy,*[325] a condition in which no tissue remaining in the body is directly lesioned, nor is there any damaging substance introduced into the organism. Here, just as in shock due to *hemorrhage, asphyxia* or *hypoglycemia,* the lack of something is the primary cause of shock, although secondarily, this lack may have led to the formation of toxic substances.

The case of *tissue-anoxia* is perhaps not entirely relevant. It is generally thought that during shock, diminished oxygen transport to the tissues and the resulting nutritional disturbance is of great importance. However, administration of oxygen under high pressure fails to improve the condition or even to augment oxygen uptake,[326] presumably because during shock considerable portions of the vascular bed are completely excluded from the circulation.[327] Thus here deficiency in a vitally important metabolite merely serves to aggravate a pre-existent local condition of damage and is not conducive to the systemic spreading of the insult by depriving the rest of the body from a needed substance.

It is perhaps more pertinent to note that an extraordinarily large amount of sugar disappears from the blood circulation through a traumatized limb.[328] It was assumed that *increased glucose combustion* in the damaged tissue may require large quantities of substances (e.g., co-enzymes) necessary for carbohydrate utilization; by attracting these into the area of damage, the body may become deficient in them.[329]

Significantly, intravenous administration of sodium-*succinate* and *fumarate* considerably improves the condition of animals in traumatic shock,[330] and *lactate* proved beneficial in burn-shock.[330a] This and similar observations led to the conclusion that "the therapeutic value of plasma is not fully explained by its colloidal-osmotic pressure. The search for labile substances in plasma which restore metabolic processes is indicated".[331]

It has also been pointed out that in shock induced by burns, the loss of *nitrogen* continues beyond the hemoconcentration period. Although many of the catabolic changes initiated by burns "simulate a toxic condition, they can be eliminated by increasing the amount of protein in the diet" . . . "hence the toxemia appears to be a conditioned amino-acid deficiency induced by an increased demand for this amino acid with consequent raiding of the tissue protein". Here *methionine* was particularly effective as a prophylactic of shock.[332]

[324] Selye B1204/46.
[325] Selye and Dosne A30702/40.
[326] Frank and Fine B26173/43.
[327] Rous and Gilding B38229/29.
[328] Dosne A36748/41,
Selye and Dosne A35802/41.
[329] Selye B1204/46.
[330] Mylon et al. A59010/43, B419/44.
[330a] Fox B18169/44.
[331] Mylon et al. A59010/43.
[332] Peters 89884/45.

On the other hand, contrary to earlier views, the *ATP* and *phosphocreatine* content of the muscles does not fall significantly during traumatic shock, except in the directly injured area. From this it was concluded that "under the circumstances, it is hard to credit the reduction in high energy phosphorus with a major rôle in shock".[333]

Hypochloremia has also been regarded as characteristic, and perhaps a fundamental factor in shock, but it is absent when muscular exercise is the evocative agent.[334] Even the reputedly typical decrease in red-cell chlorides is absent or reversed in this case.[335] Furthermore, marked hypochloremia may be elicited by DCA, without causing any shock-symptoms.[336] Thus, there is no evidence that hypochloremia is the initiating factor of the shock syndrome.

An absolute or relative *hyponatremia* should likewise be considered in connection with the deficiency theory. Injured cells notoriously tend to discharge potassium and to replace it by sodium. Damaged tissues also store Na-rich edema fluid, thus removing large amounts of Na from the circulation. Significantly, administration of Na-solutions is more effective in the therapy of shock than treatment with a variety of other solutions having the same osmotic concentration.[337] (Cf. p. 61.)

We said before that compression-treatment of crush-injuries diminishes their shock-producing action. This has been regarded as possibly due to the prevention (by mechanical pressure) of the loss of important blood-constituents into the damaged tissues.[338] However, as previously noted, the improvement obtained by compression is equally compatible with several other theories.

Several observations suggest that the shock-phase of the A-R is actually one of *"relative-adrenal insufficiency".*[339] We merely mention these here since they are considered in more detail elsewhere (cf. p. 76.)

In *summary,* it may be said that deficiency in one or more vitally important substances can undoubtedly be the cause of shock; it may, but has not been proven to be a necessary prerequisite of it. However, even the evidence in favor of the deficiency theory as one applicable to all kinds of shock, is at least as convincing as any other hypothesis so far suggested.

(7) *Shock as a disease of adaptation.* — The concept that some deficiency may be the fundamental factor in the pathogenesis of shock, forms a suitable basis for our discussion of this condition as a disease of adaptation. Let us recall that the relative lack of corticoids, sodium or certain building-stones of the larger protein- and sugar-molecules (e.g., amino-acids, succinic acid, fumaric acid) have been considered to play a special rôle in this connection. Increased corticoid-production is one of the fundamental steps in the defense against systemic stress and the corticoids in turn play an important rôle in gluconeogenesis from protein, the utilization of sugar- and protein-degradation-products, as well as the metabolism of sodium.

Before discussing the relationship of shock to the G-A-S, it is indispensable, first, **to formulate the basic problems** clearly. It appears that usually shock is

[333] Haist 93414/46.
[334] Selye A15800/38, A15674/39.
[335] Karady et al. A31125/39, 74590/39.
[336] Selye B1204/46.
[337] Bergman and Prinzmetal B38042/48.
[338] Katz et al. A57758/42,
Mylon et al. A59010/43,
Patey and Robertson 81530/41.
[339] Feyel and Varangot 99211/42,
Larget and Lamarre A38155/41,
Larguia B34027/46,
Morone B39105/47, B39106/48,
Riml 75159/39,
Selye 38798/37, B1204/46,
Selye et al. A32768/40.

initiated by the direct action of certain stressor agents upon circumscribed areas of the body (e.g., trauma, burns); yet in other instances the stressor has a direct systemic action (e.g., intravenous administration of toxic substances, septicemia, total-body x-irradiation). In the latter case, there is no need to search for a mediator, but if the stressor agent acts only upon a circumscribed part of the body, we have to account for a mediator which spreads the damage to distant organs (e.g., from a burned skin area to the gastrointestinal mucosa or the adrenal-cortex).

The secondary (distant) effects of an originally localized injury should be clearly separated into two categories: (1) *manifestations of damage as such* (*shock*) and (2) *manifestations of defense against damage* (*counter-shock*).

We do not know *what carries the impulse of stress from the directly injured tissues to distant organs.* This carrier may be a toxic metabolite or the deficiency in a vitally important body constituent. Toxic substances could be produced by the directly injured cells, but it is equally possible that substances indispensable for normal life are consumed by them so that the rest of the body is deprived of essential metabolites. In any case, this mediator appears to be blood-borne, since the production of shock depends only upon the maintenance of a humoral link between the directly damaged area and the rest of the body; nervous connections are dispensable.

It is possible that: (1) the same humoral mediator, which causes systemic damage, also initiates counter-shock, due to two distinct actions; (2) the humoral mediator initiates counter-shock through the intermediary of the systemic damage itself; (3) that shock and defense are elicited by independent mechanisms.

We analyzed the mechanism of the A-R, because unfortunately, the "shock-problem" is usually approached without dissecting it into its component parts and without realizing its intimate connection with defense and with the mild "physiologic" stresses of daily life. It will be clear from the preceding discussion that little can be learned from experiments designed to reveal "what causes shock". The essence of this condition is that it does not depend upon any one pathogenic mechanism and its diverse components are not controlled by the same regulator. Hence it would not be worth the effort to discuss the gigantic (and so largely inarticulate and redundant) shock-literature in detail. Let us limit ourselves to a few **observations which are particularly instructive in the study of shock as a disease of adaptation.**

It has been emphasized that shock tends to develop in *three stages,* just like the G-A-S. There is first an initial period of "damage", during which the blood-pressure falls; this is followed by the period of stabilization, at which a blood-pressure plateau is established; finally there is the "secondary period", which commences with a sudden collapse of the blood-pressure and terminates in death.[340] These periods are of short duration, in the usual type of experiment designed to study "shock", because the stressors employed are very severe. This apparently represents the "telescoped" version of the G-A-S, which also occurs in fulminant infections or intoxications. It develops in its most typical form, following exposure to almost any stressor, in animals deprived of their hormonal defence mechanism by hypophysectomy or adrenalectomy. (Cf. G-A-S → Resistance ← Hypophysectomy, Adrenalectomy.)

[340] Laflaquière 97307/42, Maitre 97297/42.

The *manifestations of systemic damage* appear to be characterized in all organs merely by non-specific signs of decreased vitality, such as the progressive loss of the selective permeability of cell- and capillary-membranes. This leads to capillary-leakage, with an egress of plasma-constituents into the intercellular spaces. At the same time there is "cell-membrane leakage", with a discharge from the cell of compounds in which it is usually very rich (e.g., K and PO_4), while Ca, Na, Cl and blood-plasma enter the cytoplasm from the circulating blood through the interstitial fluid. Thus, the chemical composition of cell and plasma tend to become equalized. Simultaneously, there is a systemic catabolism of protein-, glycogen-, and fat-reserves.

Numerous manifestations of the A-R such as the hypotension, the hypoglycemia, the formation of gastrointestinal ulcers, the hypothermia, hemoconcentration, etc., are regarded as manifestations of systemic damage in this sense, although they are not necessarily obvious during shock-conditions of brief duration.

The *catabolic phase,* with its protein disintegration and nitrogen loss, which usually follows severe systemic stress in man has also been correlated with the A-R. "Raiding of the body-protein may occur in order to supply endogenously the necessary substrate of amino-acids for the reparative process, and perhaps a mobilization of oxidizable material for the enhanced metabolism of the healing process and for the alarm-reaction".[341] An essentially similar view has been expressed by others, who raised the possibility that the protein-catabolites, liberated during the shock-phase, may even enhance the ability of the hypophysis to produce corticotrophin.[342] It will be recalled that during stress, corticotrophin-production is greatly augmented by high-protein or high-amino-acid diets.

It has not been possible to identify any particular amino-acid, polypeptide or protein-fraction, as "the stimulus" specifically responsible for certain manifestations characteristic of the catabolic period. A protein from the euglobuline-fraction of bovine serum was found to produce hypotension and leucopenia in the dog and guinea pig.[343] These are undoubtedly characteristic manifestations of the A-R. Yet, their evocation with this particular fraction should not be taken to suggest that endogenous euglobulines are normally responsible for eliciting comparable manifestations during stress. Obviously most toxic substances will produce hypotension and leucopenia if they are given in doses sufficient to elicit an A-R.

If we accept the deficiency theory of shock, the catabolic phase of the A-R may also be of benefit through another mechanism. Tissue-catabolism could liberate, from tissues of relatively minor importance, such essential substances of which the body may have become depleted and render them available for the more vital organs. Incidentally, the catabolic response, reduces the total mass of the body and thus the organism may become better adjusted to subsistance on a reduced amount of essential metabolites.[344]

The counter-shock phenomena, on the other hand, may be further subdivided into hormonal and nervous defense mechanisms. The *hormonal defense* is initiated by the increased production of *corticotrophin,* but we do not know through what pathway tissue-trauma acts upon the anterior-hypophysis. Perhaps this response is not mediated by a single agent. Possibly any derangement

[341] Cuthbertson 89887/45.
[342] Albright B349/43, Selye A55493/42.
[343] Guest et al. B26460/46-47.
[344] Selye 35935/ND.

in the nervous or blood-borne stimuli which affect the anterior-lobe induce the latter to discharge corticotrophin and thus to initiate the hormonal defense chain. In any event, the corticotrophin acts upon the adrenal-cortex and causes the latter to produce corticoids which are notoriously effective in raising resistance.

There are but few data concerning the rôle of *mineralo-corticoids* during shock. Observations on man, receiving varying amounts of Na, suggest that even under normal conditions "the renal sodium excretion is controlled by adrenal-cortical activity and that ingested sodium may displace intracellular potassium in normal subjects" if they are given high-Na diets for a sufficient period. From indirect evidence it was concluded furthermore that "the need to conserve body-sodium was met by increased activity of the desoxycorticosterone-like hormone".[345] Perhaps during the shock-phase of the A-R a similar over-production of mineralo-corticoids occurs in order to minimize the loss of Na and the danger of endogenous K-intoxication.

In this connection it is even more instructive that following operations and other types of traumatic injury in man, there tends to be a retention of Na and Cl and an excessive elimination of K, if the injury is not too severe and compensatory defense-mechanisms are effective. These changes have been ascribed to an increased production of corticoids, as a result of an effective A-R, in response to trauma.[346] Essentially similar observations have been made, quite independently, by others. For instance it was found that during post-operative alkalosis an actual K-deficiency may develop, with typical electrocardiographic changes abolished by K-administration. It was concluded that "these electrolyte disturbances show a striking resemblance to those observed in certain patients with Cushing's syndrome" and the "results suggest that the pathogenesis of this syndrome in post-operative patients is due to the alarm-reaction producing hyperfunction of the adrenal cortex, with loss of potassium and chloride (or retention of sodium) in the urine, associated with a low intake of potassium".[347]

There is much more evidence showing that *gluco-corticoid*-production is increased during the A-R (increased urinary elimination of gluco-corticoids, lympholysis, eosinopenia, changes in intermediate organic metabolism). Indeed pertinent data are too plentiful to be included in this theoretic discussion. It is even probable that during the A-R gluco-corticoid-production greatly predominates over the elaboration of mineralo-corticoids. The above data are given in some detail only to show that probably some mineralo-corticoid-excess can arise even after short exposure to systemic stress.

The *kidney* probably contributes to shock-defense through its endocrine activity (mainly by the production of RPS) and through its excretory function (regulation of water- and salt-metabolism). However, this contribution is surprisingly unimportant as judged by the fact that complete nephrectomy causes only a slight diminution of shock-resistance in most laboratory animals.

The *nervous defense* mechanism is mainly regulated by the hypothalamic vegetative centers. From here, sympathetic nerve-impulses travel to the cardiovascular system and tend to raise the blood-pressure by a direct action upon peripheral resistance and cardiac output. This direct action is further complemented, through the splanchnics, by the discharge of blood-borne adrenergic

[345] Leaf and Newburgh B33424/49.
[346] Feyel and Varangot 99211/42.
[347] Pearson and Eliel B33432/49.

substances (adrenaline and nor-adrenaline) from the medulla. There is also some evidence of a generalized parasympathetic discharge during stress, but this has received comparatively little attention. It may be implicated in the so-called vaso-vagal reflex and in some of the gastrointestinal derangements which occur during shock.

Waterhouse-Friderichsen syndrome. — This condition is characterized by a necrotic breakdown of the adrenals accompanied by fulminating purpura, with hemorrhages both in the adrenals and in many other tissues. The syndrome is most commonly due to meningococcal septicemia, but may occur in patients with other infections and sometimes the eliciting agent is not detectable. Animal experiments suggest that a number of micro-organisms contain "adreno-hemorrhagic factors". These also cause other manifestations of the A-R, such as hypothermia and leucopenia.[348] It was assumed that several bacterial toxins can elicit changes in animals, which resemble the Waterhouse-Friderichsen syndrome of clinical medicine. Allegedly, here, "the symptoms are due both to adrenal insufficiency and to the intoxication itself".[349] A study of the literature, and of personally observed cases with adrenal-cortical necrosis, led to the suspicion that infection, toxemia, endocrine factors and allergy may all be involved in the pathogenesis of this change. Their exact rôle could not be specified but "the possible significance and the relationship of such lesions to Addison's disease and to the Waterhouse-Friderichsen-syndrome and to intestinal ulcerations is intimated".[350]

In other connections we enumerated a great variety of stressors which cause adreno-cortical necrosis and hemorrhages (see: "Adrenals"). These lesions are often accompanied by systemic manifestations of purpura. Since excessive stimulation of the adrenal by corticotrophic preparations can likewise cause adrenal necrosis, it was suggested that in the Waterhouse-Friderichsen syndrome the lesion in the suprarenals is due to an exhaustive overstimulation of the cortical cells with an eventual breakdown. The resulting fall in corticoid-production is aggravated by a "relative adrenal insufficiency" because resistance to the evocative stressor requires particularly large amounts of corticoids. On the other hand, the accompanying purpura is probably a more specific effect of the causative agent; normally, capillary-fragility and the blood-clotting mechanism are not sufficiently deranged during the A-R, to produce a marked systemic hemorrhagic tendency.

It has been stated that in patients who die from the Waterhouse-Friderichsen syndrome, the thymus is unusually large, while the functional adrenal-cortex is narrow since most of the inner layers are completely destroyed by hemorrhage and necrosis. "Thus one could speak of a reversed alarm reaction".[351] In support of this view, we might also mention that therapy with corticoids proved especially effective in combatting the systemic stress-manifestations of patients suffering from this syndrome (cf. G-A-S → State ← Corticoids).

In the light of all these findings it is tempting to consider the Waterhouse-Friderichsen syndrome as a disease of adaptation.[352] Here, the derangement of the adaptive process appears to result from an exhaustive overstimulation of

[348] Olitzki et al. 84474/42.
[349] Lithander 97243/45.
[350] Mitchell and Angrist A57688/43.
[351] Schwarz 93714/46.
[352] Selye B1204/46.

the adrenal-cortex, with secondary, acute hypocorticoidism. Although the purpura is a superimposed specific change, produced only by a limited number of stressors, it can further aggravate the hypocorticoidism, since it leads to extensive adrenal hemorrhages and these add to the destruction of cortical tissue. In this sense, the syndrome would be one of "hypo-adaptation", a failure of the cortical response to stress.

Systemic infections. — Various systemic infections are known to produce particularly severe A-R changes. Some of these, e.g., *malignant diphtheria, cholera, acute streptococcus and staphylococcus septicemias,* are among the most potent stressor agents in clinical medicine (cf. Alarming Stimuli). Of course, the causative micro-organisms of all these diseases also have specific actions of their own; these are superimposed upon their non-specific stressor effect. Nevertheless, an important part of the resulting clinical syndrome is due to the A-R which they produce. The acute gastrointestinal erosions, the hemoconcentration, the capillary-damage, the involution and necrosis of lymphatic tissue, presumably belong to this latter category. In the event of severe infections, many of these non-specific changes are due to relative hypo-corticoidism.[352a] Corticoid-therapy with the preparations now available has not been eminently successful, yet the best results appear to have been obtained in those infections which cause the most pronounced systemic stress. (Cf. p. 67.)

Certain infections deserve special attention because they are particularly conducive to A-R changes. Thus, the adrenal- and blood-electrolyte changes in human and simian *malaria* (hyperkalemia, hypochloremia, hyponatremia), are strikingly similar to those seen in the course of an A-R produced by other means.[353] This, as well as the fact that malaria notoriously causes a type of "Addisonism", led to the conclusion that here again the syndrome is largely a disease of adaptation, upon which the specific effects of the pathogenic organism are superimposed.[354]

*Typhoid- and paratyphoid-*infections are notoriously conducive to intense systemic stress manifestations with marked involvement of the lymphatic tissue (especially in the intestinal tract), this being accompanied by widespread capillary damage, disturbances in electrolyte metabolism, renal function, etc. These changes have long been regarded as non-specific.[355] Their exact relationship to the G-A-S have not yet been established.

The "non-specific allergy", caused by *tuberculosis bacilli,*[356] also appears to be related to their systemic stress effect. However, a detailed discussion of this problem would be unwarranted, on the basis of the few scattered observations described in the literature. There is no doubt that chronic tuberculosis causes severe, long-lasting systemic stress and that here the catabolic manifestations play a particularly important rôle in the whole clinical picture. Yet, tuberculosis rarely causes adreno-cortical enlargement and hardly ever leads to hypertension or other cardiovascular diseases of the hyalinosis group. Perhaps in this case, the causative micro-organism exerts an especially prominent catabolic effect and the resulting protein-depletion "deconditions" the hypophysis-adrenal system to the stimulating effect of the systemic stress itself.

[352a] Dias B45808/47.
[353] Golden B17869/48, Golden and Overman B17868/48, de Langen B40959/47, Ortoleva and Allegra B45761/47.
[354] Flossi **B32317/48.**
[355] Albert-Weil 99346/46, Reilly 99381/42.
[356] Albert-Weil 99369/31, 99346/46.

Focal infections have been mentioned as effective stressor agents (cf. Alarming Stimuli). They can produce systemic adaptive reactions, which are quite out of proportion with the importance of the local lesion itself. In other words, they act as effective irritants. Almost all the classical diseases of adaptation (e.g., hypertension, nephrosclerosis, various forms of arteriosclerosis, rheumatic lesions) can allegedly be produced by focal infections (cf. Glossary).

Non-tropical sprue. — This is another condition which tends to produce manifestations similar to those of hypocorticoidism. Since corticoids are purported to exert a particularly striking therapeutic effect in sprue, the disease has been regarded as a condition of relative cortical deficiency.[357] In this sense, at least part of the clinical syndrome could be interpreted as a disease of hypo-adaptation. (Cf. therapeutic action of corticoids p. 69.)

Infantile diarrhea. — The so-called infantile diarrhea (diarrhea of the newborn, summer diarrhea, dystrophy of the newborn, toxic infants) is a condition characterized by a great intolerance for normally innocuous food-substances, diarrhea, vomiting and dehydration. Its close relationship to the co-called "malignant syndrome" (cf. Glossary) has been emphasized, mainly because it produces essentially the same biochemical changes, which are also characteristic of the catabolic phase of the A-R.[358] It has been pointed out that this syndrome greatly resembles Addison's disease, both clinically and as regards the metabolic disturbances. The causative agent may be an infection, a primary gastrointestinal disturbance, inadequate diet, intoxication, etc., and any one of these stressors may lead to a condition of relative hypocorticoidism. Significantly, the blood-Na concentration tends to fall whenever the patient's general condition turns for the worse and rises when there is clinical improvement.[359] In such cases combined treatment with DCA and potassium, allegedly proved to be beneficial.[359a] Potassium administration is indicated here especially since large amounts of this cation are lost in the stools.[359b] (Cf. also use of corticoids in fetal shock and collapse from infantile eczema p. 66.)

It remains to be seen why infants respond to non-specific damage predominantly with gastrointestinal disturbances. It is very suggestive to assume, however, that we are dealing with a disease of hypo-adaptation to a variety of stressors and that the clinical manifestations of this syndrome are dominated by the resulting non-specific changes rather than by specific actions of the evocative pathogen.

Aging. — In outlining the three characteristic stages of the G-A-S, we emphasized that they bear a striking resemblance with infancy, adulthood and senility respectively. At an early age, almost any stressor causes exaggerated responses (high fever, intense malaise, coma, etc.), but the child readily adapts itself to any change in its internal or external medium. The adult usually reacts less violently to stressors, perhaps because in the course of normal life it has already acquired some degree of adaptation to most of them. On the other hand, with progressing age, the ability for adaptation and learning diminishes, reaching its lowest point in senility. These reactions are singularly reminiscent of the G-A-S. There we note violent responses during the A-R, produced by

[357] Hotz A38846/40, Kraft A72513/42, Parade A50851/41.
[358] Dancis et al. B38302/49, Fanconi A32021/39.
[359] Alvarez et al. A33405/40, Gambaro B26538/47.
[359a] Barta B41172/49.
[359b] Howard and Carey B38343/49.

first exposure to a stressor, at a time when adaptability is great. Then there is a "direction of adaptation energy" to perform specific functions during the stage of resistance, and this goes hand in hand with the loss of adaptability to other stressors. Finally during the stage of exhaution there ensues an irreversible loss of the power to acquire inurement and this ends in death.

In discussing the general characteristics of the diseases of adaptation, we concluded that many of them are the so-called degenerative diseases of the aged. The concept of "pathologic aging", due to wear-and-tear,[360] fits in very well with this interpretation.

Wound-healing and regeneration are progressively impaired with increasing age and it is known that old individuals are notoriously poor surgical risks.[361] They are also very irresistant to infections.[361a] These facts likewise suggest a progressive loss of adaptability, such as occurs during the G-A-S. In this sense, the entire life-span could be compared with a protracted G-A-S, which develops in response to the ordinary stresses and strains of daily life. Perhaps the classic G-A-S, as we study it in the laboratory or clinic, is merely a "telescoped" version of essentially the same adaptive phenomena.

We have seen that nutritional factors are especially effective in conditioning the course of the G-A-S. It is particularly significant, therefore, that "retardation of growth of rats by restriction of calories alone increased significantly the average life-span, and retarded the development of inflammatory, neoplastic and degenerative diseases common to this species in old age".[362] Essentially similar observations were made on rats and dogs kept on various restricted diets.[363] Apart from the restriction of total caloric intake, at least in the rat, a limitation of the protein-content of the food is particularly beneficial for the promotion of longevity.[364]

A review of the pertinent literature concerning the human being, led to the conclusion that "famine and prolonged food-shortages are associated with a relative decline in mortality from some degenerative diseases".[365]

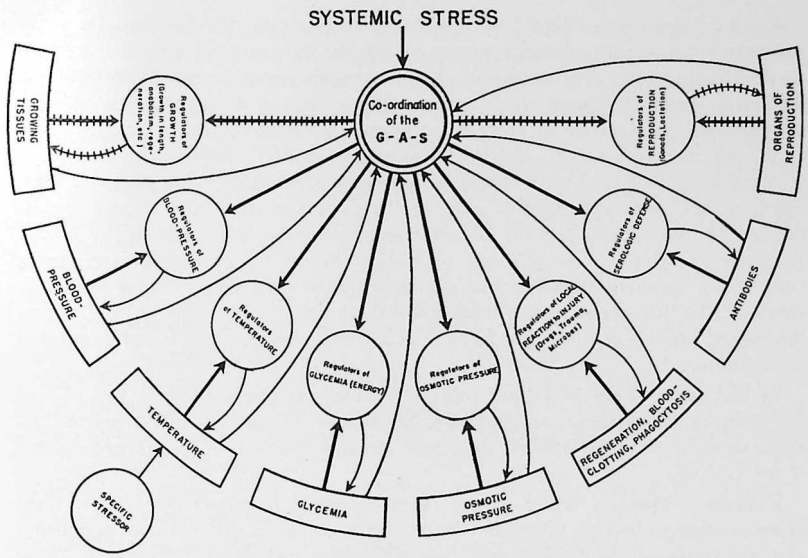
All these findings agree well with the observation that the production of hypertension and hyalinosis by stress or LAP, is inhibited in experimental animals receiving restricted diets, especially if the latter are poor in protein.

Theoretic Interpretation of Data Concerning Resistance

In discussing the theoretic interpretation of observations concerning resistance to stress, we propose to consider mainly three problems: (1) the correlations which exist between general (systemic) and specific adaptive reactions; (2) the pathways through which stress elicits systemic reactions and influences resistance; (3) the interpretation of non-specific therapy and particularly shock therapy.

Correlations between general (systemic) and specific adaptive reactions. — It is of great interest to examine how the G-A-S is correlated with the manifold, individual, specific adaptive processes necessary to maintain a constant "milieu intérieur". The following chart may help to visualize such interrelations.

[360] Hirsch B26303/27, **B33478/49**, Yardumian and Kleinerman B44658/49.
[361] Welch B26323/48.
[361a] Zeman B44205/46.
[362] Saxton 99846/45.
[363] Carlson and Hoelzel B38643/47, McCay B38023/47, Riesen et al. B38641/47.
[364] Saxton 99846/45.
[365] Keys **B23162/48.**



Systemic stress brings about the G-A-S due to a co-ordinated readjustment for defense of the principal biologic functions. Activities not immediately necessary for the maintenance of life during an emergency, such as **growth** (e.g., growth in length of the organism as a whole, anabolism of tissue, regeneration) and the phenomena connected with the process of **reproduction** (e.g., the development of the male and female gonads, the female sexual cycle and lactation) are inhibited (cross-hatched arrows). Such retrogressive changes are presumably due to a diminished production of the hypophyseal somatotrophic, ganadotrophic and lactogenic hormones. This appears to be necessary so that the pituitary may secrete the large amounts of corticotrophin required to resist and survive during intense systemic stress.

At the same time, the nervous system mobilizes and co-ordinates a number of target organs for defense, through its highly developed network of communications; it is only for the sake of simplicity that this is not depicted in our sketch.

Thus during stress the two great integrating mechanisms, the endocrine and the nervous systems, begin to exercise their action upon the peripheral sub-centers or specific regulators of: **blood-pressure** (e.g., through the internal secretions of the adrenal-cortex, adrenal-medulla and kidney), **body-temperature** (e.g., through adrenergic substances produced by the adrenal-medulla and through the action of vasomotor and vasodilator nerves), **glycemia** (through carbohydrate-active "gluco-corticoids" and adrenergic compounds), **osmotic pressure and tissue hydration** (e.g., through the "mineralo-corticoids", which influence the electrolyte composition of the blood and membrane permeability), **reaction to local injury** (e.g., through adrenaline, which influences blood-clotting and through the corticoids, which act upon protein-metabolism and thus significantly influence regeneration), **serologic defense** (e.g., through the corticoids which stimulate the elements of the reticulo-endothelial and lymphatic systems), etc.

Each of these sub-centers of regulation receives specific impulses from its respective target-organ; these messages enable the center to adjust its action so that homeostasis is maintained. Thus a specific readjustment, of any among the vital functions listed, can occur through these sub-centers without any pronounced phenomena of systemic defense, that is, without the development of a well marked G-A-S. Accordingly, in response to stressors, the organism is capable of reacting with varying degrees of specificity. For instance any agent which acts specifically upon the body-temperature and causes hypothermia, automatically induces the corresponding sub-center to raise the body-temperature, thus re-establishing normalcy. However, if such a stressor is sufficiently powerful to affect the entire organism then it becomes a systemic stressor. In this event it acts back upon the main centers (hypophysis, hypothalamus), which regulate the G-A-S as a whole and gear the entire organism for defense.

In this sense there is a close interaction between the individual, peripheral sub-centers of defense against specific types of injury and the main co-ordinators of defense against systemic stress as such, that is, the regulators of the G-A-S.

Pathways through which stress elicits systemic reactions. — Let us now examine the pathways through which a stressor elicits the systemic reactions characteristic of the G-A-S and thus influences resistance in general. Here again a chart will help to visualize the complex interrelations between the tissues involved.

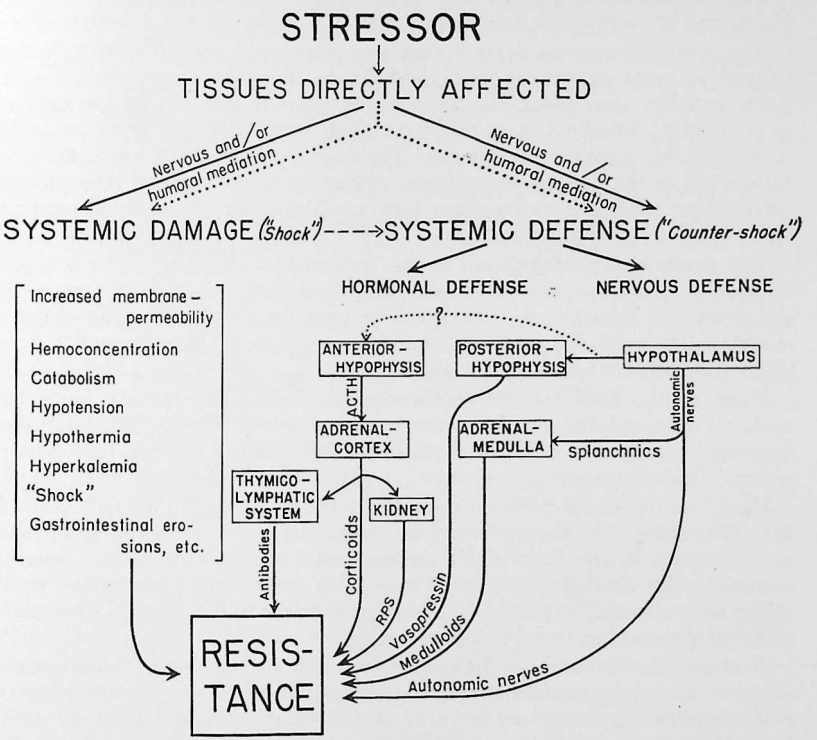
The **stressor** always influences some tissues directly. In certain instances (e.g., hemorrhage, anoxia, total-body x-irradiation) many, if not all, cells of the organism are injured due to a direct action of the damaging agent; frequently (e.g., trauma, burns), however, the **tissues directly affected** by the stressor represent only a limited part of the body as a whole. Yet, even such circumscribed lesions can elicit systemic reactions; hence, we may assume that the stimulus responsible for the latter must be carried to distant parts of the organism (those not directly affected by the stressor), through one of the two great integrating mechanisms, the blood-circulation or the nervous system. Available data suggest that depending upon the circumstances, either or both of these two integrators may carry such impulses from a directly injured area to other parts of the body.

Whether the eliciting stressor affects only a small part of the body directly or whether it exerts an immediate action upon all cells, generalized manifestations of **systemic damage** can ensue. Among these, we might mention increased capillary- and cell-membrane-permeability (with the resulting equalization in the chemical composition of inter- and intra-cellular fluid), hemoconcentration, tissue-catabolism, hypotension, hypothermia, hyperkalemia, clinical manifestations of "shock", gastrointestinal erosions, etc.

No matter how such systemic damage is produced, it is always accompanied, or followed, by manifestations of **systemic defense** or "counter-shock". Here again the mediation, from a limited area of tissues directly affected by the stressor, must occur through nervous and/or humoral pathways. Many attempts have been made to identify "the mediator" involved in the production of systemic damage or systemic defense-phenomena following injury to a limited area; yet the nature of such mediators is still unknown. Available data are quite compatible with the conception that the mediator in question

may be a nervous stimulus, a humoral factor (e.g., a toxic metabolite) or the lack of a vitally important blood-borne principle; indeed, it is rather probable that such systemic reactions do not depend upon any one specific mediator but can be induced by a variety of derangements in the chemical composition of the blood as well as by nervous stimuli.

PATHWAYS THROUGH WHICH STRESS ELICITS SYSTEMIC REACTIONS



Whatever the nature of such mediator(s) may be, the following three possibilities exists: (1) the same stimulus which causes systemic damage also elicits systemic defense (dotted arrow); (2) separate mediators are involved in eliciting systemic damage and systemic defense (solid arrows); (3) only systemic damage is elicited by mediators coming from directly injured tissues, the metabolic changes caused by such damage being themselves the stimuli which automatically elicit systemic defense (interrupted arrow).

Systemic defense reactions can in turn also be effected both through hormonal and through nervous responses. In connection with the **hormonal defense** an activation of the **anterior-hypophysis** is of special importance. During stress it produces an increased amount of corticotrophin or *ACTH;* this stimulates the **adrenal-cortex** to produce excessive amounts of *corticoids.* The latter increase resistance to a variety of non-specific stressors, presumably through their effects upon carbohydrate and mineral metabolism as well as

upon membrane-permeability. They probably also increase the production and decrease the destruction of *RPS* by the kidney and thus help to prevent the hypotension of shock.

Among other glands involved in systemic defense-reactions, we should mention the **posterior-hypophysis,** which, through the production of *vasopressin,* influences the vascular system, the blood-pressure and urine formation.

The **adrenal-medulla** participates in systemic defense through the discharge of *"medulloid"* adrenergic substances, especially adrenaline and nor-adrenaline.

The systemic **nervous defense** reactions are mainly regulated through the vegetative nerve-centers of the **hypothalamus.** From here, *autonomic nerves* carry impulses throughout the body to the vascular tree and to the organs (e.g., glands) involved in metabolism. Such stimuli play an important rôle in gearing the organism for defense. The adrenal-medulla, which is not under the control of the anterior-hypophysis, receives secretory impulses through the *splanchnics;* these are its secretory nerves, which cause a medulloid-hormone discharge during exposure to stress.

The **posterior-hypophysis** is likewise independent of anterior-lobe control; it receives secretory impulses from the hypothalamus through the *stalk* of the pituitary. Whether ACTH discharge from the anterior-lobe can also be stimulated through the stalk is debatable; under most circumstances it certainly can still occur after stalk-transection.

Thus, in the final analysis, **resistance** is influenced on the one hand by systemic damage and on the other by the terminal effector stimuli of the hormonal (corticoids, RPS, vasopressin, medulloids) and nervous (autonomic nerves) defense systems.

Here, we discussed these correlations in connection with the mediation of the stress-responses which influence resistance in general. However, resistance is determined by the sum of all the individual stress-responses and, hence, essentially the same pathways will have to be considered in connection with other, more specific, targets which are affected by the G-A-S (e.g., biochemical, morphologic and functional changes).

Non-specific therapy. — In connection with the theoretic interpretation of data concerning resistance, special attention should be given to the mechanism through which the various types of non-specific-therapy (shock-therapy, fever-therapy, parenteral protein-therapy, etc.) exert their beneficial actions in many of the so-called "chronic degenerative diseases".

It appears that after chronic stimulation, perhaps due to habit formation or partial fatigue, the body tends to overwork some pathways of the G-A-S, while others remain unused. Then, gradually, the former become worn out while the latter suffer due to disuse.[366] This may well lead to diseases of adaptation, including some mental diseases.

Perhaps shock-therapy acts because it represents a very intense new stress, which forces the body again to use all routes of defense proportionately; in other words, it shakes the pattern of defense out of the rut or "groove" into which it has gradually worked itself.

If we attempt to put these, admittedly vague, concepts into more precise terms, it might be assumed for instance that renewed production of "degranulation factor" (see Adrenals) in the course of an A-R superimposed upon the resistant stage, may play a rôle here. We know that during the stage of resistance to any one stressor, the adrenal-cortex stores increasingly more lipid-granules. Exposure to another kind of stressor again evokes a degranulation of the cortex; this may well be associated with a beneficial change in function (e.g., gluco-corticoid discharge) in a patient who "fell into the habit" of reacting with persistent mineralo-corticoid secretion in response to the original pathogenic stressor to which he became adapted.

[366] Selye B37061/49, 94572/49.

The integrity of mechanisms which are not particularly essential for the maintenance of life, is usually safeguarded only by one (or few) regulators. For instance many muscles have but a single motor nerve, if it is severed, paralysis ensues, but this is without major importance for the maintenance of life. On the other hand, vitally important functions are regulated by several alternative pathways, so that if one is injured, another can take over to preserve homeostasis. Thus, hyperglycemia can be produced by adrenaline secreted by the adrenal-medulla, by sympathin liberated at hepatic nerve-endings, by gluco-corticoids and by diabetogenic anterior-lobe principles. Similarly, resistance after adrenalectomy is raised by gluco-corticoids as well as by mineralo-corticoids. It is possible that in the case of sudden exposure to stress all routes capable of raising resistance are used during the acute emergency stage, but subsequently, due to "habit formation" or "fatigue" of certain pathways (cf. above) one mechanism is preferentially used and becomes excessive or worn out, while the others undergo "disuse atrophy". Diseases of adaptation may then ensue due to such disproportionate use of certain channels. Thus excessive gluco-corticoid secretion during chronic exposure to stress may lead to diabetes, while excessive production of mineralo-corticoids could cause hyalinosis and arthritis. This may also explain the curative effect of gluco-corticoids in rheumatoid arthritis and other diseases which are presumably caused by mineralo-corticoid intoxication. Here the exogenous gluco-corticoids would decrease both the need for, and the production of, toxic mineralo-corticoids.

An alternative possibility is that gluco- and mineralo-corticoids peripherally antagonize each other as regards these diseases, just as they do in many other respects (e.g., membrane-permeability, E.S.R., hyalinosis pressor action). There are many examples showing that different hormones produced by the same endocrine gland can antagonize each other (e.g., folliculoids and luteoids in their effect upon the uterus, adrenaline and gluco-corticoids in their effect upon the circulating lymphocytes).

The above considerations suggest the possibility that the curative value of shock-therapy, or of any other non-specific therapy, is largely due to the stimulation of endogenous corticotrophin production and the resultant normalization of a deranged adreno-cortical function.

Summary of Observations Concerning Resistance

Exposure to a systemic stressor agent causes characteristic changes in resistance, not only to the particular agent to which the organism is exposed (**specific resistance**), but also to other stimuli (**non-specific resistance**). These two types of resistance are not influenced in the same manner by the G-A-S. During the counter-shock phase of the A-R, both specific and non-specific

resistance are increased, the former much more than the latter. During the stage of resistance, specific resistance is greatly augmented, while non-specific resistance is diminished. During the stage of exhaustion both types of resistance reach a very low level.

Hypophysectomy and **adrenalectomy** greatly diminish resistance to various stressors. **Corticotrophin** rectifies this derangement after hypophysectomy, but not after adrenalectomy.

Corticoids increase the low resistance of hypophysectomized or adrenalectomized animals towards normal, but only in a few instances has it been possible to demonstrate that such therapy can augment the resistance of hypophysectomized or adrenalectomized animals above that of intact normal controls.

In intact animals, even large doses of corticoids are comparatively ineffective in raising resistance, to acute systemic stress, above the normal level. Here, the most consistently beneficial results have been obtained by corticoid therapy in those conditions in which an overwhelming systemic stress led to hemorrhages or necroses in the adrenals (e.g., malignant diphtheria, Waterhouse-Friderichsen-syndrome). In such instances, the endogenous production of corticoids probably fell below the high level necessary for optimal stress-resistance. The evident benefit derived from corticoids in uremia, potassium-intoxication, water-intoxication and insulin-shock, is largely due to the specific actions of these steroids upon electrolyte-, water- and carbohydrate-metabolism respectively. Here it would be incorrect to speak merely of an increase in resistance as such.

The **hormones of the adrenal-medulla** and of the **posterior-pituitary** play a less important rôle in resistance to systemic stress, as judged by their substitution-therapy effect upon adrenalectomized or hypophysectomized animals respectively. It must be kept in mind, however, that after adrenalectomy, the paraganglia and the sympathetic nerve-endings continue to furnish adrenergic substances, while after hypophysectomy the tuber-region can still produce hormones similar to those of the posterior-lobe.

Removal of the **kidneys, spleen** or **thymus** does not diminish resistance to acute systemic stress nearly as much as hypophysectomy or adrenalectomy. This does not prove that the above organs play no important rôle in conditioning resistance; perhaps their actions can merely be taken over by other tissues. It is also possible that the effect of depriving the body of these organs would make itself felt only during the later stages of the G-A-S, but this eventuality has not yet been adequately studied.

Numerous observations suggest that the principal derangement in certain diseases is a diminution of the resistance to systemic stress. As particularly characteristic examples of such **"resistance-diseases of adaptation"** we mentioned shock, the Waterhouse-Friderichsen syndrome, severe systemic infections, non-tropical sprue and infantile diarrhea. Indeed, even the phenomenon of aging may perhaps be interpreted in this sense.

In discussing the **theoretic interpretation of the data concerning resistance,** we placed special emphasis upon the **correlations between general (systemic) and specific adaptive reactions.** The hypothalamus- hypophysis-system appears to act as a central co-ordinator of defense against systemic stress as such. On the other hand, several peripheral sub-centers insure the homeostasis of

individual functions, such as the maintenance of blood-pressure, body-temperature, glycemia, osmotic pressure, tissue-hydration, reaction to local injury and antibody-formation. If an agent endangers only one of these individual functions, without causing any marked degree of systemic stress, the corresponding sub-center of regulation suffices to maintain homeostasis. However, if the stress becomes generalized, the main center is called into action and the entire body is geared for defense.

The **pathways through which stress elicits systemic reactions** have been subjected to a detailed analysis. It appears that some stressors injure cells throughout the body (e.g., hemorrhage, total body-irradiation), while others cause only circumscribed tissue-injury (e.g., localized burns or trauma). In either case, if the stress is sufficiently severe to elicit a G-A-S, both **systemic damage** and **systemic defense** reactions ensue. The generalization of the response is effected through nervous and/or humoral mediators.

Systemic defense is made possible through the actions of the two great integrating systems of the body, the endocrine and the nervous systems. We have briefly sketched the main pathways through which such systemic defense reactions are effected.

From a therapeutic point of view, the mechanism of **non-specific therapy,** particularly shock-therapy, deserves special attention. Certain observations have been outlined which suggest the possibility that the curative value of such non-specific therapeutic measures is largely due to the stimulation of endogenous corticotrophin production and the resultant normalization of a deranged adreno-cortical function.

METABOLISM

Changes in metabolic functions play a very prominent rôle in the G-A-S. Among these, especially careful attention has been given to the so-called "catabolic impulse" which occurs during the A-R-stage. It should be pointed out, however, that a similar great predominance of catabolic, over anabolic, phenomena reappears in the stage of exhaustion, although, during the intervening stage of resistance, anabolic phenomena prevail.

The expression "protein-catabolic phase" is often used to designate the breakdown of body-protein during the A-R. Unfortunately, this term tends to give the false impression that during a certain phase of the G-A-S there is selective catabolism of protein. Actually, in the stages of alarm and exhaustion, the carbohydrate- and fat-stores are also depleted. The breakdown of the glycogen-stores to glucose, with rapid utilization of the latter, as well as the mobilization of lipids from the fat-depots and their transfer into the liver for subsequent combustion are all just as characteristic catabolic reactions during the initial and terminal periods of the G-A-S, as the degradation of protein. Indeed, the organism appears to make every effort to preserve at least a minimum amount of structure-protein, as long as other sources of energy are available for resistance and repair during systemic stress.

Several extensive reviews surveyed the metabolic aspects of the shock problem; [1] special attention has been given to the metabolic changes induced by traumatic shock [2] and x-irradiation.[3]

[1] Engel **89587/45**, Wilhelmi **B18793/48**.
[2] Cannon A32617/23, Lambret A32664/33, Moon **A16304/38**.
[3] Ellinger **68685/35**, Jugenburg A32641/28.

BASAL METABOLIC RATE

Systemic Stress

Systematic animal experiments performed specifically to determine the **characteristic** effect of the G-A-S upon the B.M.R., revealed that a variety of alarming stimuli (drugs, surgical interventions, etc.) cause a decrease during the shock-phase; in the counter-shock-phase, however, the B.M.R. returns to or above normal in spite of continued treatment.[1] Systematic studies concerning the B.M.R. during the later stages of the G-A-S have not yet been published.

Changes in B.M.R. caused by some agents known to evoke the G-A-S deserve special consideration. Thus it was found that in the cat **traumatic** shock causes a fall in B.M.R. which was ascribed to the resulting tissue-anoxia.[2]

[1] Selye 35935/ND, Whittaker et al. A34565/40.
[2] Aub and Cunningham 40959/20.

Hemorrhage, if sufficiently severe to cause hypotension, can lower oxygen consumption by 30-50% in the dog. This was ascribed to the resulting anoxia,[3] but the development of irreversible hemorrhagic shock is not necessarily associated with a reduction in O_2-consumption.[4]

In various experimental animals the B.M.R. rises during and immediately following continuous exposure to **cold**.[5] Similar observations have been made in man,[6] but if human beings are chronically exposed to cold, the rise in B.M.R. does not tend to decline very much so that there is no significant degree of adaptation in this respect.[7] Eskimos are claimed to exhibit a B.M.R. of 14-21% above normal standards,[8] in spite of the fact that they have lived in the cold northern regions for many generations. On the other hand, a most remarkable example of adaptation to low temperatures (as regards the B.M.R.) occurs in the Australian aboriginal whose heat-production remains at a constant level during exposure to cold.[9] Of course it must be kept in mind that part of the specific adaptive reaction to cold is the rise in B.M.R. It is a well-known fact that in cold environments heat-production is raised by shivering. Furthermore, thyrotrophin-production is augmented; this secondarily increases the secretion of thyroid-hormone, which in turn maintains a high B.M.R., thus helping to preserve a normal body-temperature in spite of the increased loss of heat.[10] This response is certainly not merely a manifestation of the non-specific response to the systemic stress-effect of cold.

Severe **x-irradiation**, like most alarming stimuli, decreases the B.M.R. Simultaneously the R.Q. rises and morphologic G-A-S changes appear.[11] Conversely, milder x-irradiation raises the metabolic rate in rats; [12] presumably a counter-shock or resistance phenomenon.

During the intense muscular contractions elicited by **electro-shock**-therapy, the oxygen-consumption may rise to more than six times the normal level (!); although this is accompanied by typical manifestations of the A-R, it is obviously a specific result of muscular activity.[13]

Under the influence of **anoxia** the over-all metabolic rate decreases.[14] At the same time there is a shift from aerobic to anaerobic metabolism at the cost of a loss of efficiency, in terms of energy-yield per unit of substrate used.[15] Here again one may doubt the non-specific nature of the response, since lack of oxygen is quite specifically concerned with tissue oxidations.

A decrease in B.M.R., with typical A-R-changes, has also been noted after intraperitoneal injection of **hypertonic glucose** in the rat.[16]

Extreme **undernutrition** (famines, concentration camps) may reduce the B.M.R. by as much as 30-60% according to some investigators.[17] Although this is accompanied by typical signs of the G-A-S, it is impossible to distinguish

[3] Brofman and Green B25578/43.
[4] Post et al. B25993/48.
[5] Horvath et al. A9783/38, Ring A19411/39, Schwabe 72768/38.
[6] Hill et al. B26009/22.
[7] Horvath et al. 99993/46.
[8] Crile and Quiring B26008/39.
[9] Goldby et al. 74204/38.
[10] Selye 94572/47.
[11] Jugenburg A32641/28, Reding 39925/35.
[12] Kirschner et al. B37743/49.
[13] Delmas-Marselet B26881/46.
[14] Aub 40957/20, Brofman and Green B25578/43, Green B26010/43, Henderson et al. 59823/17, Houston B37539/47, van Liere **B26199/42**, Price et al. B26011/47.
[15] Engel 89587/45.
[16] Reiss et al. 85064/43.
[17] Govaerts and Lequime B26876/42, B26877/43, Keys B26878/46, B26879/46, B37797/48, Klotzbücher B45392/48, Lamy et al. B26867/48.

in this instance, between non-specific stress-effects and the specific adaptation to lack of food. Interestingly, however, an elevation of the B.M.R. after refeeding has been noted in starved rats.[18] Similarly, administration of an adequate diet to starved patients resulted in a rise of the B.M.R., on an average to +16.5%. This was ascribed to the need of energy for the restoration of tissues.[19] A rise in the B.M.R. following an A-R produced by other stressors could serve the same purpose with regard to the tissue-losses characteristic of the catabolic phase.

Much work has been done concerning the effect of trauma and other stressors upon the *metabolism of mammalian tissues in vitro*.[20] Unfortunately, the evaluation of these data is subject to many errors. The methods now in use to prepare tissues for in vitro metabolism studies are so crude that the handling of the material itself is bound to cause considerable non-specific stress.

Experiments on lower organisms (sea-urchin eggs) showed, contrary to expectations, that exposure to damaging agents increases tissue-metabolism. Only extremely severe damage results in a decrease. On the other hand, if sea-urchin eggs are previously treated with one type of stressor agent and subsequently exposed to another type of damage, the second exposure tends to cause a sharp decline in tissue-metabolism.[21] This may be another example of "crossed sensitization" at a time when specific resistance became high as a result of adaptation.[22]

Stimuli Influencing the Basal Metabolic Rate During the G-A-S

Hypophysectomy causes a very pronounced fall in B.M.R.; **anterior-pituitary extracts** have the reverse effect. The rise in B.M.R. caused by impure anterior-lobe preparations is largely due to their thyrotrophin and corticotrophin content, but other metabolism-stimulating principles may also be involved.[23] The undoubtedly very important rôle of the pituitary as a regulator of basal metabolism during the G-A-S has not yet been studied.

It is noteworthy that although bilateral **adrenalectomy** causes a fall in B.M.R., the decline is less pronounced than after hypophysectomy.[24] Experiments on the rat show that although unilateral adrenalectomy causes no change in the B.M.R. under normal conditions, it almost completely prevents the rise which would otherwise occur upon exposure to cold for 2-72 hours. From this it was concluded that: "One adrenal suffices for the quiet life of the ordinary laboratory rat, but two of them are a distinct advantage and may be necessary in certain prolonged stresses".[25]

In animals which are not exposed to systemic stress, **adrenaline** causes a marked though brief elevation of the B.M.R.[26] Conversely, adrenergic blocking agents diminish the B.M.R., but attention has been called to the possibility that this may be due to their non-specific stressor effect since a decrease in the metabolic rate is characteristic of the shock-phase of the A-R.[27]

[18] Quimby et al. B28218/48.
[19] Jongbloed B38637/47.
[20] Engel 89587/45, Russell et al. B26183/44, Wilhelmi B18793/48, Wilhelmi et al. 87816/45.
[21] Brock et al. 81455/39.
[22] Selye B1204/46.
[23] Selye **94572/49.**
[24] Selye **94572/49.**
[25] Horvath et al. A9783/38.
[26] Selye **94572/49.**
[27] Biörck and Hall B29352/47.

Corticoids cause little, if any, change in themselves, but tend to restore the subnormal B.M.R. of the adrenalectomized animal to normal.[28] The possible influence of exogenous adrenaline and corticoids upon the B.M.R. has not yet been examined during the G-A-S. It is very probable, however, that discharge into the blood of endogenous adrenal hormones (medullary and cortical), plays an important part in combatting the fall in B.M.R. which is normally caused by acute systemic stressors. It is presumably the lack of this defensive reaction that is responsible for the precipitous fall of the B.M.R. in adrenalectomized animals exposed to alarming stimuli.

Thyroidectomy does not interfere with the immediate elevation of the B.M.R. (or the accompanying rise in body-temperature) seen after a few hours of exposure to cold.[29] On the other hand, thyroidectomy inhibits the persistent rise in B.M.R. normally occurring in rats after weeks of exposure to a low surrounding temperature. Significantly, this rise is accompanied by a great proliferation of thyroid tissue.[30] Presumably in the early stages of exposure, the adrenal, in the later stages, the thyroid, play a prominent rôle in the defense against cold.

[28] Selye **94572/49.**
[29] Ring B25576/36, A19411/39.
[30] Ring A19411/39.

BODY TEMPERATURE

Systemic Stress

Hypothermia has been recognized as a **characteristic** sign of the shock-phase in the first publications on the A-R; [1] it proved to be a rather constant phenomenon seen upon treatment with toxic doses of various drugs and hormone preparations, muscular exertion, spinal-cord transection, etc. Conversely, fever is probably a counter-shock-phenomenon; [2] its usefulness in raising non-specific resistance, especially against micro-organisms, has frequently been emphasized.[3]

The initial hypothermia has subsequently been confirmed in the rat after intraperitoneal injection of **hypertonic glucose** [4] and certain **bacterial vaccines.**[5] In all these conditions other A-R-manifestations, especially adrenal enlargement, were simultaneously present. Allegedly special "adreno-hemorrhagic and hypothermic factors are present in certain groups of micro-organisms" . . ., . . . "One injection of bacterial vaccine or of normal serum and plasma from rabbits or from guinea pigs was followed by a period of non-specific resistance to the injection of bacteria that contained the hypothermic and hemorrhagic factor".[6] The non-specificity of this response suggests that here again we are dealing with an example of crossed resistance.

The particularly pronounced hypothermia produced by **spinal-cord-transection** in rats [7] is often mentioned in papers on the A-R. It must be kept in mind, however, that here, in addition to the systemic stress-effect, there is a more specific influence upon thermo-regulation, because the connections between the vegetative centers and the caudal part of the body are severed.

In man, hypothermia is commonly seen after extensive **traumas,**[8] severe **burns,**[9] **nervous shock,**[10] **anoxia,**[11] and other systemic stress-producing procedures.

Severe chronic **undernourishment** — such as occurs for instance during famines or among the inmates of concentration camps — also causes hypothermia; this is occasionally interrupted by fever, even in the absence of a demonstrable infection. Much has been written about this "lability of the temperature", but the underlying disturbance is still obscure.[12]
inhibited by **hypophysectomy** in animals and by spontaneous hypophyseal or adrenal failure in man.[13]

Stimuli Influencing the Body Temperature During the G-A-S.

Numerous observations have clearly demonstrated, that the ability of the organism to counteract the hypothermic effect of systemic stress is greatly

[1] Selye 36031/36.
[2] Selye B1204/46.
[3] Locke et al. 75000/39.
[4] Reiss et al. 85064/43.
[5] Olitzki et al. 84474/42.
[6] Olitzki et al. 84474/42.
[7] Dalton A34566/40, 79110/40-41, Frank A34171/40, Selye 36031/36.
[8] Hilgenfeldt 38008/36, Moon A16304/38.
[9] Simonart 63360/30.
[10] Roger A32642/16.
[11] van Liere B26199/42.
[12] Anonymous B27050/43, B27051/44, Brozek et al. B23241/46, Lamy et al. B26867/48.
[13] Selye **94572/49**, B1204/46.

The influence of **adrenalectomy** upon the temperature-curve during the G-A-S has been studied in animals exposed to cold, muscular fatigue or toxic doses of formaldehyde. It was found, in agreement with expectations, that elimination of the suprarenal defense-mechanism aggravates the hypothermia during the shock-phase and impedes the characteristic secondary rise in body-temperature.[14] Even fever-producing agents tend to cause hypothermia after adrenalectomy.[15] Substances which antagonize acetylcholine (e.g., procaine, atropine, quinidine, benadryl) cause an abnormally pronounced fall in body temperature after adrenalectomy. It was therefore assumed that the fall in heat-production may depend upon the action of acetylcholine upon combustion in muscle. [16] We must remember, however, that all stressors, if sufficiently intense, cause hypothermia after adrenalectomy, hence the above data do not suffice to implicate acetylcholine specifically in this derangement of heat-regulation.

Unlike *adrenaline,* treatment with *corticoids* offers excellent protection against the hypothermia induced by exposure to cold in adrenalectomized rats. Indeed this effect was found suitable to serve as the basis of a bioassay technique for corticoids.[17] Curiously, in adrenalectomized rats less than 16 days of age, corticoids do not offer protection against this kind of hypothermia; hence it has been assumed that these steroids influence body-temperature through some mechanism which is not yet developed during the first few weeks of life.[18]

In intact animals **adrenaline,** given in moderate doses, increases the B.M.R. and tends to raise body-temperature, while in shock-producing quantities it causes hypothermia. It is not very effective in antagonizing the hypothermia of the shock-phase at any dose-level.[19] On the other hand, adrenergic blocking agents appear to reduce the hyperthermia produced by pyrogenic material in dogs. This inhibition is attributed to the blocking of adrenergic cutaneous vasoconstriction.[20] In this sense, adrenaline may play a rôle in the production of fever by other systemic stressors as well.

Corticoids cause no significant change in temperature in the normal intact animal,[21] but *fever* induced by various spontaneous diseases is effectively combatted by cortisone in man.

The **nervous system** plays a particularly important rôle in regulating the body temperature when homeostasis is threatened by exposure to stressors. Through the hypothalamic centers the vegetative nervous system influences the production and loss of heat. This is accomplished mainly through the fibers responsible for cutaneous vasoconstriction and the activity of the viscera. Peripheral vasoconstriction — and in furry animals the creation of a protective air-coat by pilomotor-contraction — prevents the loss of heat; increased glandular or smooth-muscle activity augments heat-production. In addition, the splanchnics regulate adrenaline-secretion and the nerves of the skeletal muscles can greatly augment thermogenesis as a by-product of muscular work or shivering.[22] No doubt all these nervous mechanisms are of the greatest importance in determining the body-temperature-curve during the G-A-S and its diseases.

[14] Selye A9210/38.
[15] Grollman 58072/36.
[16] Dutta B31915/48.
[17] Selye and Schenker A15353/38.
[18] Holtkamp et al. B36669/49.
[19] Scholz et al. B28087/45, Selye **94572/49.**
[20] Wells and Rall B31739/49.
[21] Selye **94572/49.**
[22] Hess **B28498/48,** Tardieu and Tardieu **B19961/48.**

CARBOHYDRATE METABOLISM

In emergency situations glucose is the most important source of immediately available energy. Both the central nervous system and the muscles are almost entirely dependent upon glucose for the performance of their functions and neuro-muscular activity certainly plays a very important rôle during the "fight and flight" reactions of animals under stress. Furthermore, carbohydrates may be required as a source of energy for the repair and regeneration of injured tissue, for heat-production during the shock-phase when the body-temperature tends to fall due to defective thermo-regulation, etc. In contrast to fats and proteins, carbohydrates do not tend to yield toxic metabolites, even if very large amounts are suddenly catabolized. Hence, the utilization of glucose, by the peripheral tissues, proceeds satisfactorily even if severe shock interferes with the hepatic detoxification and renal elimination of metabolic end-products. Therefore in acute emergencies the organism calls primarily upon its carbohydrate reserves and first of all among these, upon blood glucose.

Blood-Sugar

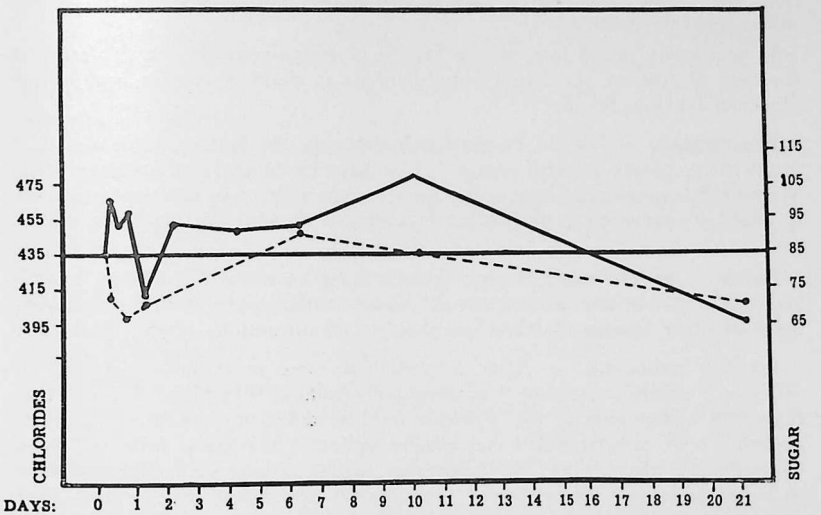
Systemic Stress

The above considerations led us to give special attention to the blood-sugar changes **characteristic** of the G-A-S. Our earliest animal-experiments along these lines had already revealed that a variety of rather non-specific stressors (e.g., trauma, infections, cold, drugs, muscular exercise) produce essentially similar glycemic curves. Immediately upon exposure (during the shock-phase of the A-R) there is a hyperglycemia, whose magnitude is largely determined by the hepatic glycogen-reserves. It is largely dependent upon the "emergency discharge of adrenaline" which occurs in all kinds of stress-situations. If the stress is sufficiently severe (especially if the glycogen-stores are low), the initial hyperglycemia is soon followed by hypoglycemia. Later during the counter-shock-phase, however, the blood-sugar returns to normal and remains at — or slightly above — this level throughout the entire stage of resistance. Only in the stage of exhaustion does it tend to decline again, often reaching dangerously low hypoglycemic levels.[1]

If we peruse the pertinent literature — always remembering that any specific glycemic actions of the stressors must be subtracted from the total picture — it is striking how closely the most diverse alarming stimuli reproduce the blood-sugar-curve outlined above as characteristic of the G-A-S. In evaluating the relevant literature the following facts should be kept in mind: (1) very acute stresses are particularly suited to elicit a marked adrenaline-discharge with a correspondingly pronounced initial hyperglycemia, (2) adrenaline-hyperglycemia depends upon the available hepatic glycogen-

[1] Dalton and Selye A17985/38, Masson A15525/38, Masson and Selye A16305/38, A17983/39, Selye A8054/38, A15800/38, A15674/39, A55493/42.

reserves, (3) comparatively few observations have been carried through all three stages of the G-A-S until death in the stage of exhaustion. Most observers merely report blood-sugar variations during an intense, single, short-term stress; this either ends in death during the shock-phase or in complete recovery after the counter-shock-phase because it is not prolonged enough to elicit the stages of resistance and exhaustion.



Blood-sugar changes (expressed in mg. %) during the G-A-S in rats chronically exposed to cold. In this experiment, the intensity of the cold was such that death ensued after 21 days of exposure. Following a brief initial rise during the shock phase (adrenaline-hyperglycemia), there is a decrease in the blood-sugar (solid line) level. In the counter-shock and resistance phases, the glycemia is slightly above the normal level, but a secondary marked fall occurs in the stage of exhaustion. The whole blood-chlorides (dotted line) — which are shown here for the sake of comparison — follow an essentially similar curve. (After H. Selye: J. Clin. Endocrinol. **6**, 117, 1946.)

Trauma. — The initial hyperglycemia is particularly pronounced and prolonged following traumatic injuries to the intestines and other intraperitoneal interventions.[2] Perhaps here glycogenolysis is especially intense due to incidental hepatic injury caused either by mechanical trauma or by toxic substances which might reach the liver through the portal circulation after traversing the damaged intestine.

But even in other types of clinical and experimental traumatic shock (including tourniquet-shock and allied conditions) the initial hyperglycemia is usually very pronounced and prolonged;[3] perhaps this is to compensate for the increased glucose-requirement of anoxic muscle. Later, however, when the

[2] Selye B1204/46.

[3] Amorosi 10135/31, Aub and Wu Hsien 40958/20, Garofeanu and Diaca B34073/42, Haist and Hamilton B639/44, Jourdan et al. B19461/43, Lamarre and Lecocq A32644/35, Lambret and Driessens A2914/37, Larget and Lamarre A38155/41, Lobello 36111/36, Neufeld et al. A63529/43, Roscher B25560/33, Sonobe A8283/37, Stolfi A2340/36, Urabe 35816/36.

glycogen stores are depleted, the secondary hypoglycemic phase ensues.[4] It has been emphasized in several pertinent papers that this glycemic response is accompanied by other manifestations of the A-R and that its course is essentially the same, irrespective of the type of traumatic injury inflicted (crushing of muscles, handling of intestines, tourniquet-shock, etc.). Even the stress of deep anesthesia preceding a major surgical operation has often been found to raise the blood-sugar, but a further rise ensues during the course of the subsequent intervention.[5]

In previously fasted rats, whose hepatic glycogen-reserves are depleted at the time of trauma, the initial hyperglycemia is slight or absent and hypoglycemia develops rapidly.[6]

Hemorrhage. — Claude Bernard was probably the first to point out that hemorrhage causes hyperglycemia.[7] This has subsequently often been confirmed.[8] It is noteworthy that in the dog it occurs only when sufficient amounts of blood are removed to elicit other biochemical changes characteristic of the A-R.[9]

Burns. — Severe burns in man likewise cause an immediate rise in blood-sugar as judged by clinical experience,[10] again simultaneously with the development of other biochemical and morphologic manifestations of the A-R.

Ionizing radiations. — After x-irradiation some investigators noted an increase,[11] others a decrease [12] or irregular variations [13] in blood-sugar. Systematic investigations of the glycemic level at different time-intervals after exposure to X-rays, revealed that usually an initial increase is followed by a hypoglycemic phase;[14] thus the changes are similar to those seen after exposure to other stressors. More recent investigators specifically emphasized that these blood-sugar variations, as the other manifestations of the radiation-syndrome, are strikingly similar "to the non-specific (alarm) reactions to a variety of diverse toxic agents given in sub-lethal amounts".[15]

Nervous stimuli. — The effect of nervous and emotional stress upon carbohydrate metabolism has received so much attention that it is hardly necessary to insist upon it here. Nervous and emotional stimuli are most effective in causing sympathetic, adreno-medullary and parasympathetic stimulation. The former two tend to raise the blood-sugar through adrenergic glycogenolysis, while the latter causes hypoglycemia, perhaps by stimulating insulin-secretion. Depending upon conditions, one or the other of these effects prevails.[16]

In connection with the interpretation of certain psychiatric disturbances as diseases of adaptation it is noteworthy that hypoglycemia and its accompanying

[4] Cleghorn and McKelvey 84886/44, Engel et al. A58685/43, Govier and Greer A37390/41, Haist 93414/46, Haist and Hamilton B639/44, Kiesel A32648/33, Trusler et al. B26112/39, Wilhelmi B18793/48.
[5] Roscher B25560/33.
[6] Engel et al. A58685/43.
[7] Bernard B26096/ND.
[8] Aggazzotti B19554/39.
[9] Nitzescu and Runceanu A32665/27.
[10] Ficarra and Naclerio B808/44, Hilgenfeldt 38008/36, Peters 89884/45, Stolfi A2340/36.
[11] Ellinger 68685/35, Painter et al. 98568/47, Prosser et al. B26618/47.
[12] Kikuchi 10150/31.
[13] Kikuchi 10149/31.
[14] Kiesel A32648/33, Reding 39925/35.
[15] Painter et al. 98568/47.
[16] Selye 94572/49.

symptoms sometimes appear to be secondary to personality difficulties; in such cases they disappear upon effective psychiatric treatment.[17] It is much more common to observe psychic derangements which are the results of a primary hypoglycemia, e.g., in hyperinsulinism.[18]

Muscular exercise. — Experiments in the rat showed that in the event of forced muscular work the initial hyperglycemia may be negligible; conversely, the hypoglycemia during the later part of the shock-phase is often particularly severe, presumably because especially large amounts of glucose are utilized for muscular work.[19] Observations on man revealed that brief, strenuous exercise invariably increases the blood-sugar, while longer periods of intense work usually cause hypoglycemia.[20]

Here the specific blood-sugar decreasing effect of muscular work is apparently superimposed upon the characteristic blood-sugar curve of the G-A-S. This is often the case whenever the alarming stimulus exerts a specific effect upon the blood-sugar. Thus, for instance, if insulin or adrenaline is used to produce systemic stress, the respective hypo- and hyperglycemic actions of these agents are so intense that they completely overshadow the blood-sugar variations typical of the G-A-S itself. Nevertheless, it is often possible to detect the typical glycemic curve of the G-A-S even if a stressor is used which exerts a pronounced specific influence upon the blood-sugar.

Anoxia and reduced atmospheric pressure. — Lack of oxygen also causes hyperglycemia.[21] It was possible to demonstrate in the dog and rat that this occurs only in non-adapted or "deacclimatized", but not in adapted animals.[22] Experiments in the rat suggested, however, that under certain experimental conditions, repeated exposure to brief anoxia (or electro-shock) may sensitize the "sympathetico-adrenal system" so that upon repeated exposure the animals react with increasingly more pronounced hyperglycemia. Repeated insulin-shock exerted an opposite effect in this series.[23] In another experiment, short periods of anoxia increased adrenaline-hyperglycemia and decreased insulin-hypoglycemia, while prolonged anoxia acted inversely.[24] An evaluation of all these data would have to take into account, not only the specific properties, but also the relative intensity of the stressors used for adaptation and for eliciting the response. In fasted rats the initial hyperglycemia produced by anoxia is followed by the typical hypoglycemia of the late shock-phase.[25]

Diet. — In fasting rats we found no initial hyperglycemia because this stimulus is not sufficiently acute to cause an important emergency-discharge of adrenaline. On the other hand, the hypoglycemic phase is well marked since starvation specifically tends to decrease the blood-sugar. However, after about four days of fasting, the blood-sugar rises again, presumably as a result of counter-shock phenomena. This has been called "fasting hyperglycemia"; at least in part, it is probably due to the liberation of gluco-corticoids. Significantly, exposure to other types of stressors (e.g., cold, formaldehyde, muscular exercise) during a period of complete starvation intensifies and

[17] Rennie and Howard B19676/42.
[18] Selye 94572/49.
[19] Selye A15674/39.
[20] Rakestraw A7856/21.
[21] van Liere B26199/42, Smith and Oster 93055/46, Tepperman et al. B4674/47.
[22] van Middlesworth et al. 84780/44, van Liere et al. B17764/48, B29441/48, Stickney et al. B29396/48.
[23] Gellhorn and Safford B19856/48.
[24] Gellhorn and Packer A30213/39.
[25] van Middlesworth et al. 84780/44.

accelerates the appearance of the secondary hyperglycemic peak. Such additional stressors also increase the adreno-cortical enlargement caused by starvation, and "fasting hyperglycemia" is not seen in adrenalectomized animals, hence the rise in blood-sugar under such conditions appears to depend upon the secretion of corticoids.[25a]

During severe undernutrition in man (famines, concentration-camps) the blood-sugar may fall to very low levels and spells of hypoglycemic coma tend to occur.[26] Fainting and postural-hypotension with syncope are common complaints among starving people, but although such derangements are often accompanied by hypoglycemia, they are not always the result of it.[27] In such starved patients glucose-tolerance is increased while adrenaline-hyperglycemia is inhibited,[28] presumably due to a depletion of the glycogen-stores. It must be kept in mind, however, that a short period of carbohydrate-restriction decreases glucose-tolerance — especially in undernourished persons — to such an extent as to simulate diabetes.[29] Thus the diet taken before exposure to systemic stress may considerably modify the response to the latter.

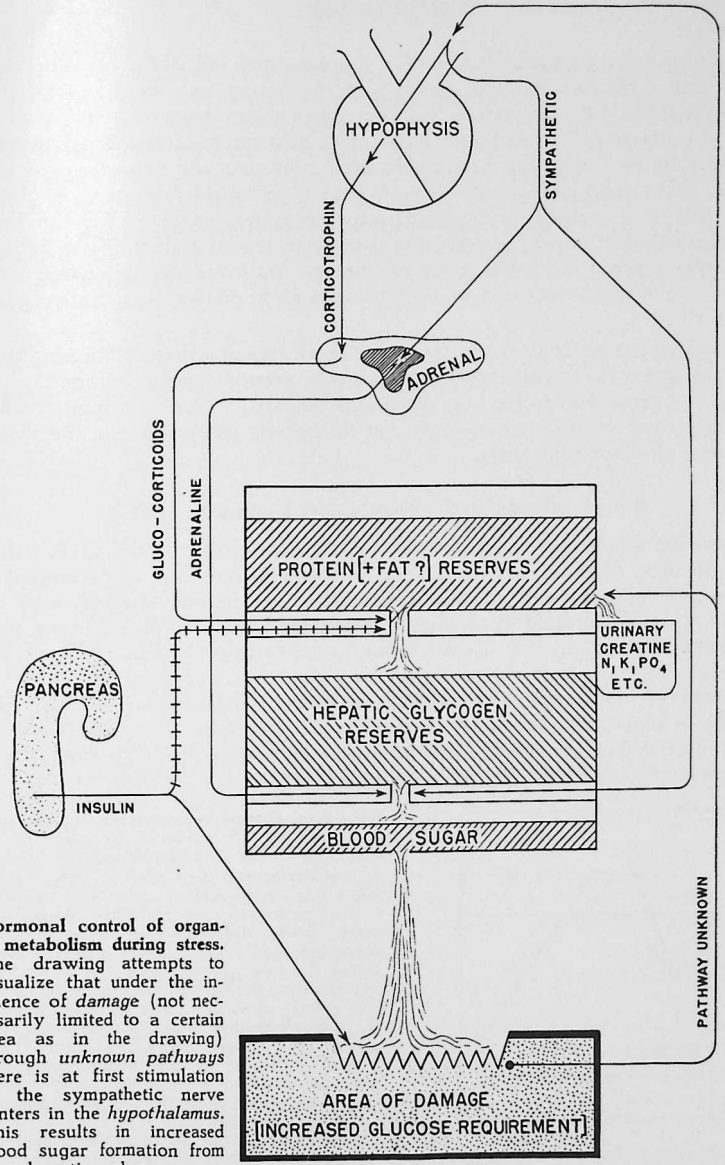
Other stressors. — Essentially similar glycemic responses have been found to occur under the influence of induced **hyperthermia,**[30] **toxic defibrinated blood,**[31] **anaphylactic shock,**[32] **metrazol,**[33] **electro-shock,**[34] and various **other damaging agents.**[35] The same is true of a variety of spontaneous **diseases** accompanied by the biochemical changes and vascular failure described as "medical shock".[36] The Exton-Rose glucose tolerance test may likewise reveal an almost diabetic response, for instance in infectious diseases.[36a]

Injection of **urea** (or urea-producers, amino-acids, peptones) causes hyperglycemia in the rabbit. This and other observations led to the view that azotemia itself tends to raise the blood-sugar in conditions of systemic stress,[37] but there are many exceptions which are inconsistent with such an assumption.

The initial hyperglycemia, followed by hypoglycemia, which usually precede the development of permanent diabetes in alloxan-treated dogs [38] and rabbits [39] strikingly resembles the blood-sugar curve of the G-A-S. Similar glycemic variations have been produced with high doses of **uric-acid** in rabbits, whose blood-glutathione had previously been diminished by dietary means.[40] (Cf. glutathione metabolism). However, this action appears to be inconstant and highly subject to individual variations.[40a]

Some,[41] though not all [42] investigators believe that during the process of *inflammation,* protein-catabolic processes and gluconeogenesis increase within the area of damage. This is noteworthy in connection with the previously-mentioned rise in tissue metabolism following exposure to mild stressors.

[25a] Selye A15673/39.
[26] Abrami and Marche B26873/43, Lhermitte and Sigwald B26880/42, Uehlinger B24304/47.
[27] Taylor et al. B23190/48.
[28] Hirscher B45240/48, Lamy et al. B26867/48.
[29] Conn B19794/40, Klotzbücher B45392/48.
[30] de Renzi and Grassellini B25216/40.
[31] Nitzescu and Benetato 18668/28.
[32] Amorosi 10135/31.
[33] Elliott et al. B31407/41.
[34] Delay and Soulairac B19816/44, Delmas-Marselet B26881/46, Elliott et al. B31407/41.
[35] Loiseleur and Nyka 68745/37, Sonobe A8283/37.
[36] Davidson et al. 87543/46.
[36a] Yoh B44801/48.
[37] Loiseleur A1941/36.
[38] Grande Covian and de Oya B23023/47.
[39] Griffiths B23068/48.
[40] Griffiths B23068/48.
[40a] Collins-Williams and Bailey B39066/49.
[41] Menkin A57481/43.
[42] Mattar et al. 85861/45.



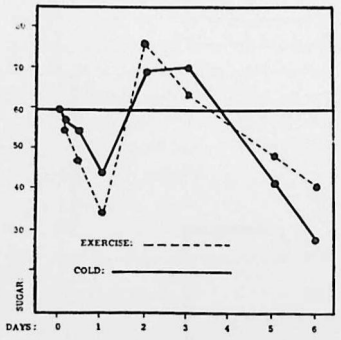
Hormonal control of organic metabolism during stress. The drawing attempts to visualize that under the influence of *damage* (not necessarily limited to a certain area as in the drawing) through *unknown pathways* there is at first stimulation of the sympathetic nerve centers in the *hypothalamus.* This results in increased blood sugar formation from the hepatic glycogen reserves. The latter is due partly to the direct effect of *sympathin* — liberated at the hepatic nerve endings — and partly to *adrenaline* discharged as a result of splanchnic irritation. — This mechanism immediately yields a large amount of free sugar, but is of limited duration. In more chronic emergencies — again through unknown pathways — the anterior-hypophysis is stimulated to produce an excess of *corticotrophin* which in turn augments adrenal *gluco-corticoid* secretion. The gluco-corticoids promote glycogen formation from protein (and fat ?) and the "protein transposition" essential for regeneration. *Insulin* inhibits (cross-hatched arrow) gluconeogenesis from non-sugar reserves and thus antagonizes the gluco-corticoids: yet it also promotes glucose utilization in the area of damage to promote regenerative phenomena and resistance. (After Selye **94572/49.**)

Severe trauma to one limb results in a pronounced fall in the *concentration of glucose in the venous blood coming from the injured limb,* as compared with the arterial blood going into it.[43] This, as well as observations on angiostomized dogs,[44] on eviscerated rats [45] and many other data recorded in the literature,[46] support the view that damaged tissues need more than the normal amount of sugar, hence, increased gluconeogenesis (due to increased formation of gluco-corticoids ?) is probably a beneficial response to trauma and likely to raise resistance to it. It is quite possible that the aggravation of diabetes by infections and other types of incidental stress may be due to a temporary defensive over-production of gluco-corticoids, or a sensitization of the body to their diabetogenic action.[47]

Observations on dogs during traumatic shock revealed that at the height of systemic stress the glucose-concentration in the hepatic veins is higher than in the portal veins; that is, the liver discharges glucose.[48] This agrees with other evidence cited in this book to show that the hepatic parenchyme is the major source of glucose during stress.

Stimuli Influencing the Blood-Sugar During the G-A-S

Systemic stress. — The glycemic curve characteristic of the G-A-S has already been discussed above. Let us merely add here that if an animal is chronically exposed and adapted (resistant stage) to one stressor, and its blood-sugar is stabilized at or slightly above the normal level, exposure to a different kind of stressor usually causes marked hypoglycemia. Thus, for instance, formaldehyde treatment in animals highly adapted to cold, or exposure to low temperature of animals highly adapted to formaldehyde, results in unusually pronounced hypoglycemic responses. This has been regarded as an example of the specialization of adaptation at the cost of adaptability to other agents ("crossed sensitization").[49]



Blood-sugar changes in hypophysectomized rats during the G-A-S produced by exercise or cold. Note that hypophysectomy decreases adaptability so that the G-A-S is "telescoped" into a brief six-day period under the conditions of this experiment: yet the three stages are again clearly distinguishable: hypoglycemia, during the A-R, return slightly above normal during the stage of resistance and secondary hypoglycemia during the stage of exhaustion. The greatly shortened stage of resistance in the adrenalectomized and hypophysectomized animal clearly show that adrenal and hypophyseal hormones are not indispensable for adaptation but they prolong the period during which resistance, to uniform and continuous exposure, is possible.
(After H. Selye: J. Clin. Endocrinol. 6, 117, 1946.)

Hypophysis. — The effect of **hypophysectomy** upon the blood-sugar response during the G-A-S is essentially the same as that of adrenalectomy (see below). The initial hyperglycemia is absent and replaced by a particularly pronounced

[43] Selye and Dosne A35802/41.
[44] Genes et al. B19656/41.
[45] Russell et al. B26111/44.
[46] Wilhelmi **B18793/48.**
[47] Selye B1204/46.
[48] Scarpello A32643/30.
[49] Masson A38380/40, Masson and Selye A17983/39.

hypoglycemia during the stage of alarm. This is followed by a return to, or slightly above, normal levels in the stage of resistance, but the length of this stage is greatly reduced in the absence of the hypophysis. During the stage of exhaustion, death occurs in severe hypoglycemia.[50] Curiously, the initial "adrenaline hyperglycemia" is also eliminated by hypophysectomy, but this may merely be due to a depletion of the hepatic glycogen reserves upon which the hyperglycemic action of adrenaline depends. The greater tendency of the blood-sugar to rise above normal during the resistant stage in hypophysectomized than in adrenalectomized animals suggests that some cortical function is preserved after ablation of the hypophysis.

It is especially interesting that after adaptation, even such stressors as *exercise* or exposure to *cold* — which markedly increase carbohydrate-utilization — can be tolerated without hypoglycemia and indeed may be accompanied by hyperglycemia even in the hypophysectomized animal. "These experiments are not in accord with the assumption that the characteristic disturbance in the carbohydrate-metabolism of the hypophysectomized animal is an inability to regenerate blood-sugar from endogenous sources".[51] Of course some deficiency in gluconeogenesis undoubtedly exists after hypophysectomy, but apparently this can be largely overcome by adaptation. Presumably the peripheral tissues "learn" to use less sugar and/or to make glucose from non-sugars without hypophyseal hormones. Unless very mild stressors are used, however, hypophysectomized animals respond with fatal hypoglycemia to most alarming stimuli and death prevents the development of the secondary hyperglycemic phase.

Hemorrhage also causes hyperglycemia in the intact but hypoglycemia in the hypophysectomized rat.[52]

Infection with T. Lewisi likewise produces hypoglycemia, e.g., in rats deprived of their pituitaries. It was concluded that "since the parasites in the blood utilize sugar which cannot be replaced, it is inevitable that a critical hypoglycemia will occur".[53] However, in hypophysectomized animals such hypoglycemia is produced by most types of stressors, hence this change cannot be specifically ascribed to sugar-consumption by the parasites themselves. It is evidently the non-specific effect of systemic stress as such. Let us incidentally re-emphasize in this connection that, according to our previously mentioned experiments, some degree of gluconeogenesis is possible, even in the absence of the hypophysis so that consumed blood-sugar can be replaced, albeit at a slow rate.

These experiments with T. Lewisi serve to illustrate the difficulty of distinguishing between specific and non-specific effects in certain instances. It is undoubtedly tempting to assume that sugar-utilization by the parasites is responsible for the hypoglycemia unless we realize that in hypophysectomized animals most other systemic stressors act in the same manner.

Impure **anterior-lobe extracts** can cause hyperglycemia and increased gluconeogenesis with a rise in glycogen-reserves. This effect is not solely due to corticotrophin but, at least partly, also to other carbohydrate-active principles (e.g., *somatotrophin, prolactin*).[54] Curiously, under certain conditions, soma-

[50] Selye and Foglia A9805/38.
[51] Selye and Foglia A9805/38.
[52] Wilhelmi and Long B19257/48.
[53] Molomut 99785/47.
[54] Cotes et al. B46554/49, Houssay and Anderson B46271/49, B45948/49.

totrophic anterior-lobe extracts can also exert *antidiabetic "pancreatotrophic"* actions.[54a] The mechanism of these effects and their possible participation in the G-A-S, have not yet been fully elucidated.

Purified *ACTH* likewise causes hyperglycemia and glycosuria in man [55] and in rats.[56] Both the hyperglycemic and the glycosuric effects of the hormone are greatly augmented by a high carbohydrate-intake.[57] Indeed the corticotrophin-pretreated human being [58] or rat [59] responds to glucose with a diabetic type of blood-sugar curve. In normal man, ACTH may also induce a relative insulin resistance [59a] and in children with "familial hypoglycemia" it tends to restore the blood-sugar towards normal.[59b]

Curiously, the hyperglycemic action of corticotrophin is most effectively inhibited by treatment with reduced glutathione in man. This has been ascribed to an "improved performance of those systems which require free sulphydryl groups for their normal function", e.g., the renal tubular reabsorption and the utilization of glucose.[60] Both the augmentation of the alimentary hyperglycemia by corticotrophin, and the selective inhibition of the latter's glycemic action, are additional examples showing that the effects of hormones produced during the G-A-S largely depend upon conditioning factors. Observations of this type help us to understand why the "diseases of adaptation", though always due to derangements of the same G-A-S, may assume such manifold aspects.

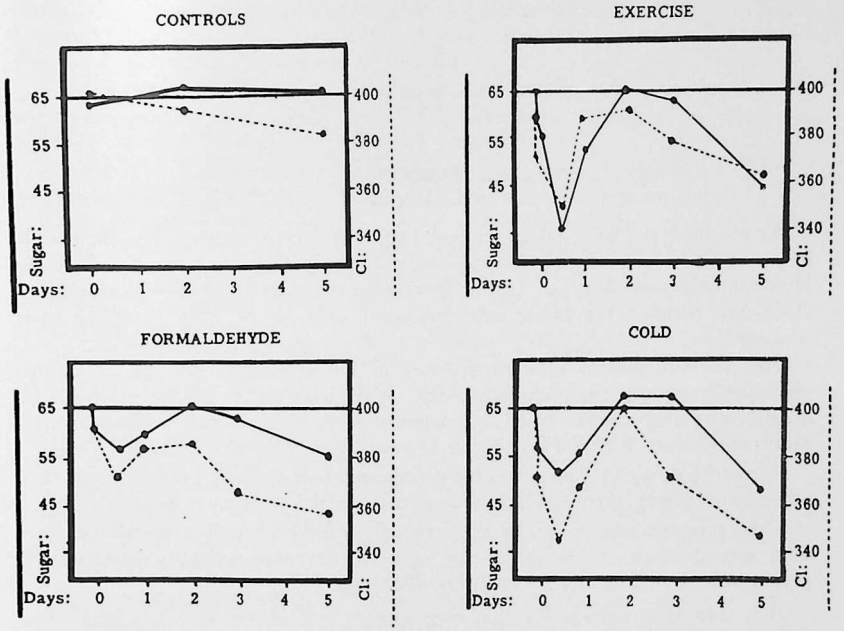
Posterior-lobe extracts (vasopressin) also raise the blood-sugar, but their participation in the glycemic changes during the G-A-S has not been proven.[61]

Adrenals. — Adrenalectomy does not significantly influence the blood-sugar-level under resting conditions. However, during fasting or systemic stress, the adrenalectomized animal readily develops marked, and often fatal, hypoglycemia.[62] This abnormal response is almost exclusively due to cortical deficiency, since, at least in the rat, a few days after enucleation of the medulla, the glycemic response to fasting is again approximately normal.[63]

In agreement with this view, most alarming agents which increase the blood-sugar of intact animals, fail to do so after adrenalectomy. In fact, in the absence of the adrenals these same systemic stressors usually cause a pronounced, and often fatal, hypoglycemia. This is presumably due to the fact that liberation of adrenaline and of gluco-corticoids is largely responsible for the hyperglycemic response to systemic stress. Yet, other factors must also be involved. In animals previously adapted to certain stressors, subsequent exposure after adrenalectomy did not cause fatal hypoglycemia, comparable to that elicited by the same agents in adrenalectomized, but not previously adapted controls.[64] Apparently, during the stage of resistance, carbohydrate-metabolism readjusts itself so that adrenal hormones become less important in the maintenance of the blood-sugar.

[54a] Gaarenstroom et al. B39096/49.
[55] Conn et al. B29612/48, B46372/48, Hoffman et al. B23331/48, Sayers et al. B37710/49.
[56] Bergner and Deane B23875/48, Houssay and Anderson B46271/49, B45948/49, Li et al. B34773/49.
[57] Ingle et al. B2709/47.
[58] Conn et al. B32328/49, B29612/48, Sprague et al. B46430/50.
[59] Constantinides et al. B38913/49.
[59a] Mason et al. B17986/48.
[59b] McQuarrie et al. B39075/49.
[60] Conn et al. B23328/49, B33407/49.
[61] Selye **94572/49.**
[62] Selye **94572/49.**
[63] Greep and Deane B37722/49.
[64] Selye A15800/38.

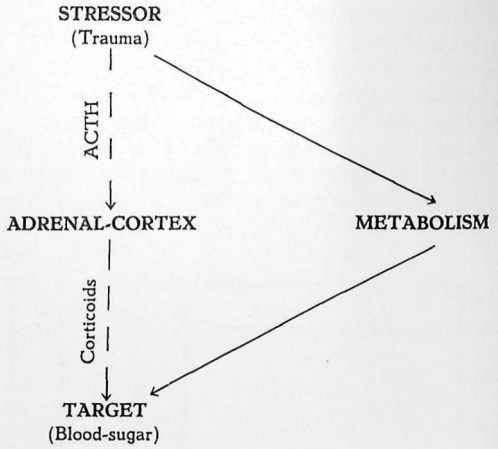
Unlike in the intact rat, *traumatic* shock also causes hypoglycemia after adrenalectomy. Cortical extracts, in doses which in themselves have little effect upon the blood-sugar-curve, reverse this response to trauma so that hyperglycemia ensues. This means that shock-hyperglycemia is not "mediated" through the adrenals (and is not due to adrenaline or corticoids alone), but depends upon the conjoint action of gluco-corticoids and systemic stress. The effect of the latter might be due to substances produced in the course of the catabolic impulse.[65]



Whole blood chloride and blood sugar changes in adrenalectomized rats, during the general-adaptation-syndrome. Note that in the adrenalectomized animals, the initial hyperglycemia of the alarm reaction fails to develop while the hypoglycemic phase is particularly pronounced. The entire general-adaptation-syndrome is "telescoped" into a brief five-day period but the three stages are still distinguishable. The first (alarm reaction) is characterized by hypoglycemia and hypochloremia, the second (stage of resistance) by a return of these values to normal and the third (stage of exhaustion) by a second period of hypoglycemia; this third stage ends in the death of the animal. (After H. Selye: J. Clin. Endocrinol. 6, 117, 1946.)

In other words, in the intact animal hyperglycemia can be produced by trauma through a dual mechanism: (1) increased gluco-corticoid-production, (2) peripheral activation of the circulating gluco-corticoids. In gluco-corticoid-treated animals this second mechanism remains effective although the first is eliminated. In untreated adrenalectomized animals both mechanisms are inactivated and the target no longer responds to stress. In the diagram below these two pathways are represented by interrupted and solid lines respectively.

[65] Selye and Dosne A37037/41.



As we shall see later, lactic-acid production is increased in traumatic shock and corticoids raise the blood-sugar only in the presence of the liver. It is tempting to assume therefore that in shock after adrenalectomy, the blood-sugar decreases because the lactic acid produced fails to be resynthetized into glucose.[66]

The adrenal-medulla also participates in the regulation of the glycemic response, although much less markedly. After destruction of the medulla in dogs, the hyperglycemia caused by trauma was slight or absent.[67] However, in such experiments, it would be difficult to avoid some incidental cortical injury.

Hemorrhage, which causes hyperglycemia in intact animals fails to elicit this response and may even produce hypoglycemia after adrenalectomy.[68]

The hyperglycemia caused by the especially intense general-stress associated with *electro-shock* in the rat is not entirely prevented by adrenalectomy [69] perhaps because of excessive sympathin-discharge.

It is especially noteworthy that even intense *muscular exercise,* which certainly consumes much glucose, can be performed by a trained adrenalectomized rat without the development of hypoglycemia.[70] Interestingly, large pantothenic-acid supplements protect even untrained rats against the hypoglycemic action of exercise (swimming) and prolong their life-span.[71]

If adrenalectomized rats are maintained on NaCl and exposed after the operation to comparatively mild doses of *formaldehyde, muscular exercise* or *cold,* they can still develop a typical triphasic blood-sugar curve; there is an initial hypoglycemia (stage of alarm), a subsequent return of the blood sugar to, or slightly above, normal (stage of resistance) and finally, fatal hypoglycemia (stage of exhaustion). These blood-sugar variations are accompanied by other manifestations of the G-A-S characteristic of these three stages respectively. Apparently the G-A-S evolves in an essentially normal manner even in adrenalectomized animals but the initial hyperglycemia is absent (lack of

[66] Selye and Dosne A37037/41.
[67] Jourdan et al. B34022/43.
[68] Engel et al. A58685/43.
[69] Delay and Soulairac B19816/44.
[70] Selye A15800/38.
[71] Dumm and Ralli B28235/48.

adrenaline), there is no marked hyperglycemia in the stage of resistance (lack of gluco-corticoids), and the entire G-A-S is "telescoped" mainly due to the fact that the stage of resistance is extremely short.[72]

Adrenalectomy (or adrenal demedullation) inhibits or reverses the normal hyperglycemic response to *emotional excitement* in the rat. This was ascribed to a predominance of the "vago-insulin" over the "sympathetico-adrenal" system. It was assumed that stress normally stimulates both insulin (through the vagus) and adrenaline (through the splanchnic) secretion, but after adrenalectomy the former effect predominates and the blood-sugar falls.[73] However, since stress causes hypoglycemia even in the pancreatectomized-adrenalectomized animal,[74] excess insulin production can hardly be the sole cause of this type of hypoglycemia.

The normal, hyperglycemic response to acute *anoxia* is also characteristically reversed by adrenalectomy in the rat.[75] This abnormal response is not influenced by riboflavin-supplements.[76]

In mice rendered mildly diabetic by alloxan, injection of killed *typhoid* organisms aggravate the hyperglycemia. This response is prevented by adrenalectomy, but since it is restored by a fixed daily amount of cortical extract, it is not mediated by the increased endogenous production of corticoids.[77] Presumably we are dealing with the same kind of conditioning by gluco-corticoids to the hyperglycemic action of stress as that previously discussed in connection with trauma.

Adrenaline causes a rapid and pronounced but transitory hyperglycemia due to its ability to transform hepatic glycogen into glucose. The initial hyperglycemia during the shock-phase is probably due to adrenaline discharge. This would explain the absence of the initial hyperglycemic response after adrenalectomy (see above) and in individuals whose hepatic glycogen stores are low. Yet even after complete evisceration, adrenaline decreases glucose-tolerance in the rat; hence it was concluded that the effect of the adrenal-medulla upon carbohydrate metabolism during stress is not solely mediated through the liver.[77a]

The hyperglycemic effect of adrenaline is increased during the A-R, but in the resistant stage the results so far obtained were inconsistent.[78] Under conditions of brief, mild anoxia the effect of adrenaline upon glucose tolerance is not markedly altered [78a] and there are no data available concerning the effect of adrenaline upon the blood-sugar during the stage of exhaustion.

The gluco-corticoids cause increased gluconeogenesis due to the production of glucose from non-sugars in the liver. Their action is slower and more persistent than that of adrenaline. Unlike the latter, they do not merely transform glycogen into glucose, but actually increase the total carbohydrate content of the body. They are presumably chiefly concerned with the secondary hyperglycemia during the counter-shock and resistant phases.[78b] Yet, even the transformation of intravenously injected glucose into liver glycogen is accelerated by cortical extract; when this effect predominates the gluco-

[72] Selye A9210/38.
[73] Gellhorn et al. 80365/41, A37798/42.
[74] Selye 94572/47.
[75] van Middlesworth et al. 84780/44.
[76] Reade and Morgan B32976/49.
[77] Tobian and Edwards B38783/49.
[77a] Ingle and Nezamis B46482/50.
[78] Masson A34562/40, A36632/41.
[78a] Keyes and Kelley B39030/49.
[78b] Selye 94572/49.

corticoids can actually increase sugar tolerance.[78c] Thus it depends upon conditioning factors (e.g., availability of carbohydrates and proteins) whether these hormones increase or diminish the blood-sugar, but under usual conditions the hyperglycemic action prevails.

Apparently the cortical hormones can thus exert a stabilizing influence upon the blood-sugar since both *insulin*-hypoglycemia and *adrenaline*-hyperglycemia are inhibited by cortical extracts rich in gluco-corticoids.[79] The effect of cortical extracts upon the glycemic response to *anoxia* is variable and presumably again depends upon conditioning factors which may accentuate either gluconeogenesis from non-sugars or the transformation of blood-glucose into hepatic glycogen.[79a]

Experiments on *partially hepatectomized* rats showed that after removal of 85% of the liver tissue, fasting causes pronounced hypoglycemia which may be completely inhibited by cortical extract. On the other hand, the decrease in blood-sugar produced by *complete hepatectomy* is not significantly influenced, even by very large doses of such extracts. This finding makes it probable that corticoids merely stimulate hepatic gluconeogenesis, but do not inhibit the utilization of the circulating blood-sugar.[80]

Long continued pretreatment with **DCA** interferes with the normal hyperglycemic response to stressors (e.g., cold, trauma, exercise, drugs). Presumably, the resulting compensatory atrophy of the adrenal cortex prevents the production of gluco-corticoids, which would normally occur under such conditions.[81] The great insulin sensitivity of DCA-treated rats is probably also due to this compensatory adreno-cortical involution.[82]

Kidney. — The **RPS,** which are so important in connection with other reactions to systemic stress, do not appear to exert any marked specific influence upon carbohydrate metabolism. Hence, they are not likely to play a major rôle in the characteristic glycemic reactions which occur during the G-A-S.

Pancreas. — An acute *inflammation* (for instance that caused by turpentine-injection into the pleural cavity) is allegedly accompanied by a marked local gluconeogenesis, in the **pancreatectomized** dog. It was thought that the surplus glucose, formed in the inflamed area, comes from products of local protein-breakdown and diffuses into the circulation, thus aggravating the pre-existent hyperglycemia. This, it was felt, could explain the greater insulin-requirements occasioned by inflammation in diabetic animals and man.[83] However, the above conclusions were based merely on comparative determinations of glucose, N.P.N., etc., in empyema fluid and in blood. Since the cell-content of the blood is always much greater than that of the effusion, these experiments have been repeated, comparing the concentration of glucose and N.P.N. in plasma and the supernatant portion of the pleural effusion. Under these conditions there was no evidence of any gradient of these substances between the two fluids . Thus, the rise in blood-sugar, which accompanies an infection in the diabetic, is probably not due to gluconeogenesis at the site of microbial invasion, but to increased sugar-formation in the liver, and possibly the kidney, which are the only organs known to produce glucose normally.[84] In certain

[78c] Keyes and Kelley B39029/49.
[79] Selye and Dosne A30701/39, Selye et al. A30865/40.
[79a] Keyes and Kelley B39030/49.
[80] Selye and Dosne A30702/40.
[81] Selye and Dosne A37249/42.
[82] Cheng and Sayers B36426/49.
[83] Menkin A57481/43.
[84] Mattar et al. 85861/45.

phases of the G-A-S most types of stressors raise the blood-sugar and there is no reason to assume that infections act through a special mechanism. Presumably pancreatectomy merely increases the normal hyperglycemic effect of systemic stress.

The hyperglycemic response itself is more marked after *hemorrhage* in pancreatectomized or alloxan-diabetic dogs than in normal controls. Yet judged by femoral arterio-venous glucose-differences, the utilization of sugar in the periphery is also increased.[85]

Since during the resistance stage of the G-A-S there is a tendency towards hyperglycemia, the effect of stress upon the diabetes of partially depancreatized, force fed rats has been systematically examined. It was found that a G-A-S produced by repeated *formalin* injections actually diminishes the glycosuria in these animals. It was concluded that "these data do not support the hypothesis that activation of the adrenal cortices during stress causes exacerbation of diabetes".[85a]

Curiously the diabetogenic effect of *folliculoids* (e.g., stilbestrol), which is usually quite obvious in partially pancreatectomized rats, gives way, after about a month of treatment, to a permanent anti-diabetic, protective action.[85b]

In evaluating these apparently contradictory results, it must be kept in mind that stress increases glucose combustion (through its direct effect upon the tissues) but at the same time it augments gluconeogenesis from non-sugars (through the discharge of excess gluco-corticoids). Presumably, it depends upon conditioning metabolic factors which of these actions prevails. The well-known fact that in diabetic patients the insulin requirements usually rise under the influence of intercurrent infections, intoxications, psychic shock and other stressors, strongly suggests that the G-A-S can exert diabetogenic effects, probably through the increased production of ACTH and gluco-corticoids (cf. also diabetes as a disease of adaptation).

The hypoglycemic action of **insulin** decreases during the A-R and increases in the stage of resistance,[86] but no pertinent observations have been made during the stage of exhaustion. After prolonged *fasting* at the time of the "fasting hyperglycemia" rats are very resistant to insulin, indeed here the hormone may cause hyperglycemia. This could be due to increased corticoid elaboration during the counter-shock phase of the A-R.[87]

It has also been shown that the hyperglycemia produced by *traumatic* [88] and *electro-shock* is singularly resistant to insulin.[89] The increased insulin-tolerance seen in patients during the immediate post-operative period after lumbo-dorsal sympathectomy, is followed by a secondary stage of increased sensitivity to the hormone. This change in insulin resistance was interpreted as a manifestation of the adaptation syndrome.[90]

Other investigators emphasized that during early stages of various *toxemias* there may be hyperglycemia, glycosuria and decreased carbohydrate-tolerance,[91] with a subnormal response to insulin.[92] Some observations suggest that in a

[85] Beatty B23924/48.
[85a] Ingle B46486/50.
[85b] Rodriguez B45951/49.
[86] Masson A34562/40, 98782/41, A36632/41.
[87] Selye A32152/40.
[88] Pignatelli B34404/46.
[89] Delay and Soulairac B19816/44.
[90] Simeone B33439/49, Simeone and Vavaudes B38983/48.
[91] Sweeney and Lackey B26104/28, Williams and Dick 7528/32.
[92] Lawrence and Buckley 21095/27.

liver damaged by toxine there may be a disturbance of the normal barrier, which separates amylase from its substrate or of the normal environment, which inhibits amylase-activity. In either case liver-glycogen would then be broken down through the abnormal pathway of amylase action as well as by normal phosphorolysis. Since only the latter is subject to control by insulin, this could allegedly account for the insulin-resistance characteristic of toxemic states.[93] It must be kept in mind, however, that gluco-corticoids are potent antagonists of insulin and their increased secretion during stress might, in itself, explain insulin-resistance under such conditions.

It is interesting that an increased insulin-resistance has also been found in malignant hypertension, collagen-diseases, active infections, neoplastic diseases and psychosomatic disorders,[94] that is, in derangements in which systemic stress presumably plays an important rôle.

Gonads. — It is difficult to understand why the so-called "diabetogenic" action of **folliculoids** — which is inhibited by adrenalectomy — reappears in corticoid-treated adrenalectomized animals.[95] It is possible, but by no means proven, that the folliculoids, like trauma and anoxia (see above), furnish metabolites which can be utilized for gluconeogenesis, with the aid of corticoids.

The literature concerning the above-mentioned influences of the hormones upon carbohydrate metabolism is too voluminous and not sufficiently relevant to be discussed in greater detail here, hence the reader is merely referred to the corresponding chapters in textbooks of endocrinology.[96]

Nervous system. — Nervous stimuli undoubtedly play a very prominent rôle in the regulation of the blood-sugar during the G-A-S. We have already mentioned that intense nervous stimuli can cause particularly pronounced systemic stress, and thus can produce a G-A-S. But beyond that, the vegetative nervous centers in the hypothalamic region specifically regulate glycemic responses through efferent autonomic nerve tracts.[97] In this connection, special importance is attached to the following facts: (1) the splanchnics are the secretory nerves of the adrenal medulla, they can cause hyperglycemia through the discharge of adrenaline; (2) the hepatic branches of the sympathetic can cause glycogenolysis through the local liberation of sympathin; (3) the pancreatic branches of the vagus are probably secretory nerves of the Langerhans islets and hence can depress the blood-sugar by the discharge of insulin. Experiments on cats and rats have shown that stimulation of the hypothalamus, or even mere emotional excitement (noise of firecrackers, struggle resulting from enforced restraint), cause hyperglycemia in the intact animal, but hypoglycemia after denervation of the adrenals or ablation of the adrenal medulla. This hypoglycemic response is, in turn, abolished by subsequent vagotomy.[98] Apparently, under the influence of systemic stress, both the sympathetic and the parasympathetic nervous system are stimulated; the first tends to raise the blood-sugar through (adrenaline-sympathin actions), the second to depress it (vago-insulin action).

It is noteworthy, in this connection, that DFP (di-isopropylfluorophosphate), which inactivates the cholinesterases, causes severe hypoglycemia in the dog.[99]

[93] Taubenhaus and Soskin 82817/42.
[94] Nuetzel and Olsen B32799/49.
[95] Ingle A55580/42, Janes and Nelson A31856/40.
[96] Selye 94572/49, Turner B19831/48.
[97] Gellhorn et al. 79539/40.
[98] Gellhorn et al. 79539/40, 80365/41.
[99] Heymans and Casier B23147/48.

Observations on psychotic patients lead to the conclusion that during intense emotional excitement the insulin content of the blood rises significantly without any change in blood sugar, while in normal individuals, excitement tends to cause hyperglycemia but no noteworthy rise in the blood insulin. It has been claimed that "the experiments suggest that emotional excitement leads to a discharge over both vago-insulin and sympathetico-adrenal systems, the effect on the former predominating in psychotics, whereas in the normal, the excitation of the latter prevails".[100] While the fundamental importance of such investigations is evident, the conclusions must be viewed with the reservation that the insulin bioassay method used (glycemic response in the hypophysectomized, adrenal-demedullated rat) is not very specific.

Thyroid. — Observations on **thyroidectomized** rats indicate that in the absence of the thyroid the hypoglycemic phase of the A-R is usually replaced by a marked hyperglycemic response. This was confirmed with a variety of stressors, such as formaldehyde, cold, muscular exercise and even complete starvation.[101] The mechanism of this peculiar inversion of response has not yet been elucidated; perhaps decreased carbohydrate-utilization may play a part during these periods of the G-A-S when gluconeogenesis is normally pronounced. In any case, the voluminous literature concerning the influence of thyroidectomy upon the supposedly specific glycemic effects of various agents will have to be revised, bearing in mind that in the absence of the thyroid almost any stressor tends to cause hyperglycemia. Curiously, in vagotomized rats thyroidectomy inhibits, while thyroxine increases, the hyperglycemia normally produced by stressors (electro-shock, metrazol, typhoid-paratyphoid vaccine); from this it was concluded that "thyroid-hormone increases the excitability of the center controlling the sympathetico-adrenal system".[102]

In completely thyro-parathyroidectomized dogs the rise in blood-sugar normally caused by hemorrhage is diminished or absent.[103] This was ascribed to an inhibition of the adreno-cortical response, but since these animals were in tetanic convulsions the resulting depletion of the glycogen reserves may have rendered them unable to develop a normal hyperglycemic reaction.

Administration to rabbits of a single large dose of the antithyroid compound dithiobiuret (DTB) causes a marked and prolonged hyperglycemia, but it has been emphasized that "the effects on carbohydrate metabolism of DTB may be non-specific effects mediated by epinephrine, particularly in view of the fact that the specific glandular changes associated with alarming stimuli have been observed in DTB-treated animals".[104]

Glucose. — According to Masson [105] it is characteristic both of the A-R and of the resistant stage that the alimentary hyperglycemia, which follows glucose-administration, is increased. This has been verified during the G-A-S produced in the rat by exposure to **cold, muscular exercise** or **formaldehyde** injections. Levulose-tolerance may also be diminished during the alarm-reaction, if the liver-function is impaired. In children after severe burns this usually occurs at about the 3th-6th day.[106]

[100] Gelhorn et al. 80365/41, A37798/42.
[101] Selve A9804/38.
[102] Gellhorn and Feldman A36634/41.
[103] Agazzotti B30887/39.
[104] Seifter et al. B37348/48.
[105] A34562/40, A36632/41.
[106] Rae and Wilkinson B26861/44.

A decrease in glucose tolerance has also been seen in dogs [107] and in man as a result of chronic intermittent **anoxia.**[108] Rats show extremely prolonged hyperglycemia and even glycosuria if fed glucose after exposure to severe anoxic conditions; some authors refer to this as "anoxic diabetes".[109]

Comparable changes in glucose-tolerance are produced by **infections;** [110] these may account for the increased insulin requirements of diabetics while they suffer from intercurrent infections.

In patients with hunger edema, glucose-tolerance may be either increased or decreased.[110a]

During **tourniquet shock** glucose administration by stomach tube causes extraordinarily high and prolonged hyperglycemic responses in the rat.[111] In children a post-**traumatic** decrease in glucose-tolerance is also very pronounced.[112] None of these studies have been extended to the stage of exhaustion, but essentially similar observations have been made in the rabbit [113] during the alarm reactions produced by various **other damaging agents.**

In summary, it may be said therefore that glucose-tolerance during the A-R is diminished, but the data concerning the later stages of the G-A-S do not yet permit definite conclusions.

[107] Stickney et al. B29396/48.
[108] Bryan and Ricketts B10396/44.
[109] van Middlesworth 93058/46.
[110] Pollack and Feibes B25210/40.
[110a] Postiglione & Lorusso B46333/44.
[111] Haist 93414/46.
[112] Mangione and Galeotti B31380/42.
[113] Loiseleur 68744/37.
Loiseleur and Nyka 68745/37.

Glycogen

Systemic Stress

The changes in glycogen stores which are truly **characteristic** of stress have not yet been systematically studied throughout the three stages of the G-A-S. A considerable amount of evidence suggests, however, that during the A-R the glycogen-reserves tend to fall both in the liver and in the muscles.

Extensive studies on various types of **traumatic and tourniquet shock** revealed that in the rat, simultaneously with the development of other manifestations of the A-R, both the liver- and the muscle-glycogen concentration fall considerably below normal. Even oral administration of glucose does not replete them to normal values. This is not due to insufficient absorption from the intestine, since ingested glucose disappeared from the gut at approximately the normal rate in shocked rats.[1] Depletion of liver-glycogen during traumatic shock has also been noted in the dog [2] and in man.[3] Experiments on rabbits suggest that even an ether or chloroform anesthesia, preceding an operation, suffices to cause a marked fall in liver glycogen.[4] Experiments with the Noble-Collip drum demonstrate that in the not-adopted rat this

[1] Haist 93414/46.
Haist and Hamilton B639/44.
Hamilton and Haist 93309/45.
[2] Jourdan et al. B19461/43.
[3] Lamarre and Lecocq A32644/35.
Lambret and Driessens A2914/37.
[4] Roscher B25560/33.

type of trauma causes the usual depletion of liver-glycogen, but this fails to occur after adaptation to trauma has been acquired.[5] From this, one might surmise that during the stage of resistance the glycogen stores are repleted.

There are no data concerning glycogen reserves during the stage of exhaustion. However, a secondary fall could be expected, not only because other manifestations of the A-R recur at this time, but also because glycogen-reserves tend to drop whenever the organism is very severely damaged.

Under the influence of **burns,** the glycogen content of the whole carcass diminishes within a few hours in the rat.[6] Essentially similar responses have been noted after a variety of other stimuli causing systemic stress.[7]

Contrary to most types of systemic stress, exposure to **low atmospheric pressure** increases the glycogen content of the liver even in the starving rat.[8] Since the total carcass glycogen also rises under the influence of anoxia, the increase in hepatic glycogen can not be attributed to a mere transfer of preformed carbohydrates from other parts of the body into the liver. This was especially emphasized [9] to show that the rise in the hepatic glycogen-stores is not due to an adrenaline discharge. While at certain dose-levels adrenaline can raise liver-glycogen, it does so merely at the expense of muscle-glycogen. Gluco-corticoids also raise the fasting glycogen-level of the liver and there are good reasons to believe that the enlargement of the adrenal cortex, seen in animals exposed to reduced atmospheric pressure, is accompanied by increased production of gluco-corticoids. We shall see later that adrenalectomy prevents the rise in liver-glycogen normally caused by anoxia. All these observations are consonant with the general concept of the G-A-S. Anoxia depresses sugar-utilization and — as does any other systemic stress — it stimulates the endogenous production of corticoids. It is reasonable to assume, therefore, that under the influence of gluco-corticoids much protein is transformed into sugar and that the latter — not being adequately utilized during anoxia — is deposited as glycogen in the liver.[10]

In early stages of shock, due to **cardiazol, histamine** or **peptone,** a transfer of glycogen from the liver to the muscles allegedly occurs in the dog, but in later stages the muscle glycogen stores are also depleted.[11] Especially marked glycogenolysis occurs during the formation of **turpentine** abscesses.[12]

The initial depletion of liver glycogen induced by **fasting** in guinea-pigs is followed by a secondary rise, which was ascribed to the production of gluco-corticoids.[12a] This is reminiscent of the "hyperglycemia of fasting" (cf. above).

In the **"gravity shock"** of the rabbit an initial hyperglycemia is followed by hypoglycemia during which the hepatic glycogen-stores become depleted.[13]

Stimuli Influencing the Changes in Glycogen-stores During the G-A-S

Hypophysectomy prevents the rise in liver-glycogen which normally occurs in rats exposed to *reduced atmospheric pressure.*[14] This is probably due to the resulting inhibition of gluco-corticoid production.

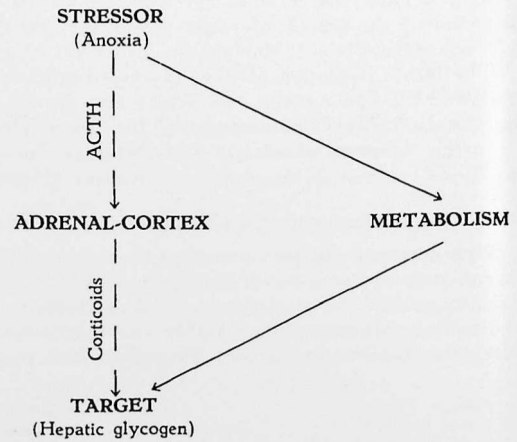
Purified **corticotrophin** is highly active in raising the glycogen-content of the liver, for instance in the rat. This effect runs parallel with the adreno-cortical

[5] LePage 93054/46.
[6] Peters 89884/45.
[7] Selye B1204/46.
[8] Evans 30599/34.
Langley and Clarke 83179/42.
[9] Evans 30599/34.
[10] Selye B1204/46.
[11] Charnyi et al. B19778/44.
[12] Brentano B25441/42.
[12a] McKee et al. B37719/49.
[13] Nastuk B26184/47.
[14] Evans 56353/36.

enlargement caused by this hormone and is presumably due to increased gluco-corticoid production.[15] The effect of corticotrophin upon the glycogen-stores of animals under systemic stress has not yet been examined.

Adrenalectomy prevents the rise in liver (and total carcass) glycogen normally seen in rats exposed to *reduced atmospheric pressure*.[16] As previously stated, this is consonant with the concept that here increased production of gluco-corticoids and the resulting rise in gluconeogenesis are due to systemic stress as such. These factors, conjointly with decreased sugar-utilization due specifically to anoxia, lead to the excessive glycogen-deposition. Adrenalectomized rats treated with sub-glycotropic amounts of gluco-corticoids also showed an increase in liver-glycogen during anoxia.[17] This agrees with our view since the factor of decreased sugar-utilization would still be operative.[18] We have previously mentioned that the hyperglycemic effect of trauma is greatly potentiated by threshold amounts of cortical extracts in adrenalectomized rats.[19] Irrespective of our theoretic interpretation of the mechanism through which gluco-corticoids augment the glycogen-depositing action of anoxia, the above experiments on adrenalectomized rats furnish another striking example of a stressor (anoxia) which influences a target (liver-glycogen) only in the presence of corticoids, but not necessarily by augmenting their secretion.

Presumably, in the intact animal, hepatic glycogen-reserves can be raised by anoxia through a dual mechanism: (1) increased gluco-corticoid-production; (2) peripheral activation of the circulating gluco-corticoids. In gluco-corticoid-treated animals this second mechanism remains effective although the first is eliminated. In untreated adrenalectomized animals both mechanisms are inactivated and the target no longer responds to stress. The diagram below, which illustrates this mechanism is very similar to that used to visualize the rôle of the adrenal in the regulation of the glycemic response to stress. The two pathways are again represented by interrupted and solid lines respectively.



[15] Bergner and Deane B23875/48.
[16] Evans 56353/36, 30599/34, A36854/41.
[17] Langley and Clarke 83179/42.
[18] Selye B1204/46.
[19] Selye and Dosne A37037/41.

Rats, in which systemic stress was produced by *burns* [20] or mere *fasting*,[21] lose their glycogen-stores much more rapidly after adrenalectomy than otherwise. DCA may slightly diminish this loss because it improves the general condition of adrenalectomized animals, but only gluco-corticoids (cortical extract, cortisone, etc.) cause a marked rise in the hepatic glycogen stores of the starved adrenalectimozed animal.[21a]

While **mineralo-corticoids** do not influence the glycogen stores significantly, **gluco-corticoids** cause marked deposition of glycogen in the liver in intact animals. Since this occurs even during starvation, it is presumably due to glyconeogenesis.[21b] Curiously, in ascorbic-acid deficient guinea-pigs gluco-corticoids do not exert this effect.[21c] Hepatic glycogen deposition also failed to occur in rats chronically treated with large doses of cortisone. This may have been due to a true adaptation to this hormone-effect or to the protein-catabolic action of cortisone that depletes the body of amino-acids from which glycogen could be formed.[21d]

Insulin treatment has no effect upon the loss of glycogen during traumatic shock in rats,[22] but (especially in combination with glucose) it can inhibit glycogenolysis in animals with turpentine-abscesses.[23]

Glucose administration can not restore the depleted glycogen-stores of a rat in *tourniquet-shock*.[24] Apparently systemic stress seriously interferes with the synthesis of glycogen from glucose, or the ability to fix glycogen in tissues, even if abundant amounts of sugar are available. Any theory attempting to explain glycogen-depletion during systemic stress must take this fact into account.

Glucose ingestion in rats during severe **anoxia** causes much more pronounced glycogen-deposition in the liver (and heart) than in not-anoxic controls. "A greatly reduced rate of glycogenolysis and an only partially reduced rate of glycogenesis might result in an overall increase in total glycogen storage during 24 hours exposure".[25]

Other Sugars

Among other sugars, especial attention has been given to the **serum polysaccharides**, which are associated with the serum proteins. Their level is significantly elevated in patients suffering from malignant tumors, arthritis, cholelithiasis, ulcerative colitis, nephritis, pemphigus, most infections, traumatic injuries and x-irradiation. "The suggestion is made that elevations of serum polysaccharide are involved in some way with tissue proliferation".[26] The possible relationship of this change to the G-A-S would deserve further study.

[20] Peters 89884/45.
[21] Evans A36854/41.
[21a] Wang and Verzar B43569/49, Selye 94572/49.
[21b] Selye 94572/49.
[21c] McKee et al. B37719/49.
[21d] Selye 35935/ND.
[22] Haist and Hamilton B639/44.
[23] Brentano B25441/42.
[24] Haist 93414/46, Haist and Hamilton B639/44.
[25] van Middlesworth 93058/46.
[26] Shetlar et al. B39188/49.

Lactic Acid

The blood-lactic-acid changes characteristic of the G-A-S have not yet been systematically studied throughout the three stages, but the accumulated data indicate a pronounced increase during the A-R, with a return towards normal as resistance is acquired.[1] When the lactacidemia reaches very high levels, considerable quantities of lactic-acid are spilled over into the urine.[2] It has also been shown that the removal of lactate from coronary blood, by the myocardium, is greatly reduced by a variety of stressors. "Adrenaline-release may be the common denominator in such situations of severe stress, leading to glycogenolysis within the heart (and liver), with endogenous production of lactate as an immediate emergency source of energy . . .".[3]

The above formulation of the lactacidemic curve characteristic of stress is mainly based upon observations on **traumatic shock,** produced by direct injury, the tourniquet technique and other essentially related procedures.[4] The typical traumatic hyperlactacidemia, is accompanied by an increase in the uptake of lactic acid by the liver, as judged by angiostomy experiments in dogs.[5] In the event of long continued exposure to the traumatic effect of the Noble-Collip drum, there is an initial hyperlactacidemia with return to normal during the stage of resistance.[6]

The systemic stress of intense **x-irradiation** likewise raises the blood-lactic-acid quite rapidly.[7] This initial rise may be followed by a fall below the normal value.[8]

Hyperlactacidemia has also been described after **hemorrhage** in the rat,[9] and during **"gravity shock"** in the rabbit.[10] It is a characteristic feature of the **"medical shock"** incident to a variety of grave diseases which cause severe systemic stress.[11] It occurs after intense **muscular work** in man [12] as well as following exposure to **reduced atmospheric pressure and anoxia** in man,[12a] dog [13] and rat.[14] In man it was found that the hyperlactacidemia of exercise is especially intense under conditions of hypoxia.[15] Apparently this action of hypoxia is similar to that of other stressors, although its effect upon hepatic and muscular glycogen-stores is so different from that of most alarming stimuli (see above). This is another illustration of the "dissociation of symptoms", which occurs in the G-A-S, if agents are used which exert a prominent, specific action on certain target-organs.

[1] Engel 89587/45, Wilhelmi B18793/48.
[2] Delmas-Marselet B26881/46.
[3] Goodale and Hackel B32751/49.
[4] Allison et al. B26108/43, Beatty B26117/45, B1137/45, Cole et al. 84978/44, Engel et al. A58685/43, Genes et al. B19656/41, Gutman et al. 81881/41, MacLeod A32690/21, McShan et al. B26113/45, Meyer et al. B26114/46, Neufeld et al. A63529/43, Richards B26109/44, Riegel B26110/27, Root et al. B26116/47, Russell et al. B26111/44, Seligman et al. B26115/47.
[5] Genes et al. B19656/41.
[6] Le Page 93054/46, Neufeld et al. A63529/43.
[7] Hayashida A32701/36, Joos and Heeren A32646/30, Kikuchi 10149/31.
[8] Kikuchi 10149/31.
[9] Engle et al. A58685/43.
[10] Cole et al. 84978/44.
[11] Davidson et al. 87543/46.
[12] Abramson et al. B33401/49, Horwitt et al. B33707/49, Peters et al. 25379/26, Winkler and Hebeler A31099/39.
[12a] Friedmann et al. B46441/49.
[13] Herber B19880/48, MacLeod A32690/21.
[14] Tepperman et al. B4674/47.
[15] Tepperman and Tepperman B38669/48.

The very pronounced hyperlactacidemia [16] and lactaciduria [71] seen in patients after **electro-shock** treatment is largely the result of the accompanying convulsions. In rats the hyperlactacidemia induced by electro-shock is accompanied by acidosis, and an increase in blood-phosphate and -sodium, "equal to that produced by desoxycorticosterone"; this is followed by a fall in blood-potassium.[18]

Emotional excitement, induced by fear in rats causes an almost immediate, transient but very pronounced increase in the brain-lactate concentration. This was ascribed specifically to increased brain-activity during nervous stress.[19] It may not be related to the G-A-S as such, but seizures induced in various species by diverse means (e.g., anoxia, electro-shock, drugs) caused similar rises in brain-lactate.[19a]

The rise in blood lactic acid caused by *hemorrhage* is not prevented by **adrenalectomy** in the rat.[20] On the other hand **cortical extracts** increase the lactic acid content of the blood as judged by experiments in the dog [20a] and, in view of the marked effect of gluco-corticoids upon sugar metabolism, there is no doubt that stress can affect lactacidemia through the adrenal-cortex. The marked hyperlactacidemic effect of **adrenaline** is too well known to deserve special consideration here.[20b]

[16] Elliott et al. B31407/41, Watkins et al. B25880/47.
[17] Delmas-Marselet B26881/46.
[18] Ward and Call B27708/49.
[19] Richter and Dawson B38716/48, B38601/48.
[19a] Bain and Pollock B37732/49, Bain et al. B37733/49.
[20] Engel et al. A58685/43.
[20a] Keyes and Kelley B39029/49.
[20b] Selye 94572/49.

Pyruvic Acid

Pyruvic acid may be regarded as an intermediate compound in the degradation of glycogen (and the glucose formed from it) to carbon dioxide and water; hence it is pertinent to our discussion of carbohydrate metabolism. Yet this same acid also represents an intermediate in the transformation of proteins (and their split-products, the amino-acids) to carbohydrates. It is probable, for instance, that gluconeogenesis from protein may, at least partly, occur through oxidative deamination of the amino-acid alanine to pyruvic acid, which is subsequently reduced to lactic acid. From the latter, the liver can readily form glycogen.

$$\underset{\text{alanine}}{CH_3\text{-}CH\ (NH_2)\text{-}COOH} \rightarrow \underset{\text{Pyruvic acid}}{CH_3\text{-}CO\text{-}COOH} \rightarrow \underset{\text{Lactic acid}}{CH_3\text{-}CH(OH)\text{-}COOH} \rightarrow GLYCOGEN$$

We have discussed this problem in detail elsewhere; [1] here, we merely wish to survey those changes in the pyruvic-acid concentration of the blood which appear to be characteristic of the G-A-S.

[1] Selye 94572/49.

A rise in the blood-pyruvic- and other α-keto-acids is a **characteristic** metabolic corollary of the systemic stress incident to various types of shock.[2]

Comparatively few studies have been undertaken concerning the metabolism of this compound during the G-A-S, but it is already evident that following exposure to mechanical **trauma,** non-adapted animals respond with a marked rise in blood-pyruvic-acid, while in adapted animals, this response is mild or absent.[3]

After **electric shock therapy** there also is a rise in blood-pyruvate [4] and large amounts of pyruvic acid are eliminated through the urine.[5] This appears to be due largely to the accompanying muscular contractions, especially since **muscular work** itself produces a similar change.[6] The pyruvate content of the brain rises in various species during seizures induced by diverse means.[6a]

Adrenalectomy does not prevent the rise in blood-pyruvic-acid which normally occurs after *hemorrhage*.[7] Yet the adrenals certainly influence the blood-pyruvic-acid level during the G-A-S, since both adrenaline [7a] and glucocorticoids [7b] raise it.

During stress (fasting, exercise, electro-shock) the lactate/pyruvate ratio of the blood is often decreased in patients with thiamine-deficiency, heart-disease and various other maladies. It has been suggested that a lactate/pyruvate ratio of less than seven is indicative of **thiamine deficiency,** especially since treatment with this vitamin restores the ratio to normal.[8] In various diseases of children the abnormally high blood-pyruvate levels are also diminished by thiamine, since this substance is indispensable for the metabolism of glucose and in its absence pyruvate accumulates in the blood.[9]

[2] Allison et al. B26108/43, Beatty B26117/45, B1137/45, Cole et al. 84978/44, Engel et al. A58685/43, Goodale and Hackel B32751/49, Govier and Greer A37364/41, McShan et al. B26113/45, Meyer et al. B26114/46, Neufeld et al. A63529/43, Root et al. B26116/47, Russell et al. B26111/44, Seligman et al. B26115/47.
[3] Neufeld et al. A63529/43.
[4] Elliott et al. B31407/41, Gounelle et al. B40748/45, Watkins et al. B25880/47.
[5] Delmas-Marselet B26881/46.
[6] Horwitt et al. B33707/49, Watkins et al. B25880/47.
[6a] Bain and Pollock B37732/49, Bain et al. B37733/49.
[7] Engel et al. A58685/43.
[7a] Selye 94572/49.
[7b] Keyes and Kelley B39029/49.
[8] Goldsmith B38108/48.
[9] Allibone and Finch B38626/46.

LIPID METABOLISM

Adipose Tissue

A sudden loss of stored fat is very **characteristic** of the A-R-stage. It is often accompanied by a temporary transfer of lipids from the adipose-tissue-depots into the liver (cf. below). The "lipoclastic" response is merely one part of the general catabolic reaction which occurs during the A-R; it is accompanied by an essentially synchronous exhaustion of protein- and carbohydrate-stores. The fat stored in common adipose cells furnishes the bulk of the lipid-metabolites discharged into the blood at this time, but it is well to remember that the hibernating gland (cf. chapter: Hibernating gland) and the adrenal-cortex (cf. chapter: Adrenal) also release their lipids at approximately the same time. Presumably, the common adipose cells furnish mainly simple fatty-acid-esters, while the hibernating gland and the adrenal-cortex contribute lipids having more highly specialized metabolic functions (e.g., steroids).

The almost complete loss of adipose tissue incident to severe inanition has often been described. Particularly striking examples of it were found in the inmates of various concentration camps who, in addition to **hunger,** were also exposed to the stress of continuous **mental anguish.**[1] In this connection, the so-called "lipophil dystrophy" among returning prisoners of war, is of special interest. It was sometimes noted just after hunger-edema had subsided,[2] commonly in association with attacks of profuse sweating and increased carbohydrate-tolerance suggestive of hyperinsulinism.[3] Curiously, this tendency to deposit excessive amounts of fat was even noted among German troops, who, after returning to their home-land, following imprisonment during the second World War, were still exposed to partial starvation owing to economic conditions existing in Germany. That the tissue stored on such calorically inadequate diets is actually fat was verified by biopsy. This change proved to be associated with manifold incretory deficiencies suggestive of a hypothalamico-hypophyseal derangement, which at the same time caused hypogonadism and impotency. Essentially similar manifestations were seen in women and in several cases, these could be traced to an initial psychic trauma. Here the adiposity tended to be accompanied by amenorrhea. It was assumed that such patients had "learned a saving mechanism which enabled them, after their return home, to put on fat on a diet which was still inadequate".[4] This "learning" may well be part of the "shift in anterior-pituitary hormone-production" characteristic of the G-A-S.

In the French literature these types of adiposity are descriptively designated as "obésités de disette" or "engraissements paradoxaux".[4a] This should not be

[1] Hottinger **B27606/48,** Keys et al. **B46730/50.**
[2] Hirscher B45240/48, Schäfer B46538/49, Steinbrinck B27374/48.
[3] Schweitzer B38178/48.
[4] Overzier **B27372/48.**
[4a] Sendrail and Lasserre B37450/48.

confused with the pseudo-adiposity of undernourished people, which is due to salt and water retention in the fat tissue, but sometimes the differential diagnosis of these two conditions is made possible only by biopsy.

Adiposity is not a constant manifestation of the resistant stage, but perhaps its development following adaptation to stress depends largely upon conditioning factors, such as heredity and the diet.

Among the stimuli likely to influence the adipose tissue during the G-A-S, hormones probably play an important rôle. Purified **growth-hormone** notoriously decreases the fat-content of the body [5] and a diminished growth-hormone production is an essential part of the "shift in anterior-pituitary-hormone-production" characteristic of the G-A-S. Hence diminished growth-hormone secretion may be a factor in the development of adiposity during the resistant stage, after the contrary effect of the catabolic impulse has been overcome. The coincident fall in the production of **sex-hormones** would tend to act in the same manner, since it also stimulates fat-deposition as shown, for instance, by the classic example of female and male castrate animals or man.[6]

Certain **corticoids** also stimulate fat-deposition, especially in the liver, but allegedly to some extent, also in other organs.[7] It remains to be seen to what extent their effect upon the adipose tissue participates in the G-A-S.

Very little is known about the factors responsible for the sudden atrophy of adipose tissue during the A-R-stage. It does not appear to depend upon the hypophysis-adrenal-kidney-system, since stress continues to cause a lipoclastic reaction after the removal of the hypophysis, the adrenals or the kidneys.[8]

Liver-Lipids

Systemic Stress

The deposition of lipids in the hepatic cells appears to be a **characteristic** manifestation of the A-R-stage although its intensity largely depends upon conditioning factor.[9] (Cf. also chapter: Liver.)

This has been shown comparatively early in the course of our work on the A-R in rats and guinea-pigs subjected to the stressor action of forced **muscular exercise, cold** or **formaldehyde** injections, especially if they were fasted during treatment.[10] During long continued, daily, forced muscular exercise, the lipids eventually disappear from the liver: their removal is also enhanced by fasting. It has been found, furthermore, that the initial lipid-deposition is more marked in adult than in young rats and, among animals of the same age, it is greater in females than in males. Curiously, the sex-difference in response seems to be relatively independent of gonadal hormones as castration does not abolish it.[11] Since, simultaneously with the lipid-deposition in the liver, the fat-tissue itself involutes, it appears possible that the lipids are merely transferred from the fat-cells into the liver.[12]

[5] Li B36466/48.
[6] Selye **94572/49.**
[7] Selye **94572/49.**
[8] Selye 35935/ND.
[9] Selye **B1204/46. 94572/49.**
[10] Foglia and Selye A8424/38, Selye A15667/39.
[11] Selye A15667/39.
[12] Selye B1204/46.

Re-examination of this subject by other investigators confirmed that fat-infiltration of the liver is a characteristic manifestation of the response to a variety of non-specific damaging agents and forms part of the A-R.[13] It has been experimentally reproduced by **x-ray treatment** in the rat [14] and in the mouse.[15] It occurs in **"toxic infants",**[16] as well as following exposure to a variety of stressors such as **cold,**[17] **bacterial toxins,**[18] **starvation** [19] and **anoxia.**[20] Occasionally an inverse reaction, that is loss of liver-lipids, has been reported after anoxia (and other stressors),[21] but this is presumably due to the fact that the reaction, like most G-A-S-responses, is triphasic and the results differ depending upon the time of observation.

The prevention by cold of the fatty liver normally produced by **hypolipotropic diets** [21a] may well depend upon this same phenomenon.

Since, at least in certain animals such as the mouse, complete **fasting** in itself causes hepatic fat-deposition, it has been suggested that the effect of other alarming agents may merely be due to anorexia of severely damaged individuals.[22] However, fasting causes much less pronounced fat-deposition than is obtained under the influence of more intense stressors and in a summary of the pertinent investigations it has been stated that: "exogenous and endogenous damaging agents such as colchicine, x-rays, cold and fasting cause a set of non-specific manifestations in the organism, which have been called the alarm-reaction. Our investigations show that one of the symptoms of this reaction is the fatty infiltration of the liver".[23] In men who died from chronic undernutrition and exhibited typical G-A-S-changes, the liver was often extremely fatty, long after the fat-depots were depleted; [24] hence "fat-migration" alone, hardly suffices to explain the pathogenesis of fatty-livers caused by systemic stress.

Stimuli Influencing Liver-Lipids During the G-A-S

Hypophysectomy. — The fat-deposition in the liver which is produced by various experimental interventions does not occur after removal of the pituitary; this is presumably due to the resulting anterior-lobe deficiency.[25] Both *ACTH* and *somatotrophin* raise the liver fat in the hypophysectomized rat.[25a]

Anterior-lobe extracts. — The fact that certain anterior-pituitary principles (corticotrophin, "ketogenic fractions") tend to cause fat-deposition in the liver is well established on the basis of extensive investigations in various animal species.[26] *ACTH* [26a] and growth-hormone have a similar effect.[26b] However, the participation of pituitary-hormones other than corticotrophin, in the genesis of fatty-livers during the G-A-S, has not yet been examined.

[13] Leblond et al. A18194/39.
[14] Leblond and Segal 82724/42, Leblond et al. A18194/39.
[15] Ellinger 93367/46, 93953/47, Smith et al. B37748/49.
[16] Marie et al. B37996/47.
[17] Lánczos 31339/35, Levin B32877/49.
[18] Mitani 4762/33, 7412/32.
[19] Chevillard et al. A9096/37, Marble et al. B26097/38.
[20] Chevillard et al. A9096/37, Loewy B26105/27, Loewy and Cronheim B26106/33, Loewy and Leibowitz 54891/28, Loewy and Mosonyi B26107/27, Rosin 42083/26.
[21] Levin B32877/49.
[21a] Sellers and You B44042/49.
[22] Chevillard et al. A9096/37.
[23] Leblond et al. A18194/39.
[24] Lamy et al. B26867/48, Uehlinger B24304/47.
[25] Selye **94572/49.**
[25a] Li et al. B44449/49.
[26] Gray, A15320/38, Levin B32877/49, Li et al. B34773/49, Payne B32809/49, Selye **94572/49.**
[26a] Li et al. B44449/49,
[26b] Li et al. B44449/49. Weil and Ross B39047/49.

The production of fatty livers by anterior-lobe extracts does not occur in adrenalectomized rats, but there is no correlation between the ACTH (or any other known hormone) content of various preparations and their ability to produce fatty livers; hence this effect has been attributed to a separate *"fat-mobilizing factor"*.[27] Since both ACTH and somatotrophin cause some hepatic steatosis we must also consider the possibility that marked fatty liver production, during the G-A-S, depends upon the simultaneous action of several principles.

Adrenalectomy. — Ablation of both suprarenals prevents the fat deposition in the liver which normally occurs, after partial hepatectomy, under the influence of various non-specific stimuli;[28] presumably because certain corticoids are essential for this response. In animals with intact livers, hepatic fat deposition during the A-R is similarly prevented by adrenalectomy.[29]

Corticoids. — It has been claimed that in the pigeon **DCA** increases the fat content of the liver[30] but no such increase could be obtained with DCA[31] or with cortical extract in normal rats or mice.[32] During the A-R, DCA can also inhibit fat deposition in the liver, for instance, that occurring in x-irradiated mice.[33] Perhaps here the compensatory atrophy of the adrenal, caused by the DCA, interferes with the formation of those corticoids which are in charge of fat mobilization.

Certain crystalline corticoid compounds, such as **Kendall's compounds A and B,** cause a marked increase in the lipid content of the whole body as judged by experiments in the mouse.[34] It is on the basis of such observations that the existence of special "lipo-corticoids" has been postulated.[35]

Glucose. — Administration of glucose during exposure of an otherwise effective stressor, or during corticotrophin-treatment, prevents or inhibits the usual fat deposition in the liver as judged by observations on the mouse.[36]

Other factors. — Fatty degeneration of the liver has long been known to occur under the influence of a multitude of spontaneous diseases in man and its association with the G-A-S is now quite well established. Nevertheless, it should be emphasized that unlike so many other manifestations of this syndrome, hepatic fat deposition is not a constant response to stressors. It appears to depend upon all the many factors which affect the mobilization of lipids from other tissues, their transfer into the hepatic cell for emergency-utilization and their subsequent combustion. Hence, this response is greatly influenced by the diet, the fat-reserves, the ability of the adrenal to respond, etc. It is presumably due to hereditary differences in these factors that certain species, such as the mouse and guinea-pig, show this change much more readily than others. The type of stressor used is also of importance. Among those tested in our laboratory, muscular exercise proved to be most effective in this respect.

[27] Payne B32809/49, B39397/49.
[28] Selye et al. 32783/35.
[29] Leblond et al. A18194/39, Leblond and Segal 82724/42.
[30] Riddle and Opdyke 81683/41.
[31] Payne B39397/49, Selye 35935/ND.
[32] Gray A15320/38, Payne B39397/49.
[33] Ellinger 93367/46, 93953/47.
[34] Kendall B3002/45.
[35] Selye **94572/49.**
[36] Levin B32877/49.

Blood-Lipids

Systemic Stress

In spite of the great attention given to changes in adrenal lipids during the G-A-S, comparatively few investigators examined the corresponding variations in blood-lipids. On the basis of the few available data, however, the **characteristic** response to systemic stress appears to be an initial decrease in total lipids and cholesterol during the shock-phase, followed by an increase during the counter-shock and early resistance phases. Pertinent data concerning variations during the later part of the G-A-S are quite insufficient even for tentative conclusions.

After **traumatic surgical interventions** the blood-cholesterol content was found to fall below normal in man, irrespective of the type of operation.[37] A more detailed study, performed on surgical patients immediately after operation, led to the conclusion that: "after injury, the various serum lipid fractions, total and free cholesterol, lipid phosphorus and fatty acids diminish by small but unequivocal decrements. The lipid components are proportionally affected without distortion such as occurs in liver disease".[38]

In the rabbit, three hours following a single, severe **hemorrhage,** the plasma-content of phospholipids and cholesterol-esters was decreased by about 40%, initial values being reached only after 12-24 hours. The concentration of free cholesterol also decreased in the plasma, but to a somewhat lesser extent and reached the initial values earlier. The neutral-fat content of the plasma showed irregular variations and there was no change in the lipid content of the erythrocytes.[39] On the other hand, repeated hemorrhage produces marked hyperlipemia in the rabbit[40] and even the drop in blood-lipids caused by a single, severe hemorrhage is eventually followed by a marked hyperlipemia.[41] This secondary hyperlipemic response is subject to great species variations. Thus, for instance, in the dog, which can normally eat and quickly dispose of large amounts of fat, it is impossible to produce an unmistakable lipemia even by very severe hemorrhage.[42] The marked hyperlipemic phase seen under similar conditions in the rabbit may be due to this animal's inability of utilizing large amounts of fat when they are suddenly discharged into the blood-stream.[43]

In a small experimental series it was found that exposure to **cold** causes no change in the serum-cholesterol concentration of the rat. However, here the degree of systemic stress must have been mild since even the adrenal cholesterol showed only a small and transitory diminution.[44] An A-R, produced by intraperitoneal injection of very cold saline solutions, allegedly causes marked hypercholesterolemia in the dog.[44a]

In carcinoma patients, who received intense **radium**-treatment, a drop in blood-cholesterol has been reported.[45] After heavy **x-irradiation** of patients or animals, there may be hypocholesterolemia,[46] hypercholesterolemia[47] or

[37] Bársony A1940/36.
[38] Man et al. 93286/46.
[39] Boyd and Stevenson A14835/37.
[40] Bloor 12921/21, Horiuchi B26099/20.
[41] Horiuchi B26099/20.
[42] Bloor 12921/21.
[43] MacLachlan A30452/39.
[44] Levin B364/45.
[44a] Morros Sarda B46148/49.
[45] Luden 33631/16.
[46] Kalecka A32652/29, Kiesel A32648/33, Luden 33631/16. Reding 39925/35, Roffo B26101/26, 95061/37, Roffo and Correa B26102/24, Roffo and Griot B26103/26.
[47] Mahnert and Zacherl 36553/24.

quite irregular variations,[48] depending upon the nutritional condition of the subject, the intensity of the irradiation, etc. Apparently x-rays, as other stressors, can influence the blood-cholesterol level in both directions. Disregard of this possibility has led to considerable confusion in the literature. Systematic studies in man showed, however, that in the great majority of the cases, x-irradiation causes an initial decrease in the plasma- and whole-blood-cholesterol content, with a subsequent return to, or above, the pre-irradiation levels.[49] The hypercholesterolemic response to x-rays in previously irradiated individuals was noticeable not only when treatment was discontinued, but even in the face of continued irradiation; hence it seems very probable that we are dealing with the usual reversal of response during the resistant stage of the G-A-S.

The microscopically visible blood-lipid granules, the chylomicrons, normally show a characteristic curve following a fat meal. After exposure to toxic x-irradiation this curve is flattened (increased fat tolerance?) and deformed.[50]

Intense **muscular exercise** may either diminish [51] or raise [52] the cholesterol content, depending upon experimental conditions. Observations on cats suggest that the rise is due to a discharge of cholesterol from the working muscle itself, as judged by the arterio-venous cholesterol difference in an exercised limb. It has been claimed that adrenal cortical extract inhibits this reaction.[53] In rats, whose blood-cholesterol level is remarkably stable under various conditions, some workers observed no change in cholesterolemia even after severe muscular fatigue, which almost completely exhausted the adrenal cholesterol-stores.[54] Others, however, report a transitory hypo-cholesterolemia." [55]

Prolonged **anoxia** increases the blood-lipid concentration in the rabbit.[56] Here again there are important species differences in the response. Systematic investigations in various species showed that short exposure to reduced atmospheric pressure causes no significant change. This was confirmed both during fasting and in the post-operative state on cats and dogs. On the other hand, in the rabbit anoxia produces a decrease in plasma-lipids within three hours; later the initial level is re-established at the end of about six hours. The initial decrease in the plasma-lipids of the rabbit is mainly due to a diminution of neutral fat. It was concluded that "the difference in the response of rabbits to short periods of reduced atmospheric pressure from that of cats and dogs may be related to their different abilities to utilize fats".[57]

In the rat, five hours exposure to decreased atmospheric pressure diminished the esterified plasma-cholesterol, but there was almost no change in free cholesterol.[58] It is especially noteworthy that 5-7 hours of exposure to comparatively mild reduction in barometric pressure, may suffice to decrease adrenal cholesterol by about 50% while the serum-cholesterol-concentration shows only an insignificant diminution.[59]

In dogs, stress caused by **burns, vesicants or turpentine** produces marked changes in the distribution of the protein-bound lipids in various electrophoretic

[48] Levy-Dorn and Burgheim B26118/26, Otuka A16368/38, Strauss B26100/23.
[49] Mattick and Buchwald A32653/27.
[50] Setälä and Ermala B26291/48.
[51] Rakestraw A7856/21.
[52] Somogyi A15467/38, A39300/39.
[53] Somogyi A15467/38.
[54] Jongh and Rosenthal 15108/33.
[55] Hasch and Hajdu A31457/39.
[56] Starup B26098/34.
[57] MacLachlan A30452/39.
[58] Tepperman et al. B4674/47.
[59] Levin B364/45.

fractions of the serum.[60] However, available data do not suffice to make any generalizations concerning the changes in lipo-proteins which are characteristic of the response to systemic stress as such. In the rat tris-(β-chloroethyl)-amine tends to raise the blood-cholesterol; this response was not significantly influenced by partial hepatectomy or partial nephrectomy.[61] The total plasma-lipid concentration is increased in the rat by trauma, vesicants and burns.[61a]

The **folliculoids**, which are notoriously potent in producing G-A-S manifestations,[62] and numerous **other stressors** [63] tend to cause a transitory hypocholesterolemia. This has also been observed to occur in **"toxic infants"**,[64] who exhibit pronounced A-R-changes. It may be significant in this connection that in man the blood-cholesterol level shows regular **diurnal variations**, independently of the food intake.[64a]

Stimuli Influencing Blood-Lipids During the G-A-S.

Corticotrophin. — After 6 - 8 days treatment with large doses of ACTH there was a sharp fall in the esterified (45%) and a less pronounced decrease in the free (28%) cholesterol fractions in man. From this it was concluded that blood-cholesterol probably is an important precursor from which corticoids are made.[65] The hypocholesterolemic effect of ACTH has repeatedly been confirmed in man.[65a]

Corticoids. — Data concerning the effect of corticoids are rather contradictory. *Cortical extracts* were reported to cause an increase,[66] a decrease,[67] or more or less irregular and insignificant variations [68] in the blood-cholesterol and total blood-lipid concentration.

In man a few preliminary observations suggest that **cortisone** causes a drop in total cholesterol, which apparently does not occur at the expense of free cholesterol.[68a]

DCA has been claimed to produce an increase [69] or no change in total blood-lipids and blood-cholesterol in the bird,[70] a decrease in blood-cholesterol in the guinea-pig,[71] hypercholesterolemia in man [72] and no change in the blood-cholesterol level of the rabbit.[72a]

We do not wish to attempt any detailed analysis of these conflicting data, but both the facts reported in the literature and our own observations suggest that under normal conditions, in the intact organism, neither cortical extracts nor DCA exert any prominent and constant effect upon the total-lipid and cholesterol content of the blood. This agrees with the fact that adrenalectomy also fails to produce any consistent change in blood-lipids.[73] In connection with the pathogenesis of the diseases of adaptation it is interesting, however,

[60] Gjessing and Chanutin A95937/46, Gjessing et al. B4999/47.
[61] Ludewig and Chanutin B19833/48.
[61a] Chanutin and Gjessing B45983/49.
[62] Levin B364/45.
[63] Gjessing et al. B4999/47.
[64] Fanconi A32021/39.
[64a] Lippi and Argiolas B41109/48.
[65] Conn and Vogel B35912/49.
[65a] Mason et al. B17986/48.
[66] Kelley and Adams B36540/48, Parhon-Stefanescu and Ornstein 77020/39, Schmidt A38408/39.
[67] d'Ambrosio A72844/42, Mors A39486/38.
[68] Beslekoev A63620/40, Capra 95328/45, Houchin and Turner A30071/39.
[68a] Perera et al. B36595/49.
[69] Riddle and Senum A31143/39.
[70] Entenman et al. A34395/40.
[71] Villela 84804/41.
[72] Sposito A63750/42.
[72a] Bruger and Lowenstein B46043/48.
[73] Mitani 7592/33, Selye 94572/49.

that in rats sensitized by *unilateral nephrectomy* and high NaCl intake, DCA causes a very pronounced and consistent elevation in blood-cholesterol.[74] This phenomenon, which is reminiscent of the hypercholesterolemia of nephrosis, can be prevented, or actually reversed, by simultaneous treatment with methyl-testosterone, a renotrophic hormone.[75]

The adrenal-cortex is certainly an important store of cholesterol. It could help to maintain the homeostasis of cholesterolemia by removing cholesterol from, or discharging it into, the circulation. The possibility of a regulation of blood-cholesterol through mineralo-corticoids, such as DCA, is suggested, but not proven, by the above observations. Since gluco-corticoids, such as cortisone, share the hypocholesterolemic effect of ACTH it is very doubtful whether the action of the latter should be ascribed to a utilization of blood-cholesterol for the synthesis of corticoids.

Kidney. — In the dog, bilateral nephrectomy causes hypertension with a parallel increase of neutral fats, cholesterol and phospholipids. Injection of a kidney-extract prevents this hyperlipemia and hence the possibility of a hormonal regulation of blood-lipids has been seriously considered.[76]

Dietary factors. — The food ingested is obviously also important in determining the lipid-content of the blood, both under resting conditions and during systemic stress. Of course here the **lipid** content of the diet must first be considered but, at least in some species, cholesterol and the steroids derived from it can also be synthetized endogenously. This was shown, for instance, in rats by feeding them a diet consisting almost exclusively of **protein.** It was noted that even on this regime the cholesterol content of the organs (adrenals, spleen, liver, skin) remained normal and indeed even tended to rise. There were no changes attributable to lack of steroid hormones.[77]

Inositol, a lipotropic factor, was shown to diminish the normally high cholesterol content of the blood, aorta, heart and liver in old hens.[78]

It remains to be seen how these factors affect cholesterol metabolism during systemic stress.

Ketone Metabolism

Systemic Stress

Available data do not yet permit us to sketch the changes in ketone-metabolism which are **characteristic** of the G-A-S. However, some pertinent findings suggest that usually an initial ketosis during the A-R is rapidly followed by an inverse response.

Following surgical **trauma** in the rabbit, post-operative ketonuria is especially pronounced if the intervention is performed under general anesthesia; it tends to be absent, or at least less marked, if local anesthesia is used.[79]

In man, post-operative ketonemia and ketonuria tend to be much more pronounced among children than in adults. Ketosis often evolves in two phases. An initial rise (immediately subsequent to the surgical intervention)

[74] Levin B364/45, Selye and Rowley A72287/44.
[75] Selye and Rowley A72287/44.
[76] Jimenez Diaz and Mendoza B37606/48.
[77] Abelin B24719/47.
[78] Herrmann B38628/46.
[79] Roscher B25560/33.

is followed within a few days, by a return to or below normal blood-ketone values and a disappearance of ketonuria. At about the 4th or 5th post-operative day, a second period of ketonemia and ketonuria may occur, which has been considered to be a kind of *"fasting acidosis"*, since it is seen especially in patients who fail to take adequate nourishment after the operation.[80] In chronically undernourished people, the *"fasting ketosis"* [81] is usually of brief duration and demonstrable at the beginning of the fast only; even the hypoglycemic coma of gradually starved men (concentration-camps) is not accompanied by any marked persistent ketonemia or ketonuria.[82]

In man, after **x-irradiation** there is a pronounced and rather persistent increase in the acetone- and especially in the β-hydroxybutyric acid content of the blood.[83] Systematic studies in the dog showed, however, that the initial rise in blood-ketones is subsequently followed by a decrease [84] which presumably corresponds to the counter-shock or early resistance phase.

Following intense **muscular exercise,** pronounced ketonemia may develop in untrained men, while after adequate adaptation, the same amount of work calls forth no such reaction. Interestingly this ketonemia of exercise can be diminished by the administration of glucose or cortical extract (see below) and is apparently dependent upon the depletion of the glycogen-stores during systemic stress.[85]

Stimuli Influencing Ketone-Metabolism During the G-A-S.

Hypophysis. — The pituitary plays an important rôle in ketone-metabolism. Hypophysectomy inhibits or abolishes the ketosis normally produced by fasting, pancreatectomy, etc., indeed it is extremely difficult to produce ketosis by any means after ablation of the hypophysis.[86]

It is also well known that certain "ketogenic" **anterior-lobe extracts** produce ketonemia and ketonuria.[87] However, these effects are not necessarily mediated solely through the adrenal cortex. Both pure corticotrophin and somatotrophin produce ketonemia in the fasting rat.[88]

Adrenals. — **Adrenalectomy** considerably reduces, or completely abolishes the ketonuria observed in a number of metabolic disturbances, for instance, those caused by *pancreatectomy,*[89] *fasting,*[90] *phloridzin*-intoxication [91] or treatment with *anterior-pituitary extracts.*[92]

Adrenaline does not appear to exert any prominent direct effect upon ketogenesis, but the depletion of the hepatic glycogen-stores, incident to adrenaline-overdosage, tends to predispose for ketosis.[93]

Much work has been done concerning the actions of **corticoids** upon ketone-metabolism. *DCA*-overdosage resulted in rather inconsistent and variable changes in blood-ketone concentration.[94] *Cortical extracts* likewise failed to

[80] Roscher B25560/33.
[81] Dick et al. B19818/43.
[82] Lamy et al. B26867/48.
[83] Willms A32656/33.
[84] Kikuchi 10149/31.
[85] Winkler and Hebeler A31099/39.
[86] Selye **94572/49.**
[87] Gray A15320/38, Selye **94572/49.**
[88] Bennett et al. B26412/48, B24514/48, B24880/48.
[89] Long and Lukens 56354/36.
[90] MacKay and Barnes 67366/37.
[91] Evans 56353/36.
[92] Fry 69602/37, Long B10147/37, MacKay and Barnes 67366/37.
[93] Selye 94572/47.
[94] Puccinelli and Melosi 95767/41, Simoncini A39139/41.

cause significant changes in blood-ketones, as judged by observations on fasting rats.[94a] The reputed ketogenic action of certain crude cortical preparations [95] has not been substantiated by subsequent work.[96] Perhaps the so-called ketogenic extracts contained impurities which may have acted through their systemic stressor effects. The occurrence of ketonuria in a rat with "steroid diabetes" due to overdosage with gluco-corticoids,[97] is difficult to reconcile with the claim that the ketosis of muscular exercise can be inhibited by cortical extracts.[98]

The available data show that the adrenal cortex influences ketone metabolism, but its exact participation in the ketosis of the G-A-S has still not been fully elucidated.

Glucose. — The increase in blood-ketone bodies, produced by intense muscular exercise, can be diminished by the administration of **glucose;** it apparently depends upon the depletion of the glycogen-stores during this type of systemic stress.[99]

[94a] Gray A15320/38.
[95] McKay and Barnes 67365/36.
[96] Grollman A15241/38, Long B26171/38.
[97] Ingle et al. 85851/45.
[98] Winkler and Hebeler A31099/39.
[99] Winkler and Hebeler A31099/39.

NITROGEN METABOLISM

Nitrogenous products, and especially the proteins, are among the most characteristic constituents of living matter. The pronounced changes in nitrogen metabolism, which occur during the G-A-S, therefore presumably play a prominent rôle among the adaptive adjustments of this syndrome. The intense catabolic phenomena, typical of the stages of alarm and exhaustion, may undoubtedly become the limiting factors of resistance, when even the essential structure-proteins of the body are attacked. However, the entire biologic significance of protein catabolism is not yet understood.

The higher cleavage products of certain proteins stimulate cell proliferation.[1] This may be useful during the catabolic impulse of systemic stress, for instance, after traumatic injury.[2]

We have also considered the possibility that perhaps somatic cells (like some unicellular organisms) can multiply asexually only a finite number of times. Should this prove to be correct, the longevity of the individual as a whole would be largely dependent upon the power of asexual cell-division, since, without the possibility of cell replacement and regeneration, life must come to an end.

Systemic stress causes rapid breakdown of cytoplasm and even of entire cells. The resulting liberation of protein catabolites furnishes the necessary building-blocks for regeneration tissues. Thus the tissues of the body are temporarily "rejuvenated" by acute systemic-stress, but in terms of the whole life-span, exposure results in aging — in the gradual exhaustion of the ability for further regeneration and adaptation.

It is perhaps significant that in senility, as in the stage of exhaustion, the living cell-mass and the protein reserves are progressively diminished, although certain depot-substances, especially fat, may be stored in excessive amounts.

As we have said in the introduction to this book, adaptation is probably the most characteristic feature of living matter. Most, if not all, biologic adjustments to change are effected through the intermediary of enzymes. Since, according to recent developments in this field, all the plasma- and tissue-proteins are actually enzymes,[3] it is evident that changes in protein metabolism are of the greatest importance in determining the course of the G-A-S and of the diseases of adaptation.

Total Non-Protein-Nitrogen

Systemic Stress

Systematic experiments on rats exposed to diverse types of systemic stress (e.g., cold, formaldehyde, exercise)[3] led to the conclusion that: "the rise in the N.P.N. content of the plasma is a **characteristic** feature of the alarm

[1] Carrel and Baker B26230/26.
[2] Cuthbertson A56384/42.
[3] Engelhardt **B46425/42.**
[3] Selye 73232/38.

reaction and not the result of a specific pharmacological action of the agents used, because this change appears, irrespective of the nature of the agent and disappears, in spite of continued treatment, as soon as adaptation occurs. Contrary to many of the changes occurring during adaptation, the initial rise in N.P.N. is not reversed after resistance is acquired but simply returns to normal".[4]

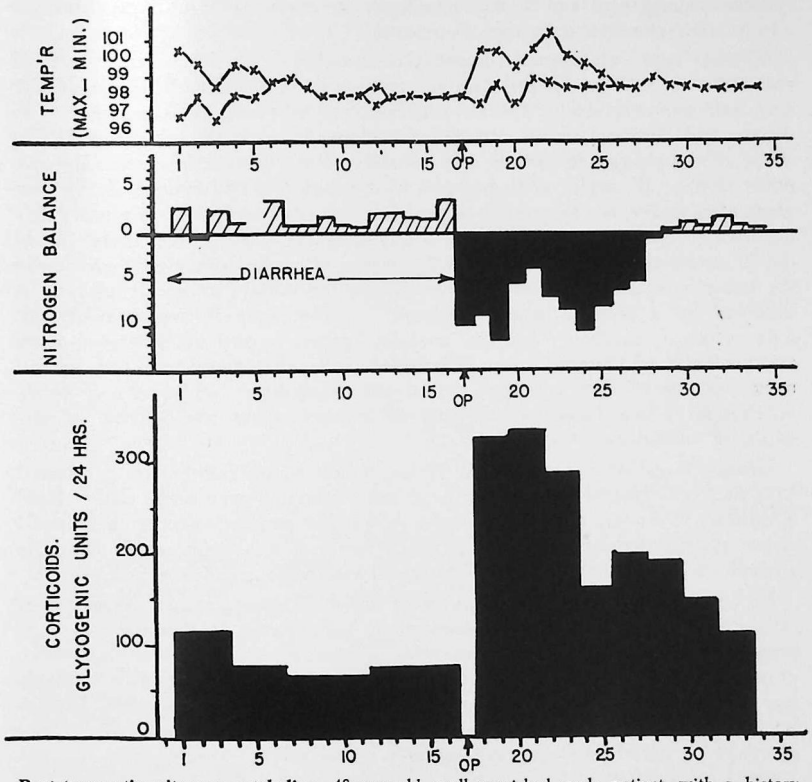
From experiments on hemorrhagic shock (see below) it appears that this rise in blood-N.P.N., characteristic of the shock phase, is chiefly accounted for by urea and to a lesser extent by ammonia. Only when the damage becomes so severe that the liver fails to form ammonia and urea from amino-acids, does the blood-concentration of the latter begin to rise significantly at the expense of blood-urea.[5] Other stressors, e.g., anoxia,[6] also reduce the deaminating power of the liver. As we shall see below, the actual level of total blood-N.P.N. is largely dependent upon the relative intensity of protein-catabolism in proportion to the ability of the kidney to eliminate nitrogenous catabolites.

The urinary elimination of N.P.N. products is likewise influenced by the G-A-S. There is an initial marked elimination of nitrogen during the A-R, with a return to or below normal in the stage of resistance; finally, pronounced loss of nitrogen ensues again during the stage of exhaustion. This typical curve has been established for a number of stressors (cold, formalin, muscular exhaustion, etc.); it is accompanied by corresponding decreases in the weight of the musculature and of parenchymatous organs with histologic manifestations of atrophy, and even pyknosis, during the initial and final stages of the G-A-S. Thus at these times there is loss of substance from organs rich in protein.[7]

It has long been known that following extensive tissue injury by **trauma,** the *blood-N.P.N.* tends to rise both in man and in experimental animals.[8] This rise has been considered a characteristic sign of "post-operative disease" [9] and some authors speak of "post-operative extra-renal azotemia" [10] as a well characterized clinical syndrome. The degree of the post-traumatic azotemia depends chiefly, on the one hand, upon the intensity of protein catabolism, and on the other, upon the ability of the kidney to eliminate N.P.N. products. In mild shock, the blood-N.P.N. usually shows only a slight and transitory elevation, because the kidney is capable of clearing the blood of the comparatively small amounts of protein-degradation products which enter it. However, as the intensity of the systemic stress increases, protein catabolism becomes more pronounced while renal function fails (especially due to the concomitant decrease in blood-pressure); at this time the rise in blood-N.P.N. may become very severe.

[4] Schenker 74711/39.
[5] Engel and Engel 99967/46.
[6] Wilhelmi et al. 87815/45.
[7] Leduc and Guillemin B27410/49, Selye 73232/38, 35935/ND.
[8] Aub and Wu Hsien 40958/20, Beresow B26220/28, Beresow et al. B26221/26, Cremer B19806/42, B19807/42, Duval and Grigaut B26211/18, Hegge B26222/32, Hermann et al. 93171/44, König A32639/32, Nicolaysen B26217/24, Nicolaysen and Nicolaysen B26218/30, Roscher B25560/33, Whipple and van Slyke B26212/18, Wilson and Stewart A53977/37.
[9] Larget and Lamarre A38155/41, Leriche B18459/34.
[10] Jeghers and Bakst B19997/38, de Luca A54791/42, Robineau A32662/33.

Observations on tourniquet-shock in the rat and cat showed that the N.P.N. is especially high in the venous blood coming from a damaged limb.[11] However, the protein catabolism caused by systemic stress is far greater than could be accounted for by the direct tissue injury alone;[12] indeed it has been shown that "the major part of the nitrogen lost from the body after an injury comes from sources other than the injured limb".[13]



Post-traumatic nitrogen catabolism. 48-year-old, well-nourished, male patient, with a history of pain in epigastrium. The duodenum was opened at the pylorus, but the mucosa proved to be normal and the wound was closed. Note intense post-operative loss of nitrogen, accompanied by slight rise in body temperature and marked increase in gluco-corticoid elimination. (Courtesy of E. H. Venning, McGill University, Montreal.)

Cuthbertson [14] came to the conclusion that "the increased catabolic processes are more general than local and appear to be conditioned by a mechanism which leads to: (a) raiding of the body-protein in order to supply endogenously the necessary substrate of amino-acids for the reparative process, and perhaps (b) a mobilization of oxidizable material for the enhanced metabolism of the healing process and for the alarm reaction of Selye".

[11] Selye and Dosne A35802/41.
[12] Cook and Whipple B26207/18, Cuthbertson B19929/30, Cuthbertson et al. B19925/39.
[13] Munro and Cumming B37341/48.
[14] 89886/45.

Experiments in rats injured in the Collip-Noble drum indicate that the post-traumatic rise in blood-N.P.N., typical of not-adapted animals, fails to occur after adaptation to trauma has been acquired.[15] This agrees with what we said about the characteristic triphasic N.P.N. curve of the G-A-S. Curiously, however, in reporting upon such experiments Noble and Toby[16] state that: "In rats shocked in the drum there is little evidence of the alarm reaction. Adrenal enlargement and thymus involution are slight. It is unlikely that the rise in nitrogen excretion is directly related."

Various types of injuries (crushing of muscles, bone fractures, intestinal manipulation, etc.) precipitate a marked *urinary excretion of N.P.N.*, especially *urea and ammonia*, during the days immediately following the trauma.[17] The degree and duration of this nitrogen loss depends upon the nutritional condition of the patient, the extent and intensity of the trauma, as well as many other factors. It may be said, however, that usually, in the course of the first week after injury, the urinary-N output rises to a peak and there is a markedly negative nitrogen balance, even on normally adequate, high-protein diets. Then the N output diminishes until about 2-3 weeks after the injury and gradually the balance tends to become positive. Thus, the initial "catabolic phase" is followed by a second "anabolic period". Accordingly it is customary to differentiate a "catabolic" and an "anabolic" period in patients suffering from various types of systemic stress. Under the influence of injury — in agreement with the G-A-S concept — nitrogen metabolism "undergoes a series of changes which follow a characteristic pattern, quite irrespective of the nature of the trauma".[18]

General anesthesia increases the N loss following operations, as compared with that occurring if the same surgical intervention is performed under local anesthesia.[19] Animal experiments have shown that general anesthesia in itself causes protein decomposition and N loss,[20] hence, it may be assumed that the stressor effect of trauma and that of general anesthesia are summated.

In connection with the *mechanism of traumatic protein-catabolism*, it is instructive that the material catabolized is mainly muscle protein. This is suggested by the nitrogen/sulphur and nitrogen/phosphorous ratios in the urine [21] in man and by actual organ-weight determinations in animals.[22] Such loss of muscle substance cannot be regarded as a mere disuse-atrophy. Immobilization in itself does not cause any comparable degree of protein catabolism, although of course in bed-ridden patients disuse of the muscles can account for part of the N loss.[23]

[15] Neufeld et al. A63529/43.
[16] B3012/45.
[17] Albright B349/43, B309/43, Bassett B356/43, Beattie B18456/47, Bywaters and Popjack B25579/42, Cuthbertson B19929/30, B19931/32, B19933/36, A56384/42, Cuthbertson and Munro B26202/37, Cuthbertson and Robertson A6664/37, Cuthbertson and Tompsett B26203/35, Cuthbertson et al. B26201/37, B19925/39, 82868/40-41, Hawk and Gies B26176/04, Howard and Bigham B3015/45, Nicolaysen B26217/24, Roscher B25560/33, Schenker et al. A95906/46, Stevenson et al. B19924/45, Waugh B26204/41, Wertheimer et al. B26205/19.
[18] Schenker et al. A95906/46, B4534/47, B4447/47-48.
[19] Roscher B25560/33.
[20] Howland and Richard B26219/09, Reicher B26216/08, Salkowski B26215/889, Strassmann B26213/889, Taniguti B26214/890.
[21] Cuthbertson A56384/42.
[22] Leduc and Guillemin B27410/49.
[23] Cuthbertson A56384/42.

There has been much discussion concerning the possibility that the N loss during the A-R might be due to "anti-anabolism",[24] rather than to true catabolism. As we shall see later, on N-deficient diets, stress fails to elicit the usually pronounced urinary N loss; this was interpreted as contrary to the concept that catabolism alone can explain the phenomenon. However, if the N intake is raised, increasingly more N is retained in spite of stress, indeed, under optimal conditions of nutrition, even severely injured patients may show a positive balance; this observation is incompatible with the anti-anabolic theory. It was therefore assumed that perhaps "both anabolism and catabolism are increased in activity after injury, but maintain their normal relationships as before the trauma. This is analogous to fever, where cooling and heat conservation are normal, but are set to maintain a higher temperature level. Two possible prerequisites for the reaction to occur are: (1) an intake of nitrogen, and (2) the presence of a reserve protein supply".[25] Observations with S^{35} labelled methionine suggest that in Cushing's syndrome, where — as in stress — ACTH production is increased, there is likewise no primary anabolic defect, "in fact there would appear to be a hyperanabolism which does not, however, compensate for the excessive catabolism that must occur".[26] Although the authors do not specifically say so, this suggests an increased protein turnover.

Our animal experiments also show [27] that, unless the protein reserves of the body are reduced to a minimum (by preliminary starvation or feeding on protein-deficient diets) systemic stress invariably causes some N loss, even if the animals receive no food during the period of exposure. Hence, exogenous nitrogen is not indispensable for this reaction. Thus all the known facts appear to be compatible with the assumption that during the catabolic impulse there is an increased tissue-protein turnover, coincident with the morphologically demonstrable increase in tissue reconstruction (pyknosis and mitosis).

Burns likewise raise the total blood-N.P.N.[28] and ammonia [29] content. At the same time, the urinary elimination of N.P.N. products is also augmented just as in traumatic shock.[30]

An essentially similar catabolic impulse, with a transitory rise in total blood-N.P.N. and in the urinary elimination of the nitrogenous end-products of protein, has been noted in experimental animals and in man following a variety of other systemic stressors such as **hemorrhage,**[31] **anoxia,**[32] **x-irradiation,**[33] extreme **heat,** especially if accompanied by "heat-stroke",[34] **insulin-shock,**[35] **electro-shock,**[36] forced **muscular exercise,**[37] treatment with **nitrogen-**

[24] Albright 84530/42-3, B309/43.
[25] Werner B4499/46.
[26] Margen et al. B35924/49.
[27] Selye 35935/ND.
[28] Abbott et al. B29501/46, Davidson 55943/26, Ficarra and Naclerio B808/44, Hilgenfeldt 38008/36, Peters 89884/45, Rosenthal and McCarthy B37557/47, Wilson and Stewart A53977/37.
[29] Harkins and Long 87814/45.
[30] Abbott et al. B29501/46, Browne et al. B2238/47, Croft and Peters B2426/45, Cuthbertson 89886/45, Davidson 55943/26, Glendening et al. 84678/44, Schenker et al. A95906/46.
[31] Bauer B26200/872, Borst 99102/38, Endres and Neuhaus B26120/25, Engel and Engel 99967/46, Hawk and Gies B26176/04, Rukstinat A32657/32, Wilhelmi et al. 87816/45.
[32] Evans 56353/36, van Liere B26199/42.
[33] Kikuchi 10149/31, Prosser B26618/47, Weichert A56943/42.
[34] Conn et al. B4468/46, Malamud et al. B18019/46.
[35] Saito B19731/42.
[36] Delmas-Marselet B26881/46.
[37] Rakestraw A7856/21.

mustards,[38] **sublimate,**[39] **bacterial toxins,** especially diphtheria, meningococcus, staphylococcus, and streptococcus[40] or turpentine (which produces sterile abscesses),[41] **"gravity shock",**[42] experimental infections,[43] **Rocky Mountain spotted fever,**[44] **typhoid fever**[45] as well as in a number of **other diseases** which cause acute loss of weight.[46]

Patients with various **debilitating chronic diseases,** on the other hand, show a great tendency to retain nitrogen, if an adequate dietary intake can be enforced.[47] Special attention has been called to "the ability of chronically ill patients to retain nitrogen after acute trauma, in contrast to individuals healthy at the time of injury, who lose nitrogen at similar or greater food intakes".[48] This is rather reminiscent of the reversal of the A-R manifestations during the resistant stage of the G-A-S.

Stimuli Influencing the N.P.N. During the G-A-S.

Hypophysis. — The hypophysis is obviously of great importance in the regulation of protein metabolism, especially through the growth-hormone, thyrotrophin, corticotrophin and the gonadotrophins.[49]

Hypophysectomy interferes with growth and the normal anabolism of protein,[49a] but does not abolish regeneration or the sudden protein catabolism elicited by an A-R. In a few experiments hypophysectomy prevented the post-traumatic N loss, and even cortical extracts failed to restore it.[50] This may have been due to a depletion of the protein reserves, but only the acute involution of the thymico-lymphatic tissue is markedly impeded, during an A-R, in the absence of the hypophysis.[51]

A crude *anterior-lobe extract,* which caused protein anabolism,[52] was also active in preventing the loss of body-weight and the excessive N excretion which normally follow upon fracture of a femur in the rat.[53]

Purified *corticotrophin* increases the urinary elimination of N in man[54] and in rats.[55] This response is most marked on a high-fat and least pronounced on a high-protein intake.[56] Thus here the "conditioning" of the corticotrophic action by the diet is very different from what we learned about LAP. It will be recalled that the corticotrophic action of the latter pituitary preparation is greatest on high-protein-diets (cf. chapter: Adrenals). LAP is also rich in somatotrophin, whose effect is markedly augmented by a high-protein diet. It is possible that somatotrophin helps to stimulate the growth of the adrenal cortex, as it is a general growth-hormone; thus, in this respect, it could act as a synergist of ACTH. Perhaps only this latter effect is augmented by proteins.

[38] Philips et al. B29996/48.
[39] Richet et al. B36282/49.
[40] Lithander 97243/45.
[41] Madden and Clay B2098/45.
[42] Cole et al. 84978/44.
[43] Fox and Ashwell B32743/49.
[44] Harrell et al. B24806/44, B24807/45, B24808/46, B24809/47, Kelsey and Harrell B24821/48.
[45] Laroche et al. B37796/48.
[46] Erdei B18506/48, Herbut 93650/46, Laroche and Trémolières B38771/49, Lewis **B34740/49,** Murphy B38929/48.
[47] Schenker et al. B4534/47.
[48] Schenker et al. B4447/47-48.
[49] Selye **94572/49.**
[49a] Kochakian **B46216/50.**
[50] Noble and Toby B23009/48.
[51] Selye B1204/46.
[52] Cuthbertson et al. 82867/40-41.
[53] Cuthbertson et al. 82868/40-41, 82869/40-41.
[54] Conn et al. B29612/48, Hoffman et al. B23331/48, Sayers et al. B37710/49.
[55] Bergner and Deane B23875/48, Li et al. B34773/49.
[56] Ingle et al. B2709/47.

Purified *somatotrophin* reduces the urinary-N excretion in fed or fasting rats.[57] In nephrectomized rats it delays the formation of blood-urea from intravenously injected amino-acids, at the same time accelerating the removal of the latter from the plasma.[58]

This anabolic action presumably participates in the metabolic changes characteristic of the G-A-S, since even the post-traumatic N loss of rats can be inhibited by growth-hormone treatment.[59] Perhaps the well-known inhibition of somatotrophin secretion during stress — which manifests itself by cessation of growth in young individuals — facilitates the development of a normal catabolic phase during the A-R. It remains to be shown whether, at this time, inhibition of catabolism by growth-hormone treatment would be advantageous for resistance.

Testoids can cause N retention even in hypophysectomized rats but this action — unlike that of somatotrophin — is only transient and "wears off" after a certain time.[59a]

Adrenals. — Albright[60] expressed the view that the catabolic impulse of the A-R may be due to an excessive production, by the adrenal cortex, of "S-hormone" (now identified as the gluco-corticoids), simultaneously with a decreased production of "N-hormone" (now identified as adrenal testoids). Undoubtedly gluco-corticoid production is increased, while testoid production is diminished during stress; furthermore ample experimental evidence confirms that gluco-corticoids cause catabolism, while testoids (and somatotrophin) facilitate protein synthesis. Yet the catabolic response of the A-R is largely independent of the adrenals (see below) and only toxic amounts of gluco-corticoids favor catabolism. In hypocorticoidism for instance, the negative N balance is rendered positive by gluco-corticoid treatment and in the young even growth is stimulated.[61] Thus, in the rat, adrenalectomy in itself suffices to cause a urinary-N loss. This is significantly inhibited by treatment with small amounts of an active adreno-cortical extract; large amounts favor N elimination under these conditions, probably as an overdosage effect.[62]

Adrenalectomy increases the loss of tissue protein, which normally occurs during the A-R; presumably because the catabolic response to stress is largely independent of the adrenals and the same alarming stimulus causes a more severe stress if the adrenal defense mechanism is eliminated. In the absence of the suprarenals, only the protein of the thymico-lymphatic system appears to be specifically protected against catabolism by stress.[63]

After adrenalectomy, acute *traumatic injuries* (bone fractures) cause only a small reduction in the usual nitrogen loss, in the rat, and administration of cortical extract restores it to the normal high level even in the absence of the adrenals. It was concluded "that the negative nitrogen balance, which characteristically develops following fractures, may require the presence of the adrenal cortical hormones, but is not caused specifically by the increase in the secretion of the cortical hormones which occurs during stress".[64]

[57] Kochakian B46216/50, Li **B36466/48,** Li and Evans **B29230/48,** Whitney et al. B24891/48.
[58] Russell and Capiello B27879/49.
[59] Bennett et al. B1291/46.
[59a] Kochakian B46216/50.
[60] B309/43, B349/43.
[61] Selye **94572/49.**
[62] Ingle and and Prestrud B28275/48, B39039/49.
[63] Selye **B1204/46,** 35935/ND.
[64] Ingle et al. B4742/47.

Interestingly, following an operation, the immediate rise in N excretion tends to be actually higher in adrenalectomized than in intact rats, however, subsequently, N elimination continues to be high in the latter, but not in the former group. Following cortical-extract treatment, on the other hand, adrenalectomized rats exhibit a sustained increase in N elimination.[65] In rats traumatized by clamping of a limb, N excretion was diminished after adrenalectomy. DCA was inactive, but suitable therapy with cortical extracts allowed a practically normal response. It was concluded that "following trauma, secretion of cortin is not responsible for the increased loss of nitrogen. On the other hand, nitrogen loss does not occur in the absence of the adrenal gland unless replacement therapy with cortin is administered".[66] Such findings suggest that, at least under certain conditions, adrenalectomy inhibits the post-traumatic N loss in the rat, while cortical extracts (in doses causing no N loss in themselves) restore the ability to respond with marked protein catabolism after trauma.[67] Apparently here we are again dealing with a peripheral synergism between the corticoids and other factors produced by stress.

The urinary-N loss, which normally occurs upon exposure to *anoxia,* is at least lessened by previous adrenalectomy in the rat.[68]

In completely *nephrectomized* rats the rate of urea formation (judged by the blood-urea level) increases progressively until death. In adrenalectomized-nephrectomized animals the rise is not progressive, unless they are treated with cortical extracts.[69] It appears that "the unchanging rate of urea formation in the adrenalectomized rat probably reflects the inability of the rat lacking cortical function to respond to the continuing stress of nephrectomy and the consequent uremia and acidosis".[70] The formation of urea from injected amino-acids proceeds undisturbed in adrenalectomized-nephrectomized rats, but after injection of rat-plasma no urea is formed unless corticoid therapy is given. Hence it was concluded that "the action of the adrenal cortex in protein metabolism is at the level of protein breakdown itself, rather than at the level of deamination of amino-acids".[71] Experiments on merely nephrectomized (not-adrenalectomized) rats yielded essentially similar results.[72]

Apparently gluco-corticoids facilitate the breakdown of tissue protein, but this can still occur as a result of extra-adrenal factors during the A-R. It will be remembered that our observations concerning the hyperglycemic response in untreated and corticoid-treated adrenalectomized animals, led to a similar conclusion as regards the adrenal regulation of carbohydrate metabolism during the A-R (cf. G-A-S → Blood-sugar).

Adrenaline causes protein catabolism in intact rats, but since toxic doses are required to elicit a marked response,[73] the hormone may act merely as a stressor. Thus there is no reason to suppose that an endogenous adrenaline discharge plays an important part in the production of the catabolic response during the A-R.

In intact animals and man, heavy overdosage with **gluco-corticoids** can elicit a marked rise in the urinary elimination of nitrogenous products, but does not tend to raise the blood-N.P.N.[74] In dogs, cortical extract may occasionally even diminish the rise in blood-N.P.N. normally produced by *tourniquet-shock*,[75] but this response is quite inconstant.

[65] Ingle B37776/49.
[66] Toby and Noble B4449/48, 98748/47.
[67] Noble and Toby B23009/48.
[68] Evans 56353/36.
[69] Bondy et al. B36436/49.
[70] Bondy and Engel 98486/47.
[71] Bondy et al. B36436/49.
[72] Engel et al. B36435/49.
[73] Noble and Toby B23009/48.
[74] Perera et al. B36595/49, Selye **94572/49.**

The increase in blood-urea formation, caused by cortical extracts in *nephrectomized* rats, is inhibited by the injection of glucose or amino-acids, presumably due to their protein-sparing effect. Insulin-hypoglycemia exerts an opposite action. It has been emphasized that an increased need for carbohydrate may play a prominent part in the catabolic response to stressors.[76]

In the intact organism **DCA** produces no consistent change in blood-N.P.N. or urinary-N elimination [77] which could play a part in the catabolic impulse of the A-R. Curiously, the rise in blood-N.P.N. normally elicited by bilateral *nephrectomy,* is greatly delayed by DCA; [78] indeed, even the life-span of nephrectomized animals is prolonged by this hormone.[79]

The rise in blood-N.P.N. caused by *traumatic* shock is not significantly influenced by DCA,[80] although one investigator [81] reported positive results. On the other hand, allegedly, DCA can prevent the N loss which normally occurs in man during adaptation to extreme humid *heat.*[82]

Kidney. — Following ligation of the renal artery, or complete nephrectomy, protein catabolism is more rapid, the toxic symptoms more severe, and the survival-time shorter in dogs previously kept on a high-protein diet than in those which had received mainly carbohydrate. "It may be concluded both that substances derived from the ischemic kidney stimulate catabolism of protein reserves and that the toxic symptoms following renal artery ligation are associated with accelerated nitrogen catabolism." [83]

Other endocrine glands. — **Testosterone,** which likewise possesses marked protein-anabolic properties [84] tends to counteract the N loss normally observed during stress, e.g., that caused by *intestinal obstruction* [85] or *burns,*[86] but further work is necessary to determine the practical applicability of this observation.

Thyroidectomy inhibits, while **thyroid hormone** stimulates protein-catabolism,[87] but these well known actions need not be discussed here since their participation in the G-A-S has not yet been investigated.

Diet. — Because of the enormous practical importance of this subject, a great deal of work has been done concerning the possibility of compensating for the N loss of the catabolic impulse. The effect, before, during and after exposure to stress of **proteins** and **protein-hydrolysates** has been studied.[88] During the first 7-10 days after injury (trauma, burns, etc.), high-caloric and high-protein diets greatly diminish (though they rarely abolish) the N loss of the catabolic period.[89] Individuals who underwent gastric or cranial operations were found to require a greater than normal intake of dietary-N and of total calories to preserve nitrogen equilibrium during the first post-operative days. "By increasing the nitrogen intake to 0.30 gm./kg. and the caloric intake

[75] Bourque et al. 84560/44.
[76] Engel B35914/49, B39042/49.
[77] Selye **94572/49.**
[78] Selye and Nielsen A35723/41.
[79] Dosne A35924/41, Selye A34190/40.
[80] Keating et al. A37500/42.
[81] de Luca A54791/42.
[82] Conn et al. B4468/46.
[83] Mylon and Goldstein B28280/48.
[84] Kochakian et al. B29992/48, B46214/50, B46216/50.
[85] Bassett B356/43.
[86] Abbott et al. B29501/46, Braasch and Wakerlin B33094/48.
[87] Selye **94572/49.**
[88] Allison et al. 97433/46, Werner B33447/49.
[89] Beattie B18456/47.

to 30 calories/kg. daily, or over, patients fed by mouth, or Abbott-Rawson tube, were usually maintained in nitrogen equilibrium. Hydrolyzed protein in the form of casein hydrolysate, combined with carbohydrate, was equally as effective as whole protein when administered by the same routes." [90]

Numerous investigators studied the relative advantages of administering the necessary amount of nitrogen in various forms and by different routes. The efficacy of ingested protein or protein-hydrolysates, was compared with that of protein-hydrolysates and amino-acid mixtures given by stomach tube or intravenous injection. Nitrogen retention has been obtained with such supplements in traumatic shock, extensive burns, fractures and in convalescence from various types of acute illnesses.[91] It is doubtful, however, whether this is advantageous during the catabolic phase.[92]

Some workers like to distinguish between "storage protein" [93] or "reserve protein" [94] which is readily utilized under stress, and "essential protein" [95] which is so fixed in the cell that it can not be released. Whipple's school,[96] differentiates: (1) fixed or indispensable cell-protein, without which cellular life ceases, (2) "dispensable protein", which can be utilized as a source of energy during stress (e.g., starvation) and (3) mobile protein which can move in and out of the cell whenever the concentration of the plasma-proteins rises or falls. Presumably, the "storage protein" corresponds to the sum of "dispensable" and "labile" protein.[97]

It is of the greatest interest that in protein-depleted animals systemic stress causes little or no increase in urinary-N excretion.[98] Thus in dogs, sterile abscesses (produced by subcutaneous turpentine injection) elicited marked urinary-N losses if the animals had previously been kept on an adequate protein intake. On the other hand, on protein-deficient diets, they maintained a strongly positive N balance if, following the injury, the protein content of the food was raised to normal. It was concluded that "the increased nitrogenous excretion after injury is again shown directly related to the state of body protein reserve. Increased catabolism, not inhibition of anabolism, best explains the excess urinary nitrogen. Protection during injury of valuable protein reserves appears possible through an adequate intake of protein nitrogen".[99]

Patients suffering from a variety of chronic debilitating diseases (pulmonary tuberculosis, rheumatoid arthritis, bronchiectasis, peptic ulcer) fail to respond with the usual, pronounced N loss when exposed to intercurrent, acute systemic stress. Indeed, in contrast to acutely damaged individuals, these "metabolically debilitated" subjects display a remarkable ability to retain dietary N on comparatively low intakes. If N ingestion is raised their N balance becomes more rapidly positive, and the gain in weight is greater than in normal individuals.[100]

[90] Riegel et al. 96951/47.
[91] Cuthbertson 89886/45, A56384/42, Cuthbertson and Robertson A6664/37, McGavack and Schwimmer B40205/48, Peters and Man B44233/47, Stevenson et al. B19924/45, Werner et al. B41222/49.
[92] Abbott et al. B29501/46.
[93] Munro and Cuthbertson B26210/43.
[94] Madden and Clay B2098/45.
[95] Madden and Clay B2098/45.
[96] Cooke and Whipple B26207/18, Madden and Whipple B26233/40.
[97] Cuthbertson et al. B19925/39.
[98] Daft et al. A55196/37, Madden et al. B26209/37, B26208/40, Munro and Chalmers B38437/45, Munro and Cuthbertson B26210/43.
[99] Madden and Clay B2098/45.
[100] Browne et al. B2238/47, B347/45, Schenker et al. B4534/47, B4447/48, Stevenson et al. B19924/45.

Experimental observations on burned rats suggest that among the dietary-protein constituents, *methionine* plays an especially important rôle. Allegedly the urinary-N losses after scalding were substantially reduced, not only by high-protein diets, but also by mere addition of 1% methionine to the diet. Alanine, cysteine or a mixture of synthetic amino-acids had no such effect. "It is suggested that the apparent toxemia is in reality a deficiency induced by a call for one amino-acid, with consequent raiding of the whole protein molecule." On the basis of these observations, methionine had been recommended for patients suffering from burns, in the hope of stopping the N loss.[101] Observations on dogs also suggested that methionine decreases the urinary elimination of nitrogen.[102] However, subsequent investigations with experimental burns yielded inconclusive results.[103] Methionine also failed to reduce the N loss in patients who received a low caloric diet following herniorrhaphy,[104] or in rats exposed to cold.[104a]

Allegedly **ascorbic acid** supplements "depressed the nitrogen output of normal and traumatized rats",[105] but this observation awaits confirmation.

Amino-Acid Metabolism

The amino-N fraction of the blood is composed chiefly of α-amino-acids, but it also comprises glutamine and several other amino-compounds whose identity has not yet been clearly established. The blood amino-acid concentration depends primarily upon: (1) intake from the intestine, (2) production from tissue- and blood-proteins, (3) withdrawal from the blood for protein synthesis, (4) deamination and further degradation, (5) elimination of entire amino-acids in the urine. Normally the deamination of amino-acids occurs only in the liver.

The **characteristic** blood amino-acid curve of the G-A-S has not yet been followed through the three stages. Available data show, however, that in the A-R there is a marked increase in the blood amino-acid concentration, with return to, or below, normal during the stage of resistance. Since the blood level of amino-acids depends upon many factors, it is obvious that the characteristic curve can readily be modified by the incidental specific actions of certain alarming stimuli, especially by hepatic or renal damage.

Retarded recovery from various types of injury and infection is, however, often accompanied by low blood amino-acid levels.[106] Perhaps protein depletion may reverse the normal blood amino-acid curve by diminishing the stores from which catabolized amino-acids could be regenerated. Depletion of protein-reserves may also be involved in the hypo-amino-acidemia of nephrosis, which occurs in patients who lose large amounts of protein through the urine.[107]

After **trauma,** the blood amino-acid concentration is usually far above normal in man.[108] During the first six hours after removal of a tourniquet there is a slight, though constant, fall in amino N in rats and dogs, but this is followed

[101] Croft and Peters B2425/45.
[102] Miller B26206/44.
[103] Gribble et al. B38583/47. Lathe and Peters B45984/49.
[104] Riegel et al. B1298/46.
[104a] Lathe and Peters B45984/49.
[105] Noble and Toby B23009/48.
[106] Farr et al. B26236/42, Man et al. 93286/46.
[107] Farr, B26238/40, Farr and MacFadyen B26237/40.
[108] Abbott et al. B29501/46, Lurje B26177/36.

by a pronounced secondary rise with a maximum at about ten hours. Curiously there appears to be no correlation between the degree of shock and the height of the blood amino-acid concentration; furthermore suitable therapy (transfusions or reclamping of the injured limb) results in recovery before the amino-acid level returns towards normal.[109]

In man, the amino-acid-N may sometimes also fall abruptly after injury, even while N catabolism is greatly increased; it often remains low until recovery is well advanced. Allegedly here "the extent of the abrupt fall is directly proportional to the severity of the operative procedure, and roughly, inversely proportional to the initial amino-acid concentration. The latter reflects the pre-operative condition of the patient. If this is normal, the plasma α-amino-acid nitrogen is greater than 4.0 mg. per cent. If the patient is seriously ill before operation, the α-amino-acid nitrogen is less than 4.0 mg. per cent before operation. If it is already greatly reduced it may fall no further as a result of the operation".[110]

It is somewhat difficult to reconcile these observations with the vast majority of pertinent data which indicate that the blood amino-acid concentration rises during the shock phase. Perhaps acute stress increases the amino-acid requirements of the body and if the protein stores are depleted, hypo-amino-acidemia results, while normally, compensatory amino-acid formation is adequate and even excessive. This would be comparable to the glycemic response whose direction during stress largely depends upon the available glycogen stores.

Studies on traumatized rat muscle showed that under the influence of local injury the amino-acid content of damaged tissue rises as a result of proteolysis. The response is similar to that seen during autolysis. The amino-acids thus formed are at least partly responsible for the hyper-amino-acidemia of the post-traumatic period.[111]

Burns also raise the blood amino-acid concentration in man.[112] Similarly, in rats with scalds produced by immersion into hot water, a progressive increase in plasma amino-N occurred within the following 12 hours.[113]

Experiments in calves showed that in the lymph draining from burned areas, the amino-acid-N reaches unusually high concentrations.[114] Presumably, considerable quantities of amino-acids, liberated from injured cells, are drained into the blood through the lymph-channels.

Following severe **hemorrhage,** a rise in blood amino-acid N is rather constantly observed both in animals and in man.[115]

In the dog, the systemic blood amino-N concentration increases steadily after the loss of much blood, reaching its highest value terminally. In the femoral vessels, the arterio-venous blood amino-N difference was zero before bleeding and increased after hemorrhage, indicating a rising output of amino-acids from muscles. At the same time, the portal concentration was greater than that of the hepatic vein, due to removal of amino-N by the liver.[116]

In rats, the free amino-N content of hepatic tissue was high during hemorrhagic shock and the rate of dl-alanine deamination by liver slices was sub-

[109] Hoar and Haist 95628/44.
[110] Man et al. 93286/46.
[111] Stoner and Green B37598/48.
[112] Abbott et al. B29501/46.
[113] Harkins and Long 87814/45.
[114] Glenn et al. B26175/43.
[115] Engel et al. B26172/44, Sayers et al. B26181/45, Seligman et al. B19870/48.
[116] Kline 85855/45, B26182/46.

normal. Urea synthesis from dl-alanine, or from ammonium lactate, was also progressively diminished in such liver slices. Apparently, hemorrhagic shock in the rat depresses both deamination and urea synthesis in the liver. The characteristic rise in blood amino-N is probably due to (1) failure of the liver to catabolize amino-acids, (2) deficient amino-acid assimilation and (3) increased contribution of amino-N from peripheral tissues.[117] Accordingly, the concentration of free amino-N rises after hemorrhage, not only in the liver, but also in muscles, the rise being mainly in the intracellular compartment.[118]

Many other types of acute systemic stress raise the amino-acid content of the blood, for instance **anoxia**[119] and **"medical shock"** (due to infections, cardiovascular disease, intoxications, etc.[120]). Of course the amino-acidemia rises to especially high levels in the case of damage by agents which specifically affect hepatic tissue, for instance in **eclampsia, acute yellow atrophy of the liver** or poisoning with **phosphorus, chloroform, carbon-tetrachloride, arsphenamine** and **cinchophen.**[121] When the amino-acidemia reaches high levels, amino-aciduria ensues.[122]

Curiously, some anesthetics such as **pentobarbital,**[123] **nitrous oxide** or **ether**[124] allegedly diminish the amino-acidemic level.

Several investigators examined the metabolism of certain individual amino-acids during different types of systemic stress. It has been found, in man, that parenteral administration of milk raises the *tryptophane* content of the serum.[125] *Tyrosinuria* is sometimes seen in patients with diseases causing autolysis of tissue, e.g., degenerating pulmonary tumors or extensive sloughs of the skin.[126] Of course, in patients with liver disease, both tyrosinemia and tyrosinuria tend to be particularly pronounced,[127] because of the interference with the hepatic deamination of amino-acids.

Hypophysectomy in the rat does not prevent the rise in blood amino-N elicited by *burns;*[128] hence, this response is not dependent upon hypophyseal hormones. Yet, in otherwise untreated rats, hypophysectomy tends to lower the blood-amino-N level.[128a]

Somatotrophin causes a very marked and consistent fall in the blood level of amino-acids. This is presumably due to their increased utilization for protein synthesis.[129] **ACTH** on the other hand, raises the blood-amino-N of the rat,[129a] probably because of its protein catabolic effect.

The rise in blood amino-acid-N, which follows a *hemorrhage* is not prevented by **adrenalectomy** either in the rat[130] or in the dog,[131] hence, it cannot be ascribed merely to an increased corticoid production. On the other hand, the rise in plasma amino-acid-N occasioned by *evisceration* is reduced by adrenalectomy in the rat and can be restored by adreno-cortical extract. This was taken to show that the protein catabolic effects of the adrenal cortex

[117] Wilhelmi et al. 87816/45.
[118] Russell and Long 99968/46.
[119] Tepperman et al. B4674/47, Wilhelmi et al. B26191/47.
[120] Davidson et al. 87543/46.
[121] Cantarow and Trumper B776/45.
[122] Cantarow and Trumper B776/45.
[123] Crismon et al. A34227/40, Hoar and Haist 95628/44.
[124] Farr et al. B26235/42.
[125] Berencsi A63964/42.
[126] Cantarow and Trumper B776/45.
[127] Jankelson et al. B26247/37, Lichtman 27794/34.
[128] Harkins and Long 87814/45.
[128a] Li et al. B46159/49.
[129] Li B36466/48, Li and Evans B29320/48, Li et al. B46159/49.
[129a] Li et al. B46159/49.
[130] Engel et al. A58685/43.
[131] Kline B23922/48.

do not require the presence of the liver and therefore are not primarily associated with alterations in the rate of urea formation.[131a]

In intact rats, large doses of **adreno-cortical extracts** raise the plasma amino-acid-N, and this effect can be abolished by simultaneous intravenous administration of *glucose;* the latter effect is retained even in the absence of the liver, after evisceration.[131b]

Experiments in **nephrectomized** rats revealed that after fatal *hemorrhage,* the high blood amino-N levels are associated with a decreased rate of urea formation from injected amino-acids. Non-fatal hemorrhage, with no change in blood amino-N, on the other hand, increased urea production. This was ascribed to the conversion into urea, not only of the infused amino-acids, but also of the protein catabolites coming from the peripheral tissues damaged by uremia. Apparently this conversion can only occur as long as the liver is still normal.[132]

The arterial plasma amino-N levels, rose about equally after *hemorrhage,* in intact and alloxan-treated dogs, but considerably more than in **pancreatectomized** animals. Conversely the discharge of amino-N from the legs into the blood was highest in the latter group.[133] Apparently, in the absence of the pancreas, both the production and the disposal of amino-acids rises more than normally after hemorrhage. The clearance of certain amino-acids (injected intravenously) is delayed during hemorrhagic shock in dogs. Yet here amino-acid clearance is not accompanied by any equivalent rise in blood-urea; this was regarded as a probable indication of protein synthesis in spite of shock.[134]

Thyroidectomy reduces the rise of plasma amino-acids in the eviscerated rat. This is prevented by moderate doses of thyroxine, but not by adreno-cortical extracts. From this it was concluded that the protein catabolic effects of the thyroid hormone are independent of the adrenals.[134a]

Polypeptides

Various investigators claim that systemic stress causes a **characteristic** rise in the polypeptide content of the blood. This was noted after **trauma,**[135] **infections, intoxications** and other pathological conditions associated with extensive tissue injury,[136] such as **neoplastic disease,**[137] **renal**[138] and **hepatic insufficiency,**[139] **myocardial infarction**[140] and a variety of **other diseases including hypertension.**[141] Indeed, the concept of the **"syndrome polypeptido-toxique"**[142] developed from the hypothesis that the excessive blood-polypeptides may represent the much discussed, hypothetic split-products of protein which are supposed to cause the manifestations of shock.

[131a] Bondy B45922/49, B46247/49.
[131b] Bondy B45922/49, B46247/49.
[132] Engel and Engel 99967/46.
[133] Kline 98551/47, B23922/48.
[134] Seligman et al. B19870/48.
[134a] Bondy B45922/49, B46247/49.
[135] Gaujard 97306/46, Jourdan and Gaujard B38539/47, Larget and Lamarre A38155/41, Polonovski and Driessens 56625/31.
[136] Duval et al. B26119/34, Gangitano B26174/40, Lambret et al. B3939/36, Loiseleur A32659/34, Stolfi B26179/40.
[137] Schweriner B26244/20.
[138] Becher and Hermann 54077/32.
[139] Becher and Hermann 54076/32, Martens B26246/28.
[140] Simkin et al. B38981/49.
[141] Blau, B26245/23.
[142] Liègeois and Terache A6268/37.

In dogs, following **x-irradiation** there was a transitory decrease in blood-polypeptides followed by a terminal increase; the latter was ascribed to renal failure.[143]

In nephritis, there is often a marked rise in blood-polypeptides. This does not parallel the total blood N.P.N. but it is claimed to become most pronounced whenever clinical manifestations of uremia are especially prominent. This was again interpreted as indicating a "polypeptidotoxic effect".[144]

Recent investigations cast some doubt upon all these findings, since many technical factors tend to vitiate the validity of earlier blood-polypeptide determinations. Yet, even using an improved procedure, patients suffering from a variety of severe diseases proved to have somewhat increased average blood-polypeptide levels, although after surgical interventions, a definite rise in blood-peptides was not detectable.[145]

The chemical methods employed to measure "serum polypeptide" or "proteose" are similar in principle to those used for the determination of "serum mucoprotein"; hence, findings reputedly concerning any one of the above-mentioned blood-constituents may actually depend upon the same metabolite. It has been emphasized that the only common denominator in the many clinical conditions which raise this fraction, appears to be that they all produce an A-R.[146]

Proteins

Systemic Stress

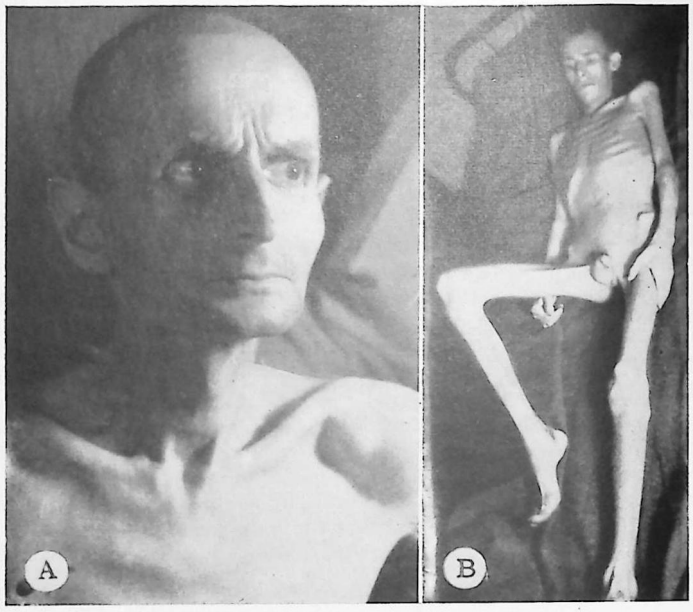
The observations discussed in the previous chapters showed that large amounts of N.P.N. products originate from the proteins of the blood and tissues during the catabolic impulse of the A-R.

As far as it can be sketched on the basis of available data, the **characteristic** derangement in protein metabolism may be summarized as follows: during both the stages of alarm and of exhaustion, there is pronounced protein catabolism with loss of tissue-protein reserves. At these times, the breakdown of the reserves is particularly severe in well-nourished individuals, with abundant protein stores, while in patients whose protein reserves are depleted, due to undernourishment or chronic debilitating diseases, the protein losses are comparatively mild. It appears as though the body's efforts to save protein would become increasingly more effective as the "dispensable protein" is lost.

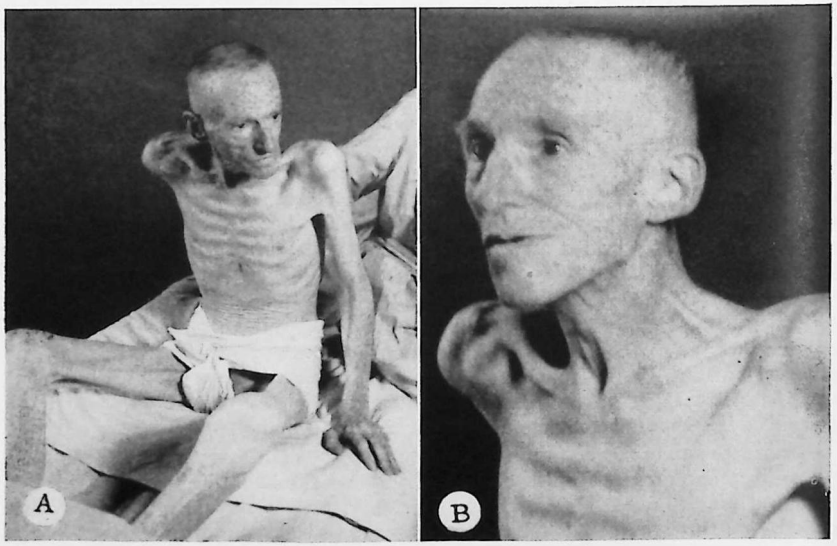
Between these two catabolic periods, during the resistant stage, there is a tendency to replace the tissue protein which was lost during the A-R. However, unlike with many other metabolic responses, there appears to be no true reversal of the A-R response. The previously negative nitrogen balance becomes positive, but only until the protein reserves are built up to about the normal level; excessive nitrogen storage is exceptional.

During the two catabolic periods — the stages of alarm and exhaustion — *tissue-proteins* are lost most readily from the thymus, the other lymphatic organs (lymph-nodes, spleen, etc.), the large, parenchymatous glands (liver, pancreas), the connective tissue and the musculature, approximately in the

[143] Prosser B26618/47.
[144] Puech and Cristol A32660/29.
[145] Christensen et al. B2728/47.
[146] Simkin et al. B38981/49.



Cachexia due to starvation. **(A)** Undernourished concentration-camp inmate who suffered from extreme loss of weight, pyodermia, and phlebitis. Note energetic facial expression indicative of unbroken moral despite considerable suffering. — **(B)** Cachectic undernourished prisoner of war. Height 178 cm., weight 39 kg. Note loss of pubic hair and atrophy of external genitalia.



Extreme cachexia due to malnutrition. Severely undernourished concentration-camp inmate. Height 192 cm., weight 50 kg., myocardial damage, hunger edema, nephritis, pyodermia, intense diarrhea and loss of certain reflexes. Patient eventually died from miliary tuberculosis presumably due to great decrease in resistance. (Courtesy of Gsell and Hottinger B27610/48).

order mentioned; other tissues, such as the cardiovascular and nervous systems do not give up their proteins easily, even when the body-weight falls far below normal. The adrenal cortex is the only organ which tends to gain weight and acquire protein during the catabolic phases of the G-A-S. Since this increase in adrenal-protein occurs even during complete starvation, the gland must be capable of N anabolism at the expense of other organs.[147]

Comparative studies concerning the protein loss, which occurs in various tissues of the rat during the A-R, confirmed that the thymus, lymph-nodes, spleen and liver undergo the most rapid involution, while the weight of the heart, kidneys and brain remains almost unchanged. The carcass (mainly muscle) and skin take an intermediate position as far as percentual involution is concerned, but since these are large organs, they quantitatively represent important sources of protein degradation products.[148]

It has repeatedly been emphasized that the protein degradation products liberated during the catabolic impulse, may be of use in the phenomena of regeneration, cell-renewal and wound-healing, which are an essential part of adaptation to systemic stress. An example will illustrate how the transfer of protein from one tissue to another can be useful in raising resistance. It has been found that a sterile abscess affords protection against hepatic damage due to chloroform anesthesia.[149] Under the influence of such an abscess the total hepatic protein, and especially the purine-N, increase. Since an increment in nucleic acid content is usually associated with active protein regeneration, the protection here is presumably due to stimulation of hepatic protein synthesis.[150]

The *plasma-proteins* tend to fall below normal during the two catabolic phases of the G-A-S. At the same time, the normal *albumin/globulin* ratio of about 2/1 is decreased or actually reversed, because albumin is more readily lost through the urine, or destroyed in metabolism, than globulin, while the latter is more easily regenerated. As a generalization, it may be said, perhaps, that the total protein concentration of the blood, and especially the albumin fraction, rarely rise above normal although dehydration may simulate a rise. On the other hand, a great variety of systemic stressors (diseases, intoxications, hemorrhage, malnutrition, etc.) tend to diminish the total blood-protein, and especially the serum-albumin concentration.

Electrophoretic analysis of the serum-proteins in dogs subjected to various types of injury (dichloroethylsulphide-mustard, nitrogen-mustards, burns, freezing, turpentine, x-rays, bone fracture) showed that the characteristic response to all these stressors is a rise in the *α-globulin* fraction after a latent period of about 48-72 hours; at the same time, the albumin content decreases. "The concentration of α-globulin appeared to be roughly proportional to the degree of injury, this increase apparently represented a non-specific response to tissue damage".[151] Essentially similar observations have been made in man after injury and disease.[152] On the other hand, electrophoretic patterns of whole sera of dogs, rats and goats injured with vesicants, heat or turpentine showed a definite increase in the *β-globulins*.[153]

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147 Selye A55493/42, 35935/ND.
148 Leduc and Guillemin B27410/49.
149 Ravdin et al. B25566/39.
150 Schultz and Vars B2500/47.
151 Gjessing and Chanutin A95937/46, Gjessing et al. B4999/47.
152 Stern and Reiner B26251/46.
153 Chanutin B24321/47, Gjessing and Chanutin 98612/47.

Some data concerning changes in the γ-globulin content of the blood will be mentioned below (in connection with individual stressors and hormones), but it must be emphasized here that the evidence at hand does not yet permit generalizations concerning γ-globulin changes during the G-A-S.

A rise in the concentration of plasma-*fibrinogen* is a rather constant and characteristic feature of the response to a variety of noxious stimuli.[154] Following exposure to acute, systemic stress, the rise in the blood-fibrinogen level is not immediate; it may take several days to reach its maximum, but then it tends to remain high for weeks, even after a single exposure to a stressor. A careful survey of the entire pertinent literature led to the conclusion that: "elevation of plasma fibrinogen is one of the most common non-specific responses of the body to a variety of disease conditions and is comparable to other non-specific reactions of leucocytosis and hyperpyrexia. The fibrinogen response may vary independently of variations of other plasma proteins".[155]

Fibrinogen is made in the liver and its production largely depends upon adequate food intake. hence the normal increase in the blood concentration during stress is impeded in patients suffering from liver disease, pernicious anemia and malnutrition.[156]

The rôle of fibrinogen in the G-A-S is not yet known. It obviously plays an important part in defense by aiding the development of inflammatory exudates and the formation of clots, which prevent hemorrhage from mechanically traumatized vessels. Perhaps it also helps to prevent excessive, diffuse seepage of blood-constituents through the walls of capillary and pre-capillary vessels. It may accomplish this by forming microscopic fibrin-plugs throughout the vascular tree (even at a distance from the direct injury), wherever the endothelial lining becomes defective and plasma enters into contact with tissue-fluid. The close histochemical resemblance of fibrin and "hyalin" suggests that some relationship may even exist between fibrin formation and the "hyalinosis" of the diseases of adaptation.

It is unfortunate that hitherto, fibrinogen has been studied almost exclusively in connection with blood-clotting. As a precursor of fibrin, fibrinogen is indispensable for the formation of inflammatory transudates and granulomas, the scabs which protect epithelial defects during healing, and the temporary scars in which collagenous tissue can form. As a liquid cement-substance it safeguards the integrity of the vascular tree.

Thus fibrinogen participates in many fundamental phenomena concerned with reaction to local and systemic injury. As a circulating blood constituent, it necessarily reaches any injured part of the body and since it becomes solid (fibrin) upon contact with tissue, wherever vessels are damaged, it is ideally suited to serve as a temporary protein mold for tissue regeneration. In this sense, fibrinogen is undoubtedly of such paramount importance in the G-A-S, that its metabolism would deserve more careful attention than it has received hitherto. We know that fibrinogen comes from the liver, but we ignore the subsequent fate both of this compound itself and of that fraction of it which is transformed into fibrin. We know that fibrin is destroyed by fibrinolysin, but the intimate mechanism of this reaction and the possible significance of the

[154] Favre-Gilly **B27618/47.** Foster and Whipple B26264/22, B26265/22, Gram B26267/22.
[155] Ham and Curtis **B18189/38.**
[156] Ham and Curtis **B18189/38.**

resulting split-products are still a mystery. We know that the blood-fibrinogen concentration rises after systemic stress, but it remains to be seen whether at this time there is an actual increase in the "utilization" of fibrinogen, perhaps due to continuous fibrin formation with subsequent fibrinolysis. It is well established that blood-fibrinogen levels can be raised by high-protein diets or by intravenous injection of the compound itself. It would obviously be of the greatest practical interest to know whether such measures could raise resistance to stress by facilitating the normal hyperfibrinogenemic response. It is suggestive, in this connection, that "a failure of fibrinogen to increase above normal in instances of severe infection may be a poor diagnostic sign...".[157]

Proteinuria is rather characteristic of shock and the immediate recovery-period in man, irrespective of the eliciting stressor. It has been noted after traumatic injury, burns,[158] infections, intoxications, etc.[159] It is especially noteworthy that proteinuria was frequently observed in our experiments on rats in which hypertension and nephrosclerosis were produced by chronic exposure to various damaging agents such as parenteral injections of formaldehyde or foreign proteins, excessive muscular exercise and especially cold. These animals were sensitized to the stressors by partial nephrectomy as well as a high-protein, high-sodium diet and the proteinuria coincided with the development of hyalinosis and adrenal-cortical enlargement.[160]

Allegedly some degree of albuminuria is quite characteristic of the A-R no matter how it is elicited. This has been ascribed to an increased permeability of the glomerular tufts. In rabbits in which an A-R was produced by formaldehyde, histamine or forced exercise — unlike in controls — intravenously administered human serum albumin was rapidly excreted into the urine. From all these observations it was deduced that the "physiologic albuminuria" of man (which may occur during stress in the absence of renal disease) is due to the A-R.[160a]

Traumatic injuries increase the blood-protein level only if there is marked hemoconcentration; [161] there is no close relationship between the degree of hypoproteinemia and the clinical severity of traumatic shock.[162] The absolute amount of blood-proteins is diminished.[163]

The permeability of membranes to albumin, globulin and fibrinogen diminishes in that order, [164] since it is inversely proportional to molecular size. A study, by precipitation methods, of the plasma-protein fractions revealed a marked rise in globulins and fibrinogen with a diminution of albumin, after trauma. This may be related to the above differences in membrane permeability; [165] however, the ability of the organism to make these proteins must also be taken into account. In any event, the increase in plasma-fibrinogen occurs regularly in men exposed to traumatic injuries.[166]

In the rat, laparotomy is immediately followed by an increase in the fibrinogen and globulin and a decrease in the albumin content of the plasma. The albumin and fibrinogen levels returned towards normal after about 18 days, but the

[157] Ham and Curtis B18189/38.
[158] Moon B26013/47.
[159] Cantarow and Trumper B776/45, Herbut 93650/46.
[160] Selye A62756/43.
[160a] Karady and Földi B44928/43.
[161] König A32639/32.
[162] Mills and Gordon 93421/46.
[163] Blalock and Beard 8726/32.
[164] Oswald B26262/10.
[165] Cuthbertson A56384/42.
[166] König A32639/32. Ham and Curtis B18189/38.

globulin fraction remained high throughout this period.[167] The post-traumatic rise in blood-fibrinogen is unaffected by starvation of up to 72 hrs. in the rat. It is probably related to the A-R.[167a]

From experiments in the mouse it was concluded that the tissue-protein concentration does not rise in a limb damaged by tourniquet. Electrophoretic analyses of the fluid in the injured leg disclosed no component with the mobility of albumin, but a faster new component appeared, whose sedimentation-constant in the ultracentrifuge was greater than that of albumin. It was concluded that contrary to common views, plasma-proteins do not accumulate in limbs damaged by tourniquet.[168] However, in view of the many contrary data listed in this chapter, this cannot be accepted as a rule valid in all cases.

During and immediately after severe traumatic injuries in man, the urinary elimination of albumin is probably due to the increased permeability of damaged glomeruli.[169]

Burns decrease the total blood-protein concentration,[170] mainly due to loss of albumin, presumably by leakage into burned tissues.[171] Hence a diminution of the albumin/globulin ratio is a constant accompaniment of severe burns.[172] In this case much protein is lost on and around the burned surface itself, but this does not always account for such changes since other systemic stressors likewise tend to diminish the albumin/globulin ratio.

Electrophoretic studies show that in dogs three abnormal α-globulin-rich fractions appear after injury by burns.[173] Subsequent studies revealed that, both in the rat and in the dog, thermal injury increases the α- and β-globulin and decreases the γ-globulin and albumin fractions of the plasma.[174]

Electrophoretic analysis of the burned tissue and its surroundings led to the conclusion that, in the mouse, thermal injury is not accompanied by any detectable leakage of protein into the burned area,[175] but it is difficult to reconcile this observation with the bulk of pertinent data derived from observations on other species.

The albuminuria frequently noted in patients with severe burns [176] is presumably due to glomerular damage such as is seen after various types of systemic stress.

Since fever is a common accompaniment of infectious diseases, the question arose whether this could be the immediate cause of the increase in blood-fibrinogen so often noted in infections (see below). However, fever induced by high environmental **temperature** produces little or no elevation of plasma-fibrinogen hence "fever per se probably is not the cause of the abnormally increased fibrinogen concentrations observed in many febrile diseases".[177]

While most stressors tend to cause an increase in blood-fibrinogen, exposure of rats to cold elicits a marked fall, within the first day. This is followed by a rise, to a still subnormal level, which is maintained for several weeks. During

[167] Chanutin et al. A14834/38.
[167a] Henriques et al. B44030/50.
[168] Fox and Moore B4525/47.
[169] Moon B26013/47.
[170] Ficarra and Naclerio B808/44, Peters 89884/45, Simonart 63360/30, Taylor et al. B26261/43.
[171] Peters 89884/45.
[172] Eden and Herrmann B26252/26, Hilgenfeldt 38008/36, Murakami B26253/33, Schreiner B26254/26.
[173] Gjessing et al. B4999/47.
[174] Gjessing et al. B5000/47, Ludewig et al. B4667/47.
[175] Fox and Moore B4525/47.
[176] Moon B26013/47.
[177] Ham and Curtis B18189/38.

the initial pronounced fall, the changes in the adrenals and thymus are typical of the A-R, while later they correspond to the resistant stage of the G-A-S. Thus, undoubtedly, cold influences the blood-fibrinogen in a rather specific manner; yet the non-specific rise in blood-fibrinogen, characteristic of the resistant stage, may have been superimposed upon the specific fibrinogen-depressing effect of cold.[178]

Interestingly, proteinuria is common among patients who react with a marked rise in blood-pressure and diminished renal function (clearances) in the "cold-pressor test".[179]

The regeneration of blood-proteins following **hemorrhage** has been the subject of very extensive studies.[180] This type of stress naturally leads to a loss of plasma-proteins, but under normal conditions, this is rapidly compensated for by increased synthesis of blood-proteins from food stuffs.[181] Experiments in the dog showed, furthermore, that even in the absence of preformed protein, the parenteral administration of the ten essential amino-acids suffices to restore the blood-proteins after hemorrhage.[182]

In patients who simultaneously suffer from trauma and hemorrhage, the loss of plasma-proteins may play an important rôle in the development of secondary shock, especially if blood-protein regeneration is impeded by a superimposed hepatic damage.[183]

A brief report mentions that in **anoxia** there are electrophoretically detectable changes in the β- and γ-globulins of the blood, but curiously, the direction of these deviations has not been divulged.[184] If guinea-pigs are exposed to a decreased atmospheric pressure for 30 minutes no obvious change in serum-albumin is detectable,[185] but perhaps such brief anoxia is not sufficient to cause severe systemic stress. In mountaineers ascending to very high peaks, the total plasma-protein level rises during the first day, then it falls considerably, while the fibrinogen concentration rises.[186]

Total body **x-irradiation** has been claimed to cause an increase in total serum-protein and γ-globulin content. In previously immunized mice at the same time, an anamnestic response was elicited. In view of the accompanying adreno-cortical enlargement and thymico-lymphatic involution, it has been suggested that the changes in the blood-proteins are due to a discharge of lymphocyte-protein into the blood, perhaps partly caused by excessive secretion of corticoids.[187] This work requires confirmation. In dogs various types of ionizing radiations (x-rays, Sr^{89}, Pu^{239}) raised the α_3- and α_4-globulins and the β-globulins.[188]

The blood-fibrinogen content rises following x-irradiation, as it does with most types of systemic stress [189] in man. Experiments on mice revealed a striking increase in total serum-protein during the first 6 hrs. after x-irradiation, but this was unaccompanied by any significant change in the relative distribution of the various protein fractions as judged by electrophoresis. Significantly, cortical extracts produced similar results.[189a]

[178] Henriques et al. B27601/49, B44030/50.
[179] Odell and Aragon **B26603/47.**
[180] Madden and Whipple B26233/40.
[181] Blalock and Beard 8726/32.
[182] Madden et al. B26234/44.
[183] Rukstinat A32657/32.
[184] Malméjac B2243/47.
[185] Hopps and Lewis B37875/47.
[186] Schönholzer and von Sinner B37506/48.
[187] Dougherty and White 95612/46.
[188] Prosser et al. B26618/47.
[189] Ham and Curtis **B18189/38.** Prosser et al. B26618/47.
[189a] Milne and White B43457/49.

In man a large variety of **infections**, such as *malaria*,[190] *pneumonia*,[191] *subacute bacterial endocarditis*,[192] *streptococcus infections*, *relapsing fever* and *scarlet fever*,[193] *tick typhus*,[194] *tuberculosis*,[195] etc., are accompanied by a decrease in total protein and albumin, sometimes with an increase in the α-globulin content of the serum. These changes are essentially the same in the various infections and indeed, similar to the plasma-protein derangements noted in a variety of *other diseases*.[196] Even simple protein depletion produces the same type of derangement, hence it was concluded "that the alterations of normal plasma pattern are in fact due to the same fundamental mechanism, i.e., inadequate protein retention as an incidental phenomenon in each of the diseases studied. It is not surprising then that in the patients with low albumin content of the plasma, if treated by the administration of an adequate protein hydrolysate, thus correcting the protein deficiency, a rise of albumin occurs quite promptly and this is accompanied by a decrease in the concentration of α-globulin".[197]

A variety of *cardiovascular* and *neoplastic* conditions have been intensely studied from this point of view. A fall in albumin with a corresponding rise in globulins was rather constant, irrespective of the nature of the disease, but sometimes the α- at other times the γ-globulin fraction rose more markedly.[198] Such observations also led to the conclusion that these variations "are non-specific and do not yield sufficient information for diagnosis".[199] The so-called "fibrinogen-B" appears in the blood of patients with congestive cardiac failure, coronary occlusion, thrombotic states and sepsis; [200] its relation to non-specific stress has not yet been elucidated.

Experiments on rhesus monkeys again showed essentially the same pattern. Following infection with malaria or tuberculosis, electrophoretic analysis revealed a marked diminution of plasma-albumin, accompanied by an increase in α-globulins and fibrinogen.[201]

Only in very acute, fulminating infections, for instance, in grave diphtheria, is there a rise in the total blood-protein level, presumably due to the accompanying hemoconcentration.[202]

Considerable interest attaches to the blood-fibrinogen, because in man a variety of infectious diseases, localized inflammations, as well as treatment with various bacterial toxins cause a pronounced and very prolonged increase in this plasma constituent. Such deviations are manifestly non-specific, since they are quite comparable to those seen in other conditions associated with tissue-destruction (e.g., neoplasms, x-irradiation, intoxications, etc.).[203] It has been stated that a lack of the normal fibrinogen response is a sign of bad

[190] Dole and Emerson B26256/45, Taylor et al. B27693/49.
[191] Longsworth et al. B26257/39, Sunderman et al. 63583/26.
[192] Cardon et al. B36609/47.
[193] Dole et al. B26258/45.
[194] Harrell et al. B24809/47, B24808/46, Kelsey and Harrell B24821/48.
[195] Chow B2729/47.
[196] Codounis B27007/34, Jager and Nickerson B18633/48, Knapp and Routh 98618/47.
[197] Chow B2729/47.
[198] Dryer et al. B32864/49.
[199] Pearsall and Chanutin B32888/49, B46373/49.
[200] Dunn et al. B44150/49.
[201] Morrison et al. 98628/47.
[202] Nitschke and Krätschell B20000/38.
[203] Ham and Curtis B18189/38, Fahraeus B26259/21, Foster 23122/24, Foster and Whipple B26264/22, B26265/22, Govaerts and de Harven B26266/28, Gram B26267/22, Howe B26268/25, Moen and Reimann B26269/33, Peters and Van Slyke A63225/31, Starlinger and Winands B26282/27, Risak B26270/35, Whipple 47112/14

prognosis and tends to occur especially in very severe infections which are associated with liver damage.[204]

Special attention has been given recently to the serum-proteins in cancer with the purpose of finding a specific diagnostic test for malignancy. In the blood of cancerous patients there is "a quantitative deficiency in one of the albumin fractions ('Albumin A', positively charged albumin); decreased cystine as indicated by decreased sulfur catalytic waves; decreased reducing groups; deficient thermal coagulation. The defect is not specific for cancer, occurring also in infections. The mechanism of the production of the albumin abnormality is unknown, but presumably is due to the effect of some chemical agent on hepatic synthesis".[204a] It is difficult to assess the significance of these changes in the absence of data concerning their possible relationship to stress produced by neoplasms and infections. They may be due to the G-A-S.[204b]

Nutritional factors play a very prominent rôle in the regulation of plasma- and tissue-proteins. On low-protein diets the plasma-proteins of the rat may fall so markedly that "hunger-edema" ensues.[205] It is particularly noteworthy that all the essential amino-acids must be present in the cell simultaneously if new protein is to be formed. A basal ration containing all ten essential amino-acids is normally adequate for growth in the rat. If, however, this same diet is administered so that the ten amino-acids are subdivided into two groups, fed alternately at hourly periods (with an hourly fasting period between each feeding), then the animals lose weight and apparently cannot synthetize their body-proteins.[206]

The extraordinarily pronounced fall in plasma-proteins frequently seen during famines in man, may lead to such a diminution of the protein-osmotic pressure of the blood that "famine edema" ensues.[207] In this case, as in most other types of systemic stress, the plasma-*albumin* falls most markedly and the relative concentration of plasma-*globulin* rises.[208]

Electrophoretic studies revealed a decrease in albumin and an increase in α-globulins following various types of malnutrition in man.[209] Yet, the quality of the diet is probably also important since on certain rations semi-starvation may actually increase the serum-albumin concentration in man.[210] In the "isohydric famine edema" the volume and protein-concentration of the blood remains normal; hence even hunger-edema is not necessarily dependent upon a diminished protein osmotic pressure of the plasma.[210a]

Allegedly, in mice the γ-globulin content of the serum increases during inanition. Since this is accompanied by adrenal enlargement and thymic involution, it was assumed that this type of stress also acts by stimulating the production of corticoids which, in turn, cause destruction of lymphoid tissue and liberation of γ-globulin from the cytoplasm of the degenerating lymphocytes.[211] In man, chronic starvation (concentration-camps) allegedly raises especially the β-globulin content of the plasma, while the albumin concentration falls.[212]

[204] Ham and Curtis B18189/38.
[204a] Huggins B37408/49.
[204b] Bodansky and McInnes B46908/50.
[205] Heller and Dicker B37604/47.
[206] Cannon B25558/48.
[207] Brull B26141/40, Klotzbücher B45392/48, Kurnick B45782/48, Lamy et al. B26867/48, Lloyd et al. B44877/48, Wellers and Waitz B46013/47.
[208] Datta and Chakravarty B38151/47, Gsell B27611/48, Uehlinger B24304/47.
[209] Chow B2729/47.
[210] Taylor et al. B27693/49.
[210a] Beattie et al. B45482/48, Berkman et al. B46014/47.
[211] Dougherty and White 85504/45.
[212] Lamy et al. B26867/48.

Starvation decreases blood-*fibrinogen* concentration,[213] presumably due to lack of building-blocks for the synthesis of fibrinogen or as a result of the accompanying hepatic damage. Only one publication states that the plasma-fibrinogen concentration in man "is not significantly influenced by the condition of fasting, food ingestion...", etc.[214]

Proteinuria may also occur in severely undernourished people, for instance, in starved prisoners. This is due to glomerular lesions, as we shall see later.[215]

While starvation decreases the total *hepatic-protein* content in the rat, it does not affect any one fraction specifically; hence there is no reason to believe that a certain type of liver protein is selectively utilized in emergencies.[216]

Toxic doses of various **drugs** likewise influence the plasma-proteins, due to their non-specific stress effect.

Using fractionation procedures, it was found that dogs damaged by *turpentine* injection exhibit new α-globulin fractions which are not detectable in normal dog serum. This type of damage, as most other kinds of systemic stress, results in a rise in serum α-globulins with a corresponding decrease in albumins.[217] If a local inflammation is produced by an irritant, such as turpentine, the protein-catabolic processes are especially stimulated in the inflamed area itself.[218]

Since the formation of serological antibodies appears to be associated with the globulin fraction of the blood-proteins, it is of interest that injection of mice with toxic substances, such as *benzene* or *potassium arsenite,* was claimed to liberate antibodies from lymphocytes, in the sense of an anamnestic reaction.[219] One investigation concerning serum-proteins during *metrazol*-shock, revealed no characteristic changes,[220] but *insulin*-shock elicits the characteristic fall in blood-albumin with a rise in globulin.[221]

Parenteral administration of foreign *proteins* in the rat may cause the elimination through the kidney, not only of the injected material, but also of rat serum-proteins.[222] Consequent precipitation of protein casts in the renal tubules may play a rôle in the pathogenesis of the nephrosclerosis and hyalinosis caused by parenteral administration of various protein-containing preparations (e.g., sera, tissue-extracts). The possibility of causing renal damage in this manner must therefore be kept in mind in connection with the interpretation of the diseases of adaptation.

An increase in the relative concentration of plasma-globulin was produced in rats with an aqueous *testicular extract,*[223] but since this preparation was toxic and produced marked adrenal enlargement, thymus atrophy and lymphopenia, all its effects were ascribed to the resulting A-R.[224]

The blood-fibrinogen level rises following the injection of various toxic substances, especially foreign protein, proteose or peptone.[225]

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213 Foster and Whipple B26263/22, Henriques et al. B44030/50, Vars B26283/30.
214 Ham and Curtis B18189/38.
215 Lamy et al. B26867/48.
216 Dumazert and Grac B37608/48.
217 Ludewig et al. A95947/46, Gjessing et al. B4999/47.
218 Menkin 82684/41, A57481/43.
219 Dougherty et al. B142/45.
220 Kondritzer and Barrera B19534/41.
221 Saito B19731/42.
222 Lippmann B39072/49.
223 Simonnet 99953/47.
224 Courrier B26255/47.
225 Foster et al. B26265/22, Gram B26267/22, Schultz et al. B26281/45.

Many other damaging agents, e.g., **"gravity shock"** diminish the plasma-protein concentration,[226] presumably due to their non-specific stress effect.

Plasmapheresis (repeated bleeding with return of the washed red cells) is particularly effective in this respect, but its action is of course largely specific. However, even in this case, the blood-protein level is readily restored by the subcutaneous or intraperitoneal administration of protein digests.[227]

Stimuli Influencing the Protein Concentration in Blood and Tissues During the G-A-S

A decrease in the albumin/globulin ratio of plasma has been demonstrated after **hypophysectomy** in the rat, both by electrophoresis[228] and by chemical fractionation.[229] This suggests that the relative hyperglobulinemia of systemic stress (in this case, the stress of the hypophysectomy itself) is not dependent upon hypophyseal hormones. Electrophoretic analysis of the plasma in hypophysectomized rats, treated with either somatotrophin or ACTH, revealed an increase in the albumin/globulin ratio without any corresponding increase in antibody-containing globulin fractions.[230]

In the intact organism the pituitary continuously exerts a pronounced effect upon protein metabolism. It acts chiefly through **somatotrophin** and the **gonadotrophins** (especially L.H.) which have strong anabolic effects; the former because of its "growth-hormone" action, the latter, at least in the male, through the liberation of anabolic testoids. Furthermore, **thyrotrophin** tends to cause catabolism by discharging thyroid hormone. When present in excessive doses, the latter so stimulates metabolism that food intake cannot keep pace with wastage. **Corticotrophin** can influence protein metabolism both through the production of gluco-corticoids, which tend to catabolize proteins for the production of carbohydrate, and by stimulating the elaboration of anabolic testoids in the adrenal-cortex.[231] Usually the former action prevails.

In our experiments with crude LAP, the protein-anabolic effect manifested itself mainly by the great increase in the weight and protein content of the kidneys, liver, spleen and the body as a whole. All these effects were due mainly to somatotrophin, but perhaps partly also to special renotrophic and hepatotrophic principles. In rats sensitized by partial nephrectomy, NaCl and a high-protein diet, these effects were associated with marked proteinuria, due to accompanying pathologic kidney lesions.[232] This loss of protein is somewhat reminiscent of that seen in the nephrotic syndrome.[233]

Many investigators studied the influence of corticotrophic and corticoid hormones upon the γ-globulin fraction of the plasma and the production of antibodies. This work is especially pertinent to our problem since it had been claimed that, coincidently with the marked thymico-lymphatic atrophy and lymphopenia typical of a severe A-R, the γ-globulin fraction of the blood increases. At the same time, there is a discharge of antibodies into the plasma in animals immunized to some specific antigen before exposure to stress. This sudden discharge of stored antibodies from the lymphatic tissue of immunized animals is the "anamnestic reaction". Changes in the adrenals, thymico-lymphatic tissue, blood-globulins and antibodies, similar to those

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226 Cole et al. 85357/43.
227 Madden et al. B2100/45.
228 Li 86623/44, Moore et al. 85045/44.
229 Levin and Leathem A55527/42.
230 Li and Reinhardt 98234/47.
231 Li **B36466/48**, Li and Evans **B29320/48**, Selye **94572/49**.
232 Hay et al. 96831/48.
233 Selye 35935/ND.

caused by systemic stress, have allegedly been reproduced by the injection of corticotrophin, but both the hormone and systemic stress fail to exert these actions after *adrenalectomy*.[234] However, others obtained no rise in plasma γ-globulin following ACTH treatment in man;[235] indeed in most diseases conducive to a hyper-γ-globulinemia, ACTH causes a drop.[235a] The thermal coagulation of serum proteins, as defined by the "iodoacetate index", also decreases after ACTH, as it does during the A-R.[235b] Furthermore in several (unpublished) cases of acute systemic infections, ACTH caused a fall of the previously elevated blood-fibrinogen level.

The corticoids themselves, allegedly raise γ-globulin and antibody titers even after **adrenalectomy,** hence it was concluded that the discharge of corticoids and the resulting thymico-lymphatic atrophy are prerequisites for the antibody and γ-globulin response to systemic stress.[236] Only in the case of severe x-irradiation was the γ-globulin increase obtainable after adrenalectomy. Small doses of x-rays apparently work through the usual A-R mechanism since their effect was prevented by adrenalectomy.[237] However, re-examination of the problem revealed identical concentrations of serum-antibodies and γ-globulins in adrenalectomized rats, irrespective of whether or not they were injected with cortical extract (or DCA) during immunization. "It is concluded that adrenal cortical activity is not essential for the fabrication or release of antibodies and γ-globulin".[238]

Nevertheless this problem is far from being settled. In adrenalectomized rats cortical extracts apparently cause a much more pronounced rise in γ-globulins than saline injections and although typhoid vaccine can raise the serum γ-globulin level even after adrenalectomy, corticoids enhance this response.[238a]

As judged by experiments on rats fed glycine tagged with heavy nitrogen, the turnover of serum-protein is unaffected by adrenalectomy or the administration of adrenal-cortical extracts and/or DCA.[239]

The post-traumatic rise in the blood-fibrinogen of the rat is greatly diminished by adrenalectomy, but its duration is prolonged. Apparently "the adrenals play an important rôle in fibrinogen metabolism" especially during the A-R.[239a]

An increase in plasma-antibodies has been claimed to occur after treatment with impure **cortical extracts**[240] and it had been reported that repeated, simultaneous administration of adrenal-cortical extracts and antigen to intact animals produces higher antibody titers than does injection of antigen alone.[241] In mice adreno-cortical extracts caused a rapid and marked rise in total serum-proteins, but no change in their electrophoretic pattern.[241a]

Cortical extract produced no marked change in the plasma-proteins in children.[242] Experiments on hens likewise yielded negative results,[243] but in these latter instances perhaps the dosage used was too low.

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[234] Dougherty and White 95612/46, **B18513/47,** Dougherty et al. B142/45, Feinstein B25672/47.
[235] Forsham et al. B17987/48, Sayers et al. B37710/49.
[235a] Freeman et al. B46993/50, Stillman and Bayles B46981/50.
[235b] Bodanski and McInnes B46908/50.
[236] Dougherty and White 95612/46, **B18513/47,** Dougherty et al. B142/45, Feinstein B25672/47, Simonnet 99953/47.
[237] Dougherty and White 95612/46.
[238] Eisen et al. 98924/47.
[238a] Lewis and Page B37772/49.
[239] Stoerk et al. B25605/47.
[239a] Henriques et al. B44030/50.
[240] Fox and Whitehead B26284/35.
[241] Chase et al. B4950/46.
[241a] Milne and White B43457/49.
[242] Kelley and Adams B36540/48.
[243] Shapiro and Schechtman B27704/49.

In man, whenever serum-globulin is increased and albumin-globulin ratios are low or reversed, **cortisone,** within a few days, tends to lower the concentration of globulin and normalizes the albumin-globulin ratios.

In patients treated with **DCA** during convalescence from various conditions conducive to hypoproteinemia (enterocholitis, hepatitis, nutritional disturbances) there was a fall in total serum-protein. This was mainly due to a decrease in the albumin-fraction. The total globulin concentration showed only a transitory fall, followed by a rise to approximately the level prevailing before DCA-administration. The euglobulin fraction declined parallel with the albumin curve while pseudoglobulins I and II, as well as the fibrinogen, rose during treatment. These changes were not secondary to blood dilution, since the different fractions were unequally affected and the pseudoglobulins rose even more in absolute than in relative terms.[244]

In rats in which nephrosclerosis is produced by DCA overdosage, marked proteinuria is a common occurrence. It can be diminished by simultaneous treatment with renotrophic testoids.[245]

Obviously, the effects of the G-A-S and especially the corticoids upon globulins and specific serological immune-reactions are of the greatest importance and deserve to be carefully re-examined, but the data now available permit no definite conclusions (cf. chapter: Serologic reactions).

Injection of **adrenaline** considerably increases the blood-fibrinogen content within ten minutes in the dog; this coincides with a decrease in the blood-coagulation time.[246] The marked adrenaline and sympathin discharge during the A-R, probably participates therefore in the causation of hyperfibrinogenemia during systemic stress.

Adrenaline also raises the total plasma-protein concentration both in animals and in man. This is allegedly prevented by splenectomy and has consequently been ascribed to splenic contraction, such as also occurs during emergencies.[246a]

In dogs with experimental **renal hypertension,** the γ-globulin content of the blood was greatly increased and in one animal which showed severe vascular disease, the β-globulin and fibrinogen values were also far above normal. It was suggested that "elevation of β-globulin seems in some manner associated with the occurrence of vascular disease".[247] (Cf. Blood-proteins in human hypertension.)

In rats bearing an "endocrine-kidney", protein catabolism is always very rapid and intense. Interestingly, here even the ensuing considerable weight loss is quite ineffective in preventing the development of hypertension and generalized cardiovascular hyalinosis.[248]

Renin or hypertensin injections cause an intense, but transient proteinuria, associated with the excretion of fibrinogen, in the rat. This is unaccompanied by evidence of glomerular damage and has been ascribed to the rise in blood-pressure.[248a] It remains to be seen, however, whether chronic endogenous overproduction of RPS could not cause permanent renal damage through this mechanism.

Testosterone propionate can exert an anabolic effect in patients suffering from nephrosis. It increases the rate of protein deposition in the tissues but

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[244] Gülzow and Pickert B25883/47.
[245] Selye and Rowley A72302/44.
[246] Riecker and Winters 10917/31.
[246a] Benhamou and Gille B45847/47.
[247] Lewis and Page B4181/47.
[248] Selye and Stone 94202/46.
[248a] Addis et al. B44879/49.

at the same time, it also tends, at least slightly, to increase proteinuria. Testosterone is strongly renotrophic, hence, at a suitable dose level, it might actually counteract the renal defect itself. This possibility has not yet been adequately investigated, but the protein anabolic properties of testoids have been demonstrated beyond doubt both in animals and in man.[248b]

Partial **hepatectomy** seriously impedes the usual rise in blood-fibrinogen and globulin caused by traumas in the rat.[249] This is in agreement with expectations since fibrinogen is made in the liver.

Creatine and Creatinine

It will be remembered that creatine is of paramount importance in muscle-contraction; indeed the force of contraction is dependent upon the breakdown of phosphocreatine, while recovery of contractility presupposes the resynthesis of the resulting phosphate and creatine.

Creatine is presumably derived from glycine, guanidine or guanidine derivatives. It is eliminated in the urine as creatinine (creatine anhydride). The total daily amount of creatinine normally excreted in the urine is remarkably constant and being almost entirely of endogenous origin, it represents a rather accurate indication of muscle catabolism. In patients with nephritis, the urinary excretion of preformed creatinine may be greatly delayed.[250]

Normally, no significant amounts of creatine are excreted as such, excessive creatinuria occurs in starvation, febrile and wasting diseases, diabetes mellitus, hyperthyroidism, that is, whenever marked catabolism (especially of muscle) is in progress. More specifically, creatinuria is characteristic of eunuchs and eunuchoids, post-encephalitic Parkinsonian rigidity and of some myopathies.[251] Testosterone strengthens the flabby musculature and simultaneously tends to diminish creatinuria in eunuchoids and castrates, while curiously, methyl-testosterone was found to exert an opposite action. The cause of this unexpected difference between the two testoids has not yet been explained.[252]

The **characteristic** creatine-excretion curve during the G-A-S shows two maxima, one during the A-R, the other during the exhaustion-stage, while in the stage of resistance, creatine elimination may fall below normal. Creatinine elimination shows no such typical triphasic pattern. Yet, many stressors (see below) can cause marked creatinine excretion, presumably as a result of sudden tissue-catabolism. This must be kept in mind especially in connection with studies which employ the urinary *uric-acid*:creatinine quotient as an indicator of ACTH-production.[253] This type of response was observed in rats chronically exposed to such different types of stressors as cold, exercise and formaldehyde. Usually creatine excretion during the stage of exhaustion was slightly above normal, but not as high as during the A-R, presumably because at the end of the G-A-S much of the creatine-containing muscle tissue has been lost already.[254]

Few other pertinent investigations were carried through all three stages of the G-A-S, but it is well established that following **trauma** due to injury or

[248b] Knowlton et al. B2227/47, Kochakian 96671/46, Wilkins and Fleishman B1277/46.
[249] Chanutin et al. A14834/38.
[250] Cantarow and Trumper **B776/45.**
[251] Cantarow and Trumper **B776/45.**
[252] Selye **94572/49.**
[253] Selye 35935/ND.
[254] Browne et al. A18203/39.

tourniquet, there is a rise in blood-creatine.[255] The tissues of animals in traumatic shock exhibit an elevated inorganic phosphate and a decreased phosphocreatine concentration.[256] Anoxemia of muscle — such as occurs in tourniquet-shock — results in an almost complete and irreversible hydrolysis of phosphocreatine if it lasts more than three hours. Hence, when circulation is re-established, the compound is not re-synthetized and both creatine and inorganic phosphate are rapidly washed out of the muscle by the blood.[257]

Following fracture of a bone, creatinuria rises very considerably and usually it takes more than a week before normal levels are reached. The elimination of preformed creatinine shows no consistent parallel changes.[258]

After severe **burns,** rats show a sharp rise in creatine excretion for about two days. At the same time, there is a slight but constant fall in creatinine-excretion. The latter was ascribed to impairment of renal function due to hemoconcentration.[259] Subsequent investigators confirmed these findings,[260] and emphasized that the creatinuria after burns is not affected by high-protein diets although the total N loss (as urea and ammonia) is greatly reduced.

Following **electro-shock** the creatinine excretion rises intensely within a few hours. This is accompanied by various manifestations of an ACTH discharge, including a marked rise in uric-acid elimination.[261]

Increased urinary elimination of creatine and creatinine has also been found to be a constant accompaniment of various **wasting diseases.**[262]

A rise in the uric-acid/creatinine ratio is a rather constant accompaniment of systemic stress and can be reproduced with **ACTH.**[263] The change in this ratio is due to a rise in the elimination of uric-acid (see below). Creatine excretion is also increased by ACTH in man.[263a]

Adrenalectomized dogs, maintained in good condition with cortical extract, have a normal creatinine clearance, but this falls rapidly when hormone treatment is discontinued.[263b]

As judged by observations on the dog, even large doses of **DCA** cause no significant change in the creatine content of skeletal and cardiac muscle.[264] Presumably ACTH influences the uric-acid/creatinine ratio through the liberation of **gluco-corticoids.** Cortisone causes creatinuria in man.[264a]

It is perhaps also pertinent that following complete ischemia of the **kidney,** causing a decrease in the renal extraction of p-amino-hippuric acid (PAH), marked discrepancies have been observed between the *clearance of creatinine* and PAH on the one hand, and direct renal blood-flow measurements on the other.[265] It appears that following severe bleeding, the creatinine clearance also loses its value as a measure of glomerular filtration, as it remains reduced to a far greater extent than could be expected with the existing conditions of blood-pressure and renal blood-flow.[266] These observations are of especial interest both in connection with the evaluation of endogenous creatinine elim-

[255] Aub and Wu Hsien 40958/20, Duncan and Blalock B26288/42, Koletsky and Gustafson 93288/46.
[256] Le Page 93054/46.
[257] Bollman and Flock B26287/44.
[258] Cuthbertson et al. 82868/40-41.
[259] Clark et al. B26285/45.
[260] Croft and Peters B2426/45.
[261] Altschule et al. B37252/49.
[262] Gabrielli B26286/35, Schittenhelm and Bühler 31079/35.
[263] Cleghorn et al. B19125/48, Forsham et al. B17987/48, Reifenstein et al. B18892/48, Wolfson and Cohn B46971/50.
[263a] Sprague et al. B46430/50.
[263b] Lockett B46575/49.
[264] Muntwyler et al. B28066/44.
[264a] Sprague et al. B46430/50.
[265] Selkurt B1134/45, 91146/46.
[266] Selkurt 87832/46.

ination in conditions of grave systemic stress and in relation to creatinine clearance tests in individuals with pronounced hypotension due to shock.

It has already been mentioned that **testosterone** (unlike methyl-testosterone) tends to diminish creatinuria, while an excess of **thyroid-hormone** increases it. This is presumably related to the respective anabolic and catabolic effects of these hormones, whose participation in the G-A-S has not yet been adequately examined.[267]

Purines, Nucleic-Acids, ADP, ATP, Uric Acid and Allantoin

Purines and Nucleic acids

The **Purine-N** content of the liver rises following various types of injury (abscesses, anesthesia) in the rat. This change is chiefly due to the purine-N of proteins, and is "characteristic of the relationship observed in tissues actively forming new proteins".[268] (Cf. ADP and ATP.)

In view of the manifold important physiologic actions of **nucleic acids**[269] — especially in connection with wound-healing and regeneration — it is noteworthy that the ribonucleic-acid content of various organs (liver, spleen, heart, kidney, muscle, brain) rises significantly in rats after treatment with diverse toxic chemicals or implantation of Jensen-sarcomas. This change is non-specific, but under the influence of these same agents the desoxyribonucleic-acid content of the organs showed allegedly specific changes.[270]

There is probably a continuous turnover of desoxyribonucleic-acid in all living cells especially when they are actively dividing.[271]

In the rabbit and rat, various forms of **trauma** are followed by an increase in the concentration of both the total pentose and its phosphorylated fraction. Similar changes have been produced by **burns** and injection of fatal doses of **ATP.** "It is concluded that trauma is accompanied by an increase in the concentration of nucleotide metabolites in the blood stream".[272]

The metabolism of nucleic-acids in hemopoietic tissues has been studied through microchemical and isotope procedures, employing P^{32} following **x-irradiation.** In the bone-marrow, the desoxyribonucleic-acid content decreased within the first 24 hours after exposure. Similar changes were noted in the spleen and thymus where, in addition to the above, a decrease in ribonucleic-acid was also observed.[273] The ribonucleic-acid turnover is inhibited by such intense alarming stimuli as **vesicants.** These stressors do not actually destroy the desoxyribonucleic-acid, since the latter remains demonstrable (at least as judged by Feulgen's reaction) in the disintegrating nuclei of thymico-lymphatic cells even after their ingestion by macrophages. The vesicants may merely depolymerize (and thus inactivate desoxyribonucleic-acid).[274] Ribonucleic-acid is also very sensitive to mustards in vitro,[275] but it remains to be seen whether this bears any relationship to in vivo observations.

[267] Selye **94572/49.**
[268] Schultz and Vars B2500/47.
[269] Symposium **B32000/47,** Demerec et al. **B24935/47.**
[270] Rerabek B23201/47.
[271] Andreasen and Ottensen B26976/44, Greenstein B26975/44.
[272] Green et al. B38921/49.
[273] Carter B32943/49.
[274] Kindred 99940/47, Tenbroeck and Herriott B26977/46.
[275] Elmore et al. B38696/48.

In connection with the humoral mechanism which might play a part in such responses to stress, it is noteworthy that **hypophysectomy** decreases the turnover of both ribonucleic- and desoxyribonucleic-acid in the rat thymus.[276] **Somatotrophin** augments the ribonucleic-acid content of the liver[277] and increases the nucleic-acid turnover in the thymus.[278]

In the doses used up to now **corticoids** did not exert any marked effect upon the nucleic-acid turnover in rats.[279] Yet, the renal elimination of purines is increased in rats receiving large doses of cortical extract. Since the purine content of the blood is not influenced by such treatment in nephrectomized rats, the corticoids appear to act on the kidney itself. DCA proved to exert no such effect under similar experimental conditions.[280]

Adenosine Diphosphate (ADP) and Triphosphate (ATP).

It has been suspected that shock is largely due to an exhaustion of important energy yielding compounds, such as the adenosine-polyphosphates.[281] While this remains to be proven, it is certain that **ischemia** greatly reduces the ATP content of rabbit[282] and rat[283] muscle; indirect evidence also suggests that adenyl compounds may be released from heart tissue in **burned** guinea-pigs.[284] The adenosine equivalent of rabbit blood is increased by **cyanide** poisoning,[285] **limb-ischemia,**[286] **trauma** and "**gravity shock**".[287] This is all the more noteworthy since ATP itself — when given intravenously in large doses — proves to be rather toxic, hypotensive and shock-producing. (Cf. Theory of shock.)

Rats **traumatized** in the Noble-Collip drum showed a greatly decreased tissue-ATP content during the catabolic phase. This may have been related to energy transformations occurring in the A-R, since animals rendered resistant to this alarming stimulus, did not exhibit any ATP deficiency during exposure.[288] All these data were considered to support the view that depletion of high-energy phosphorus compounds, such as ATP, is an important factor in the development of shock. However, animal experiments, with the radio active-phosphorous technique, revealed that 2½ hours after removal of a tourniquet, there is no appreciable reduction, either in the concentrations or turnover, of high-energy phosphorus compounds, except in the damaged limb itself. This was found at a time when hypothermia, disturbances of carbohydrate metabolism and other signs of shock were already evident. It was concluded that "under the circumstances, it is hard to credit the reduction in high-energy phosphorus with a major rôle in shock".[289] In another experimental series, adenosine compounds could be demonstrated in the plasma coming from the injured limbs of shocked dogs, but the plasma-concentration was too low to account for the resulting hypotension and shock. It was also emphasized that injection of adenosine-deaminase, adenyl-pyrophosphatase

[276] Fraenkel-Conrat and Li B37281/49.
[277] Li B36466/48.
[278] Li and Evans B29320/48, Fraenkel-Conrat and Li B37281/49.
[279] Fraenkel-Conrat and Li B37281/49.
[280] Friedman et al. B32748/49.
[281] Meyer et al. B26114/46, McShan et al. B26113/45.
[282] Green B26010/43.
[283] Bollman and Flock B25577/44.
[284] Bennet and Drury 9569/31.
[285] Stoner and Green B26933/45.
[286] Zipf 8904/32.
[287] Stoner and Green B26931/44, B26932/45, B26933/45.
[288] LePage 93054/46.
[289] Haist 93414/46.

and alkaline-phosphatase (which counteract the toxic, depressor effects of adenosine compounds given by injection) had no effect in traumatic shock.[290]

Fatal cutaneous **burns** markedly raise the "adenosine equivalent" of the blood, in rabbits.[290a]

Significantly, the "Frühgift" (see below) has been stated to be adenosine or adenylic acid [291] and that adenine has a "suggestive community of structure with histamine".[292]

In summarizing the pertinent literature, a recent reviewer came to the conclusion that "there is some evidence that adenyl-compounds are released from injured tissues, and that there is a close biological similarity between shock induced by ATP and by trauma. Whether it has a specific rôle in shock or whether it is just one of the many substances capable of producing large-scale tissue-injury, is not yet known".[293]

Uric acid and Allantoin

Uric-acid-metabolism likewise suffers **characteristic** changes during stress. It is well known that an attack of gout, with an accompanying increase in blood uric-acid is elicited by a variety of alarming stimuli in predisposed individuals. Hence a relationship between gouty arthritis and the A-R has been postulated.[294]

Traumatizing surgical interventions often precipitate attacks of gouty arthritis.[295] This may be related to the post-operative hypoproteinemia which is frequently accompanied by hyperuricemia. It has been claimed that: "an elevated uric-acid results because, under the circumstances mentioned, the patient attempts to replenish his protein deficiency through endogenous protein secured from his own body",[296] a process which would have to liberate uric-acid from its combination with proteins in the cell.

In man **electro-shock** causes a rapid rise in uric-acid elimination, but since this is accompanied by pronounced creatinine excretion, the ratio between the urinary excretion of these substances is not necessarily changed.[297]

During exposure of healthy men to the stress of **cold, heat** or **muscular exercise,** the rise in the uric-acid/creatinine ratio proved to be a less sensitive indicator of ACTH secretion than the eosinopenia. It was emphasized, furthermore that these two criteria of adreno-cortical function do not always run parallel.[298]

The effect of certain mitotic poisons, such as **colchicine and nitrogen-mustard,** has been studied in mice bearing lymphoid tumors, since lymphoid tissue is particularly rich in nucleoproteins. It was found that the uric-acid/creatine and (to a lesser extent) the allantoin/creatinine ratios of the urine rise markedly 6-48 hours following administration of these drugs. At the same time the blood-uric-acid level is raised. In non-tumor bearing animals, similar, though milder, changes were noted.[299]

"In mice the response of malignant lymphoid tissue to colchicine is more striking than that of the lymphoid tissue of the normal spleen. As reduction

290 Kalckar and Lowry B4757/47.
290a Stoner and Green B38479/49.
291 Zipf B27008/30.
292 Dale 16500/33.
293 Green 89887/45.
294 Hellman B32329/49.
295 Ficarra and Adams 89581/45.
296 Ficarra B2479/47.
297 Altschule et al. B37252/49.
298 Stein et al. B37251/49.
299 Bass and Place B32904/49.

in weight of the spleen in the mouse is consistently seen when "alarming" stimuli are employed, it is suggested that the increase in uric acid excretion and tumor regression observed are due to a specific action of the chemical on the lymphoid tissue." [299a]

As previously stated, not only stressors but also **ACTH** injections cause an increased elimination of uric-acid, which reveals itself by a rise in the uric-acid/creatinine ratio in the urine.[300] It is suspected that the pronounced decomposition of lymphocytes, which occurs under such conditions, represents an important source of the liberated uric-acid.[301] ACTP exerts similar actions in man.[301a]

Marked rises of this quotient have also been noted after ACTH treatment in *myasthenia gravis* [302] or *lymphatic leucemia.*[303] However, patients with *gastric cancer* do not respond with increased uric-acid elimination following ACTH administration,[304] perhaps because wasting diseases destroy the lymphatic tissue which is a major store of uric-acid.[305]

Addisonians also fail to respond in this manner to corticotrophin, but their uric-acid excretion can be raised by gluco-corticoids. This suggests that the effect is mediated by the adrenal-cortex.[306] In agreement with this view, unlike healthy individuals, Addisonians exhibit no sign of ACTH secretion, and fail to excrete an excess of uric-acid following glucose administration.[307]

In patients suffering from *gout* ACTH causes a fall in the plasma level and a rise in the urinary excretion of uric-acid; simultaneously the acute arthritic changes disappear.[308]

Cortisone and probably other gluco-corticoids as well, increase the elimination of uric acid in man.[309]

299a Bass and Place B44857/49.
300 Cleghorn et al. B19125/48, Conn et al. B29612/48, Forsham et al. B17987/48, Hoffman et al. B23331/48, Reifenstein et al. B18892/48, Sayers et al. B37710/49, Sprague et al. B46430/50, Thorn et al. B31972/48, Watkins et al. B25880/47.
301 Cleghorn et al. B19125/48, Reifenstein et al. B18892/48.
301a Luft et al. B45270/49.
302 Hellman B32768/49.
303 Hellman B32769/49.
304 Reinfenstein et al. B18892/48.
305 Reifenstein et al. B18892/48.
306 Forsham et al. B17987/48.
307 Pincus B37780/49.
308 Hellman B32329/49, Wolfson and Cohn B46971/50.
309 Sprague et al. B46430/50.

SALT AND WATER METABOLISM

Changes in salt and water metabolism deserve special attention in studies concerned with responses to systemic stress. During the G-A-S there are characteristic derangements in the distribution of electrolytes between the cells and the extracellular fluid, changes in osmotic pressure, acid-base balance, renal function, water balance, etc. All of these are closely interrelated and largely non-specific in nature.

Sodium and Chloride

Since most of the sodium in the body exists in combination with chloride, the metabolism of these two ions is so closely interdependent that it appears advisable to discuss them conjointly. Na and Cl play prominent rôles in maintaining the constancy of the "milieu intérieur", especially the water balance and distribution, the osmotic equilibrium and the physiologic neutrality of the tissues. Hence ever since we began our work on the G-A-S, we placed especial emphasis upon the elucidation of the NaCl metabolism changes which are characteristic of exposure to systemic stress. Before discussing these it may be well, however, to enumerate some of the fundamental facts concerning NaCl metabolism.

Chloride is the most abundant anion in the extracellular (plasma, intercellular fluid) compartment but little, if any of it, enters the cell body. The Cl ion migrates readily across membranes, e.g., capillary walls, which separate two types of extracellular fluid, namely protein-rich plasma and protein-poor intercellular fluid. However, when two solutions are separated by a membrane which is impermeable for one of the ions present in one of these solutions (in the above instance protein in plasma), free migration is limited due to the "Donnan equilibrium". The presence of protein (which acts as an anion) on one side of the capillary membrane, must impede the entrance of the freely permeable Cl anion if the osmotic equilibrium and the pH level is to be maintained.

Sodium is the chief cation in extracellular fluids, but comparatively little of it enters the cell-body; here potassium takes its place as the principle cation. The difficulty of Na and Cl to enter into, and of K to migrate out across cell membranes, has not yet been satisfactorily explained in terms of physical chemistry; in vitro, all these ions diffuse readily across semipermeable membranes.

In **blood** the plasma contains most of the Na and Cl, the erythrocytes most of the K. However, unlike other cells, erythrocytes do contain comparatively large amounts of Cl, which can quite readily be exchanged with plasma-Cl and vice versa. For instance, loss of plasma-CO_2 during hyperventilation draws Cl from erythrocytes into plasma as a compensatory adjustment. Na is much less diffusible. To illustrate the greater mobility of the Cl- as compared to the Na-ion, it may be mentioned that the intraperitoneal injection of neutral NaCl solution in the rabbit markedly raises chloride concentration in the erythrocytes and plasma; at the same time it causes acidosis with a fall in blood-alkali-reserve, while in the peritoneum, the pH rises because the excess Na, left behind at the site of injection, results in local alkalosis.[1] In the plasma, most of the Na is combined with Cl, yet considerable quantities are bound to HCO_3, protein and other anions; on the other hand, almost all the Cl is present as the Na salt.

Normally, elimination of Na and Cl from the body occurs chiefly through the **urine.** Since these ions are "threshold-substances", their excretion ceases completely when their concentration in the blood falls below a certain level. Even under normal conditions, more than 99% of the NaCl filtered through the glomerular capillaries is reabsorbed in the proximal convoluted tubules; this reabsorption becomes practically complete when the blood levels of these ions fall below the threshold. The urinary excretion of Na and of Cl is relatively, but not strictly, interdependent since Na can appear in the urine as phosphate, sulfate, etc., while Cl can be eliminated in combination with NH_4, K, and other cations.

In the event of profuse sweating, large amounts of NaCl are lost through the **skin.** In sweat, the concentration of Na and Cl are approximately equal.

In profuse vomiting, and especially after pyloric obstruction, considerable quantities of Cl are lost as HCl, and a smaller amount as NaCl, by excretion through the **gastric mucosa.** This leaves the body with a disproportionate Cl loss, thus causing alkalosis. A very large proportion of the body's Cl reserves are used up daily in the production of gastric secretion, but normally, this results in no loss to the organism since almost all of the Cl is subsequently reabsorbed in the small intestine.

In diffuse diarrhea, huge quantities of NaCl are lost through the **intestine.** This is largely due to lack of NaCl absorption, but partly also to abnormal excretion of NaCl through the damaged intestinal epithelium which normally does not participate to any significant degree in the elimination of NaCl.

Students of this field should keep in mind that because of the technical difficulties inherent in Na determinations, many of the pertinent data in the literature are not reliable. Some statements concerning the Na concentration of blood or urine have even been based merely on Cl determinations (which are technically easier), on the erroneous assumption that all the chlorides were present as NaCl.

Systemic Stress

During the G-A-S the whole-blood chlorides describe a very **characteristic** curve. There is an initial fall (A-R), followed by a return to or about the normal level (stage of resistance). Eventually (stage of exhaustion), there is often, but not always, a second phase of hypochloremia. This response was observed in the rat after exposure to a number of stressors (histamine, cold, formaldehyde, etc.). The hypochloremia of the A-R is most pronounced in fasting, the hyperchloremia of the resistant stage in fed animals. Hypochloremia is usually associated with low, and hyperchloremia with high resistance; hence the former is probably a sign of damage, the latter of inurement, or at least of recovery.[2] (Cf. p. 117.)

[1] Loiseleur A32659/34.

[2] Selye A15800/38, 73232/38.

It is often claimed that whole-blood-Cl determinations are not instructive since the plasma contains much more Cl than the blood cells; hence hypochloremia is allegedly "simulated" by any condition raising the hematocrit values and vice versa. It will be remembered, however, that Cl shifts readily from the red cells into the plasma and back. Hence, whole-blood chlorides give us a more accurate picture of the total available Cl than plasma-Cl determinations. Thus in rats treated with formaldehyde or cold, the *red-cell* chlorides are markedly diminished during the A-R and increased during the stage of resistance, while the plasma-chlorides show much less pronounced variations.[3]

The hypochloremia of the A-R is readily reversible during rest; rats exposed to cold for 24 hours, and exhibiting very low red-cell chloride values, accumulate more than the normal amount of Cl in the erythrocytes following a rest of only two hours.[4] These observations furnish further support for the view that some degree of correlation exists between resistance and blood-Cl concentrations.

The Cl concentration of the *tissues* increases characteristically as a result of injury. This rise is mainly due to accumulation of Cl-rich intercellular fluid, but some NaCl may also enter the damaged cells themselves.[5] Usually the rise in Cl concentration is pronounced only in the directly damaged area. Thus, in the cat, a marked rise in muscle-Cl concentration was observed in the leg following application of a tourniquet, while the intact leg of the same animal showed no corresponding increase.[6]

The daily *urinary*-Cl excretion in the rat falls during the A-R, rises to or above normal in the stage of resistance and then again decreases to very low levels during the stage of exhaustion.[7]

During an A-R produced in rats by gastric and intestinal manipulation or by histamine injection, the urinary excretion of intravenously injected NaCl is delayed and tissue-edema ensues. "The effect of damaging agents in producing water and sodium retention should be borne in mind in assaying crude extracts for anti-diuretic activity and in drawing conclusions as to the cortin-like nature of the action of certain compounds in causing sodium retention".[8]

Leriche [9] had pointed out that **traumatic** hypochloremia and hypochloruria are characteristic of the "postoperative disease". Similar findings have been reported by numerous authors who studied patients after extensive operations and it was emphasized that the fall in blood-Cl affects both the erythrocytes and the plasma, but it is more pronounced in the former.[10]

The so-called "hepatic shock" produced by extensive partial hepatectomy in the rat likewise causes a pronounced fall in whole-blood-Cl.[11]

Simultaneously with the hypochloremia and hypochloruria, the Cl concentration in the directly damaged tissues rises during shock. It was assumed

[3] Karády et al. 74590/39, A31125/39.
[4] Karády et al. A31125/39, 74590/39.
[5] Crismon and Fuhrman 94392/46, Fox B18169/44, Fox and Baer B4517/47, Fox and Keston B18168/45, Fuhrman and Crimson 98509/47, Moore and Langohr B4487/46.
[6] Selye and Dosne A35802/41.
[7] Browne et al. A18203/39.
[8] Howlett and Browne 70108/37, 77132/40.
[9] B18459/34.
[10] Boulanger et al. B40927/45, Chabanier and Lobo-Onell A32663/34, Dubois-Ferriere 99368/45, Lambret and Driessens A2914/37, Legueu et al. A32661/33, de Luca A54791/42, Robineau A32662/33.
[11] Selye and Dosne A30702/40.

that the chlorides in the blood and urine fall because they are deviated into the site of injury.[12]

Only one paper reports an increase in red cell-Cl, with unchanged plasma-Cl, after traumatic injury in the dog.[13] The singular nature of this finding was apparently not appreciated by the authors since they made no mention of the many contrary reports in the literature.

Concurrently with the hypochloremia, the plasma and urine sodium concentration also falls during traumatic shock in man.[14] Many investigators emphasized the resemblance between the post-operative decrease in blood- and urine-NaCl and that seen in adrenal insufficiency.[15] Several authors also expressed the view that the post-traumatic derangement in NaCl-metabolism corresponds to the shock phase of the A-R in which a condition of relative adrenal insufficiency prevails.[16]

The tissue-Na concentration rises under the influence of trauma, at least in the region directly exposed to injury. For instance, after release of a tourniquet, both Na and water are retained in the gastrocnemius muscle of the rabbit, but the gain in Na exceeds the rise in water content "to such an extent that it is concluded that sodium has penetrated into the intracellular compartment".[17] Experiments with radioactive Na in mice also showed that "the sodium content of injured skin and muscle is greatly increased and exceeded the gain in water (edema). This indicated that additional sodium accumulated in the intracellular compartment. As a result of the redistribution of sodium and water, approximately one half of the total of extracellular sodium was sidetracked and rendered unavailable". According to these investigators, even administration of additional sodium by injection was followed by nearly complete retention of the Na in the injured animals, while normal controls excreted it in the urine.[18] The Na which enters the injured cells displaces K.[19]

After a single **hemorrhage,** the plasma-Cl concentration was found to be unchanged in dogs.[20] In patients with recurrent gastric hemorrhages due to peptic ulcer, who were not allowed to take water, hyperchloremia was associated with an almost complete cessation of Na and Cl elimination through the urine. If NaCl was given during the period of post-hemorrhagic blood dilution, the plasma-NaCl rose far above normal, but almost all of this extra salt was retained. This was considered to be "a regulating mechanism established for the purpose of restoring the normal filling of the arterial system by way of an augmentation of the total extracellular fluid and therefore of blood-plasma".[21] Presumably the normal hypochloremic response to systemic stress is largely dependent upon available water and may actually be reversed by dehydration.

Bleeding, sufficient to produce fatal shock, decreases the K and increases the Na and Cl content of the liver in the rat. With prolonged, repeated small hemorrhages however, the liver-K rises considerably above normal while the Na falls correspondingly. Increase in dehydration of the liver accompanies

[12] Legue et al. A32661/33.
[13] Allison et al. B4739/47.
[14] Cuthbertson A56384/42, Cuthbertson and Robertson A6664/37, Feyel and Varangot 99211/42.
[15] Feyel and Varangot 99211/42, Keating et al. A37500/42, Larget and Lamare A38155/41.
[16] Feyel and Varangot 99211/42, Pearson and Eliel B33432/49.
[17] Fuhrman and Crismon 98509/47.
[18] Fox and Keston B18168/45.
[19] Fox and Baer B4517/47.
[20] Allison et al. B4739/47.
[21] Borst 99102/38.

this latter type of change. The loss of Na was interpreted as a terminal event since it was noted only when the animals became moribund.[22]

Patients with extensive **burns** likewise show low blood-Cl values, especially while their general condition is critical. This often occurs at about the 5th day.[23] At the same time, there is generally a decrease in the urinary elimination of Cl.[24] In animals, burns also produce hypochloremia.[25]

The plasma-Na likewise diminishes in patients with burns. Here again a minimum is often reached around the 5th day, with a return towards normal of both blood and urine Na and Cl between the 2nd and 6th day if the patient's condition improves.[26] Indeed, during this recovery phase, the blood-Na concentration may exceed the initial value;[27] this could perhaps represent an inverse response due to overcompensation (counter-shock phenomenon).

The fall in the level of serum-Na, after severe burns, in man [28] and animals,[29] led to the suggestion that here Na is lost into the injured tissues.

Further studies on burned patients revealed "an early negative potassium balance with positive sodium balance reversing itself after 48-72 hours, and an ingress of sodium into the cells of burned skin".[30] Observations with radio-Na, as a tracer, showed that in the mouse, enormous quantities of Na entered the burned muscle and skin.[31] Curiously, even burns which do not cause any significant local fluid accumulation result in extrusion of K and a corresponding accumulation of Na in the intracellular compartment.[32] These investigations suggested the use of Na-solutions in the therapy of burns. Here Na appears to exert a rather specific therapeutic effect which is not merely due to the concomitant fluid administration or the osmotic pressure of this ion.

Exposure to extremes of **temperature** induce similar changes in Na and Cl metabolism. We mentioned that in rats exposure to *cold* causes an initial hypochloremia and hypochloruria during the A-R, followed by return to or beyond normal levels in the stage of resistance and a second period of hypochloremia and hypochloruria in the terminal stage of exhaustion.[33] The initial hypochloremia is mainly due to a decrease in erythrocyte-Cl; the fall in plasma-Cl is less marked.[34] All these changes are essentially similar to those elicited by other stressors. In man, increasingly marked Cl losses were noted upon repeated brief exposures to cold.[35] The plasma-Cl remained unchanged,[36] but here the degree of stress was hardly of the same magnitude as in the above-mentioned animal experiments.

Injury by immersion of a leg into a cooling mixture (— 55° C) for three minutes, led to an increase in the water content of the injured muscle in rabbits, but the simultaneous rise in Na concentration was proportionately much larger, and the plasma-Na fell. It was concluded that these results,

[22] Darrow and Engle 87820/45.
[23] Davidson 55943/26, Duval B26829/33, Ficarra and Naclerio B808/44, Fox B18169/44, Hilgenfeldt 38008/36, Scudder and Elliot B26227/42, Stenger A31097/39.
[24] Davidson 55943/26, Hilgenfeldt 38008/36.
[25] Chiariello B26828/33, Seung B26830/31, Simonart 63360/30.
[26] Ficarra and Naclerio B808/44, Fox B18169/44, Hilgenfeldt 38008/36.
[27] Fox B18169/44.
[28] Wilson et al. B26835/38.
[29] Lowdon et al. A30429/39.
[30] Moore and Langohr B4487/46.
[31] Fox B18169/44, Fox and Baer B4517/47, Fox and Keston B18168/45.
[32] Fox and Baer B4517/47.
[33] Browne et al. A18203/39, Selye A15800/38.
[34] Karády et al. A31125/39, Selye A8054/38.
[35] Elliot et al. B33097/48.
[36] Eliot et al. B32737/49.

together with observations concerning various other types of injury, "suggest that redistribution of sodium is a non-specific event which follows severe injury regardless of the means by which the injury was produced".[37]

Exposure to excessive *heat* leads to profuse sweating and considerable losses of Na and Cl through the perspiration.[38] Because of the simultaneous loss of water and hemoconcentration this may actually be accompanied by an increase in the NaCl concentration of the plasma. However, if excess water is ingested, the plasma concentration of NaCl falls.[39] This condition is often accompanied by the so-called "miners' cramps", a derangement in the contractility of the muscles.

NaCl losses in heat-stroke have been reported by many investigators although apparently they are not always manifest.[40] In any event, prophylactic administration of NaCl appears to be indicated.[41]

The tendency to lose Cl upon exposure to external heat is in sharp contrast to the Cl-retention typical of diseases which cause fever, and especially of pneumonia (cf. below). Apparently in the former case, the salt loss is largely a consequence of the sweating, which is an integral part of the specific adaptive response of individuals attempting to defend themselves against undesirable overheating.

Comparatively few other stressors have been systematically examined for their ability to cause G-A-S changes in NaCl metabolism. Most observations are concerned only with the A-R and in some instances, the beginning of the resistant stage. However, generally speaking, the available data are consonant with the above description of the "characteristic response" to systemic stress. Thus, it was found that following **x-irradiation** the serum-Cl concentration falls,[42] and this is accompanied by hyponatremia.[43] In experiments on the rat a transitory increase in the Na, Cl and K elimination was noted during the first few days after x-irradiation.[44]

Following maximal **electrically-induced seizures,** the plasma-Na concentration rises in the rat, simultaneously with manifestations of respiratory and metabolic acidosis.[45] Interestingly, even small changes in plasma-Na are accompanied by a change of the electric seizure thresholds in the same direction. The elevation of electric seizure thresholds by DCA, for instance, has been duplicated by the administration of NaCl.[46]

Certain stressors appear to elicit changes in NaCl metabolism which differ from the typical G-A-S pattern. Thus intense, forced **muscular exercise** causes hyperchloremia in the rat, with no, or only a slight, initial hypochloremic phase. However, animals forced to perform intense muscular exercise tend to bleed from their paws, and since the hyperchloremia is accompanied by marked hemodilution and a fall in the hematocrit values, these results are not necessarily opposed to the view that hypochloremia is the response characteristic of acute systemic stress. The apparent rise in whole blood-Cl may have been

[37] Crismon and Fuhrman 94392/46.
[38] McCance 58928/36, 58929/36, 58930/36.
[39] Cantarow and Trumper B776/45.
[40] Ferris et al. B26803/38.
[41] Conn et al. B4468/46, Schlegel A56984/41.
[42] Haenisch et al. B26804/40, Holfelder et al. B26805/38, Jüngling B26806/38, Kikuchi 10149/31, Weichert A56943/42.
[43] Jüngling B26806/38, Holfelder et al. B26805/38, Weichert A56943/42.
[44] Edelmann B32735/49.
[45] Ward and Call B27708/49.
[46] Woodbury and Davenport B37243/49.

simulated here by hemodilution due to hemorrhage and the concomitant proportional increase in the Cl-rich plasma.[47]

Interestingly, in man, even mild muscular exercise causes Na-retention, allegedly because it augments the tubular reabsorption of this ion from the glomerular filtrate.[48]

Exposure to **anoxia** appears to cause a temporary rise in Na and Cl excretion subsequently followed by a compensatory reduction during the period of recovery.[49] In men working at high altitudes, the major electrolyte change in the blood was claimed to be an increase in the Cl and a decrease in the Na and bicarbonate content of the serum.[50]

Especially pronounced changes in NaCl metabolism occur during certain **infectious diseases.**

As early as 1852 Beal [51] and twenty years later Salkowski [52] found that the blood-Cl concentration falls and no Cl is eliminated in the urine at the height of lobar *pneumonia.* This has been confirmed,[53] but allegedly there are no correspondingly severe changes in Na metabolism. Since the concentration of organic acids increases during pneumonia, both in the blood [54] and in the urine,[55] it was claimed that the hypochloremia and hypochloruria could be due to displacement of Cl by organic acid radicals.

Even administration of NaCl causes no significant change in the plasma concentration of these electrolytes during pneumonia and huge doses must be given (preferably intravenously) before any of the injected salt reappears in the urine.[56] From these observations it was concluded that in pneumonia large amounts of NaCl are accumulated in the pulmonary exudate itself, especially since the Cl balance (which on a normal diet is positive before the crisis) suddenly becomes negative when the exudate is absorbed. If much NaCl is given before the crisis, edema may form, so that perhaps some salt and water retention also occurs outside the lung.[57] After the crisis, with the excretion of fluid and salt, the body weight tends to fall markedly; this likewise implies that greater NaCl and water retention must have occurred than could be explained on the basis of accumulation in the lung only.[58]

It is especially noteworthy that many investigators reported clinical improvement following intravenous administration of hypertonic salt solutions in lobar pneumonia.[59] Furthermore, the degree of the hypochloremia is allegedly a valuable index of prognosis since blood-chlorides of less than 87m.eq./L. are always indicative of a severe condition.[60]

In various other infectious diseases, especially in *tick typhus,*[61] *typhoid, recurrent fever, erysipelas, peritonitis, diphtheria* and other very acute infections causing considerable systemic stress, the NaCl balance is often similarly,

[47] Karády et al. A31125/39, Selye A15674/39, A8054/38. A15800/38.
[48] Sinclair-Smith et al. B36358/49.
[49] Burrill et al. B678/45, van Middlesworth et al. B28285/48.
[50] Dill et al. 77873/37.
[51] B26807/852.
[52] B26818/871.
[53] Darrow and Hartman 26808/29, Hutchison B26831/898, Killian B26832/21-22, McLean 85669/15, Mellinghoff et al. B44827/47, Peabody B26834/13.
[54] Peters et al. 25379/26, B26816/26.
[55] Holten B26812/26.
[56] Prigge B26817/22, Straub B26821/35, Sunderman B26822/29, B26823/31. Sunderman et al. 63583/26.
[57] Maver and Schwartz B26833/16, Sunderman et al. 63583/26.
[58] Wilder and Drake B26826/29.
[59] Haden B26810/27, Prigge B26817/22, Scholtz B26819/30.
[60] Ipsen B26813/36.
[61] Harrell et al. B24806/44, B24807/45.

though less markedly disturbed, as in pneumonia.[62] These findings further support the view that the disturbance is not specific for pneumonia and may be regarded as characteristic of exposure to systemic stress in general. Nevertheless, the lung appears to play some special rôle in these electrolyte changes since even chronic diseases affecting the lung, such as *pulmonary tuberculosis* and *pulmonary tumors* [63] cause similar metabolic disturbances, even if they do not produce acute systemic stress.

Non-infectious diseases which produce acute stress, e.g., *porphyria* [64] and the many conditions conducive to *shock* (see above), cause a fall in the Cl and Na level of the blood reminiscent of the electrolyte changes seen in hypocorticoidism.

During **anaphylactic shock** in rabbits the Na and Cl content of the blood also decreases, while that of the skin increases. In other tissues the changes are less manifest.[65]

Toxic doses of various **drugs** cause similar changes. Thus a fall in plasma-Na has been noted in rats in which an A-R was produced by intraperitoneal injection of hypertonic *glucose.*[66] It will be remembered that daily, subcutaneous administration of *formaldehyde* in rats was one of the interventions which we had used in our earliest experiments designed to determine the characteristic triphasic blood-Cl response during the entire course of the G-A-S.[67] Such formaldehyde treatment was also among the stressors employed to show that a more pronounced fall in erythrocyte- than in plasma-Cl occurs during the A-R.[68]

Severe intoxication of dogs with *nitrogen-mustard* causes great losses of Na, Cl and K through the urine. This has been ascribed mainly to increased catabolism, but its exact relationship to the G-A-S has not been examined.[69]

In **nutritional** deficiencies, especially in starvation [70] hypochloremia is also common.

Rats on *low-K diets* replace muscle K by Na to a large extent, but the normal equilibrium is soon reëstablished if they are again given a normal diet.[71] This is obviously a specific effect not attributable to stress. We mention it merely to illustrate that under certain conditions considerable amounts of Na can enter into the cell body.

In rabbits during **gravity-shock** — unlike in other types of systemic stress — the ratio plasma-Cl/cell-Cl allegedly rises above normal. This is due to the fact that the plasma-Cl slightly falls or fails to change, while the erythrocyte-Cl concentration definitely rises.[72]

The cause of such apparent deviations from the typical NaCl pattern during systemic stress will have to be further investigated. As we have repeatedly stated in this book, all stressors exert some specific effects upon certain targets, and these tend to modify the typical G-A-S response.

[62] Broch 97241/45, Dieckhoff B26809/39, Haden and Orr B26811/25, Lautrop and Madsen B26814/42, Mellinghoff et al. B44827/47, Nitschke and Krätschell B20000/38, Overman B28216/48, Salkowski B26818/871, Stenger B32003/39, A31097/39, Sunderman et al. B26824/29, Tesdal B26825/34.
[63] Sunderman et al. B26824/29, Winkler and Crankshaw B26827/38.
[64] Prunty B37297/49.
[65] Saïto B33791/40.
[66] Reiss et al. 85064/43.
[67] Selye A8054/38, A15800/38.
[68] Karády et al. A31125/39.
[69] Philips et al. B29996/48.
[70] Lorusso and Postiglione B31602/44, Uehlinger B27612/48.
[71] Conway B38088/47.
[72] Allison and Cole B20411/44.

Stimuli Influencing Na and Cl Metabolism During the G-A-S

Hypophysis. — In itself, **hypophysectomy** causes no very specific changes in NaCl metabolism,[73] but if a hypophysectomized rat is exposed to *stress* (e.g., forced exercise, cold) the whole-blood-Cl may rise to unusually high levels, even though hemoconcentration and hypoglycemia show that the animals are in the shock-phase of the A-R.[74] This hyperchloremic response is all the more remarkable since adrenalectomy (see below) was found to sensitize the rat to the hypochloremic effect of systemic stress. Curiously, in hypophysectomized rats even *DCA* fails to elicit the usual hypochloremia, while the diuretic and chloruretic effect of the compound is even greater than in intact animals.[75] Here, pure *ACTH* increases, impure anterior-lobe extracts decrease the urinary elimination of Na.[76] Perhaps the pituitary can produce some factor other than ACTH (presumably contained in impure anterior-lobe extracts), which greatly modifies the changes in Na and Cl metabolism caused by stress or DCA. Vasopressin may also play a rôle here.

Selective removal of the posterior-lobe in animals — as spontaneous diabetes insipidus in man — impedes the water and NaCl reabsorption in the proximal convoluted tubules. Thus it causes polyuria with loss of NaCl, unless adequate substitution therapy is instituted with the antidiuretic (vasopressor) *posterior-lobe hormone*. Since emotional stress stimulates the production of the latter hormone,[77] it is possible that the posterior-lobe also participates in the pathogenesis of the NaCl changes characteristic of the G-A-S. This participation is rather complex, however, since other emergency reactions, such as adrenaline discharge and sympathetic stimulation, inhibit the secretion of antidiuretic hormone which occurs under the influence of emotional excitement.[78]

Chronic treatment with an impure **anterior-pituitary preparation** (LAP) — under conditions conducive to hyalinosis and hypertension — caused no marked change in plasma Na, Cl and K concentration in the intact rat. Considerable Na and Cl losses in the urine occurred only after the resulting nephrosclerosis had caused severe renal damage. In short-term experiments on the other hand (under conditions not conducive to nephrosclerosis), purified *corticotrophin* causes Na and Cl retention accompanied by hypokalemia and hyperkaluria.[79] This is presumably due to a mineralo-corticoid action not complicated by renal damage.

Various animal experiments suggest that LAP and ACTH can exert diametrically opposite effects (e.g., upon the thymico-lymphatic tissue, experimental arthritis, anaphylactoid reactions) even if the dosage-levels are so chosen as to result in the same degree of adrenal enlargement. Hence it was assumed that some principle in the impure LAP antagonizes certain functional effects of the ACTH contained in LAP, although it does not prevent its morphologic action upon the adrenal cortex. In all these respects LAP acts, like the mineralo-corticoid DCA, and ACTH like the gluco-corticoid cortisone.[80]

In support of this view it may be mentioned that purified ACTH causes Na excretion, while certain crude anterior-pituitary extracts produce Na retention in hypophysectomized rats [81] (see above). Furthermore, even in the presence

[73] Selye **94572/49.**
[74] Selye and Foglia A9805/38.
[75] Selye and Bassett A33566/40.
[76] Rubin and Dorfman B18885/48.
[77] Verney B18117/47.
[78] Verney B18117/47.
[79] Selye B1204/46, 94572/49.
[80] Selye B39702/49, B39703/49.
[81] Rubin and Dorfman B18885/48.

of the hypophysis ACTH in itself causes no change in Na or Cl excretion in the rat,[82] but the elevation of plasma-Na by DCA is inhibited by ACTH.[83]

In man ACTH elicits a biphasic response. A single injection of 10-25 mg. increases the renal elimination of Na, Cl and K; after several days of such treatment, however, there is Na and Cl retention, accompanied by hyperkaluria. These latter findings show that — at least under certain circumstances — corticotrophin can increase the production of adrenal hormones having some mineralo-corticoid actions.[84] ACTP acts similarly.[84] However, most observers claim that the usual pattern of response in man is an initial Na and Cl retention, followed by an increased excretion of these electrolytes.[84b] Perhaps a single injection is immediately followed by the "recovery phase" (salt excretion), while in the event of prolonged treatment this ensues only after several days.

The intense elimination of Na and Cl through the sweat, normally induced in man by exposure to humid heat, is inhibited by ACTH. This has been ascribed to the production of mineralo-corticoids by this corticotrophin [84c] since DCA exerts a similar action (cf. below). It should be kept in mind, however, that pure gluco-corticoids (e.g., cortisone, Kendall's "cpd. F") also possess a certain degree of mineralo-corticoid potency.

In connection with the regulation of NaCl metabolism during stress it is well to remember that in the process of concentrating the glomerular filtrate into urine, the reabsorption of water is controlled chiefly by the **antidiuretic posterior-lobe principle,** while the reabsorption of Na is facilitated by the mineralo-corticoids. Both these hormones probably exert their respective actions mainly through their influence upon the distal part of the proximal convoluted tubule, the "spiral segment" [85] (Cf. G-A-S → Kidney).

Adrenals. — **Adrenalectomy,** like Addison's disease, renders the Na and Cl balance negative and causes a decrease in the Na and Cl concentration of the plasma. All these changes are readily corrected by cortical extracts and various corticoids, not only by those with pure mineralo-corticoid properties.[86] Adrenalectomy also decreases the **erythrocyte-Cl/plasma-Cl** ratio; a change similar to that observed in intact animals during the A-R.[87] This further emphasizes the close resemblance between the shock-phase of the A-R and the condition of suprarenal insufficiency.

Using the excretion of Na or radio-Na as indicators, a large number of steroids have been found to possess mineralo-corticoid properties when tested in adrenalectomized rats. DCA proved to be most active among the compounds so far examined. 1 γ sufficed to cause Na-retention.[87a]

Our experiments in the rat showed that the characteristic triphasic blood-Cl response to *stress* can develop even in the absence of the adrenals. Here, however, the duration of the syndrome being greatly shortened by hypocorticoidism, the initial hypochloremia of the A-R gives way only to a brief rise, followed by a pronounced terminal fall in blood-Cl.[88] Interestingly, in adrenalectomized

[82] Bergner and Deane B23875/48.
[83] Cheng B35910/49,
Woodbury et al. B46344/50.
[84] Forsham et al. B17987/48.
Hoffman et al. B23331/48,
Prunty et al. B36504/48,
Sayers et al. B37710/49.
[84a] Luft et al. B45270/49,
Kinsell et al. B46958/50.
[84b] Doughaday and McBride B46962/50,
Sprague and Power B46979/50,
Sprague et al. B46430/50,
Wilkins et al. B46966/50.
[84c] Conn B46371/49,
Conn and Louis B45972/50.
[85] Selye **94572/49.**
[86] Selye **94572/49.**
[87] Karády et al. A18207/39.
[87a] Dorfman B43447/49,
Denning and Luetscher B47054/50.
[88] Selye A9210/38.

rats even forced exercise (which unlike most stresses normally causes hyperchloremia during the A-R) produced the same typical triphasic response in blood-Cl levels as any other systemic stress. In rats kept in a running mill several hours a day, there was a pronounced initial hypochloremia followed by a return to normal levels within two days and then the blood-Cl fell again until death.[89] Here, removal of the suprarenals apparently "unmasked" the characteristic G-A-S response to exercise. (Cf. graphs on p. 125.)

The **corticoid hormones,** especially the mineralo-corticoids, tend to influence Na and Cl metabolism in the intact organism. However, some investigators doubt that purely mineralo-corticoid compounds are produced by the adrenal. Desoxycorticosterone has been isolated from suprarenal tissue but once.[90] It is difficult to exclude the possibility of this having been an artefact which arose during purification.[91] However, some "sodium factor" has been prepared from the amorphous fraction of adrenal extracts, and this is even much more potent than DCA in causing Na retention. It differs from the latter in its solubility and in that it does not appear to affect K excretion.[92]. Whether or not such DCA-like pure mineralo-corticoids are normally secreted by the adrenal, it is certain that even the predominantly gluco-corticoid compounds, such as cortisone (Kendall's cpd. E),[93] corticosterone (Kendall's cpd. B)[94] or 17-hydroxy-corticosterone (Kendall's cpd. F),[95] possess a considerable Na-retaining and K-excretion promoting action. 11-dehydrocorticosterone (Kendall's cpd. A), another compound normally produced by the adrenal, appears to occupy an intermediate position in that its gluco- and mineralo-corticoid potencies are about equal, the latter perhaps predominating somewhat in man.[96]

It appears most readily compatible with all pertinent data, to assume that the cortex produces DCA-like, "pure" mineralo-corticoids, but this has admittedly not yet been proven with certainty. For the sake of simplicity we shall meanwhile continue to speak of mineralo- and gluco-corticoids as naturally occurring compounds, until evidence against the in vivo production of the former is forthcoming. It will be kept in mind, however, that even if DCA-like material were not normally produced it could well be discharged during abnormal responses to stress. Furthermore, under pathologic conditions, even gluco-corticoids can cause lesions resembling those of DCA-overdosage, if their mineralo-corticoid effects are greatly exaggerated due to "conditioning factors".[97] Thus the theory holding that the hyalinoses are caused by "mineralo-corticoids" would merely have to be reworded to read "mineralo-corticoid actions". The importance of such conditioning factors is illustrated, for instance, by the fact that in Addisonians, cortisone causes Na and Cl retention, while supplementary treatment with DCA elicits a "paradoxical loss" of Na and Cl.[98] We shall cite other examples of such "conditioning" below.

It is now well established that, on an average NaCl intake, high doses of DCA diminish Na and Cl elimination through the urine and induce a highly positive NaCl balance.[99]

[89] Selye A9210/38.
[90] Reichstein and v. Euw A19374/38.
[91] Hartman and Brownell B36274/49.
[92] Hartman and Brownell **B36274/49.**
[93] Forsham et al. B35919/49, Perera et al. B36595/49, Sprague and Power B46979/50, Sprague et al. B46430/50.
[94] Hartman and Brownell B36274/49.
[95] Fourman et al. B39685/49.
[96] Homburger et al. B29743/48.
[97] Selye B41762/49.
[98] Forsham et al. B35919/49.
[99] Forsham et al. B17987/48, Selye **94572/49.**

Somewhat unexpectedly, DCA, which raises the low blood-Cl level of the adrenalectomized rat, causes a slight diminution of plasma-Cl, with an especially pronounced fall in erythrocyte-Cl in intact animals ("conditioning" ?).[100] However, even after adrenalectomy, sufficiently prolonged and intensive treatment raises the originally subnormal blood-Cl level towards normal only at first; later this is followed by hypochloremia, although the good general condition of the animals proves the adequacy of the corticoid substitution therapy. Hence, apparently both a deficiency and an excess of mineralo-corticoids is associated with hypochloremia.[101] The former because Cl is lost in the urine, the latter because Cl is displaced into the tissues.

The plasma-Na level rises in rats given large doses of DCA,[102] but this rise is not as marked and constant as the accompanying fall in blood-Cl.[103] Since the blood-Cl, on the other hand, rather regularly falls during DCA overdosage, the plasma Na/Cl ratio invariably declines.[104] Cortisone tends to depress plasma-Na in man.[105]

In the event of DCA overdosage, the storage of NaCl and fluid in the extracellular spaces of the tissues causes a pronounced edema tendency. In DCA-treated rats for instance, this manifested itself in a greater than normal local water accumulation following subcutaneous formaldehyde injections.[106] With still larger doses, pronounced and diffuse edema ensues, even without local irritation. This has been noted both in experimental animals [107] and in man, for example in Addisonians who receive the hormone for therapeutic reasons.[108] The production of edema, like that of most DCA-overdosage symptoms, is dependent upon "conditioning" by simultaneous NaCl administration.[109]

In fasted and thirsted rats the urinary Cl elimination is not significantly changed even by high doses of DCA; however, if NaCl solutions are given to drink, chloruria is increased and accelerated by DCA ("conditioning").[110]

On a very high NaCl intake DCA causes marked diuresis and increased Cl excretion in the rat (especially after hypophysectomy).[111] Perhaps this type of "conditioning" is due to the resulting renal damage which impedes NaCl and water reabsorption, thus raising the turnover of these metabolites.

A similar "paradoxical" stimulation of NaCl excretion by DCA was noted in Cushing's disease.[112]

It is noteworthy that in intact rats overdosed with DCA and exhibiting marked hypochloremia, intravenous administration of saline caused the blood-Cl to rise even higher than in non-treated controls. Perhaps here the tissues were already so saturated with NaCl that additional saline "conditioned" the organism to react paradoxically to DCA. Yet at the same time the tissue- and especially the brain-NaCl concentration also rose higher in DCA-pretreated, than in control NaCl-injected animals.[113] This may have a bearing upon the production of brain lesions by DCA (G-A-S → Nervous System).

On an essentially normal NaCl intake, DCA causes no significant change in the liver- and muscle-Cl content of the rat, even if the dose given suffices

[100] Selye and Dosne 95371/39-40, A32151/40.
[101] Selye and Dosne A32941/41.
[102] Cheng B35910/49, Woodbury et al. B46344/50.
[103] Selye B1204/46, Woodbury et al. B46344/50.
[104] Selye et al. A94329/45.
[105] Perera et al. B36595/49.
[106] Selye et al. A32768/40.
[107] Selye **B1204/46.**
[108] Selye **94572/49.**
[109] Selye et al. B19413/49.
[110] Winter and Selye 82219/42.
[111] Selye and Bassett A33566/40.
[112] Soffer et al. **B39087/49.**
[113] Selye and Hall A56583/43, Parviainen et al. B46923/50.

to produce marked hypochloremia.[114] In dogs DCA tends to raise the Na (and diminish the K) content of the musculature.[115] Rabbits react similarly.[115a]

The NaCl changes caused by DCA, as well as those elicited by stress, are also largely dependent upon the blood-proteins (colloid osmotic pressure) and water metabolism. In an effort to explain the formation of edema in cardiac failure, Peters [116] expressed the following view: "The development of a serum-albumin deficit causes a reduction of colloid osmotic pressure that results in the escape of fluid from the circulation; reduction of the circulating blood volume accelerates the reabsorption of sodium salts (presumably through the influence of increased secretion of an adrenal-cortical hormone), resulting in the accumulation of sodium salts in the serum; an increased concentration of sodium in the serum causes thirst and accelerates reabsorption of water through increased secretion of posterior-pituitary antidiuretic hormone, resulting in the retention of water, which, with the retained salt, produces edema."

In view of its important effects upon NaCl metabolism, it is not unexpected that DCA also influences the NaCl-metabolism changes produced by *stress*. In rats in which a compensatory atrophy of the adrenal cortex had been produced by chronic pretreatment with DCA, the blood-Cl decreases, after exposure to various stressors (cold, formaldehyde, atropine, trauma, exercise), to much lower levels than in not pretreated controls. Since the DCA pretreated animals had a lower initial blood-Cl concentration, this hypochloremia was perhaps merely added to that induced by the alarming stimuli. It is noteworthy, however, that even forced muscular exercise, which normally causes hyperchloremia, induced a fall in blood-Cl in DCA-pretreated animals. Such a reversal of the chloremic action of exercise had also been noted after adrenalectomy (see above), hence the compensatory adrenal atrophy produced by DCA appears to result in a functional adrenal insufficiency.[117]

In rats damaged by formaldehyde injections or by intestinal trauma, cortical extracts prevented the development of the typical hypochloremia, but DCA was ineffective.[118] The hypochloremia normally elicited by partial hepatectomy in the rat is likewise readily prevented by cortical extracts.[119] Since such preparations are rather poor, while DCA is very rich, in mineralo-corticoid activity, the above observations suggested that the strict separation of mineralo-corticoids from other cortical hormones is not entirely justified. In the presence of a very acute, actual (adrenalectomy) or relative (A-R) adrenal insufficiency, the rapidly acting, highly soluble gluco-corticoids in the extracts may be more effective in preventing fatal hypochloremia than the mineralo-corticoids themselves.

In men exposed to extreme heat, the usual loss of NaCl through the perspiration is allegedly diminished, both by DCA [120] and by cortical extracts;[121] hence, in addition to NaCl ingestion, corticoid treatment has been recommended to combat the effects of a hot environment. Furthermore, "under standard conditions of testing, the electrolyte composition of thermal sweat affords a constant index of adrenal production of DCA-like corticosteroids".[121a]

[114] Selye and Dosne 95371/39-40.
[115] Muntwagler et al. B28066/44.
[115a] Parviainen et al. B46923/50.
[116] B26232/48.
[117] Selye and Dosne A37249/42.
[118] Selye et al. A32768/40.
[119] Selye and Dosne A30702/40.
[120] Conn B46371/49, Conn et al. B4468/46.
[121] Edelmann et al. A56665/43, Schlegel A56984/41.
[121a] Conn and Louis B45972/50.

In the treatment of shock from burns, cortical extracts have been used to increase the plasma volume and to prevent excessive fluid loss by diminishing capillary permeability. Under such conditions, large doses of extract were often found to cause considerable Cl retention and hyperchloremia.[122] Usually, adrenocortical extracts likewise reduce or prevent the fall in plasma-Na which normally occurs in patients receiving fever therapy.[122a]

Allegedly cortical extracts can also increase the rate of Na and Cl excretion during the A-R if the latter is accompanied by marked edema. Presumably, here the NaCl loss is merely a secondary consequence of the reduction of extracellular fluid.[123]

All these observations confirm that under certain circumstances cortical extracts can exert marked effects upon mineral metabolism, although they are poor in DCA-like (predominantly mineralo-corticoid) compounds.

Kidney. — Little is known about the effect of **renal hormones** upon the blood-Cl beyond the fact that, in the rat, the "endocrine kidney" tends to cause hypochloremic alkalosis, similar to that elicited by DCA.[124]

Other Factors. — Though not strictly pertinent to the problem under consideration, it is interesting that **progesterone**, which is not endowed with any specific NaCl-retaining properties, likewise causes diuresis in animals. Rats receiving distilled water to drink show equally pronounced diuresis following progesterone and DCA treatment. Urinary-Cl elimination in fasted and thirsted rats is increased by progesterone; yet this hormone induces no change in the elimination of orally administered NaCl and thus characteristically differs from DCA.[125]

Testosterone tends to decrease, while **folliculoids** increase the blood-Cl concentration,[126] but the changes are slight and the participation of these hormones in stress reactions is hardly important.

Thyroidectomy increases the hypochloremic effect of various stressors during the A-R (formaldehyde, cold). It is noteworthy that here again — as after hypophysectomy, adrenalectomy or DCA-overdosage — the normal hyperchloremic effect of muscular exercise is reversed. Consequently in the hypothyroid animal even muscular work elicits the usual hypochloremia characteristic of the A-R.[127]

The study of factors influencing NaCl metabolism during the G-A-S would obviously deserve much more attention. The effects of exogenous Na, Cl, K, water and other osmotically active substances, variations in blood pH, etc., are of particular interest. Several investigators demonstrated the efficacy of **NaCl administration** in combatting shock (cf. p. 76). They found that under its influence, the post-traumatic hypochloremia can be inhibited. Allegedly the maintenance of homeostasis in man, on extremely high or low Na intakes, is regulated by the action of a DCA-like hormone upon the kidney. The relationship of this response to the G-A-S has been discussed,[128] but no systematic investigations on NaCl metabolism have as yet been carried through the three stages of the G-A-S.

[122] Rhoads et al. A37675/41.
[122a] Edelmann et al. A56665/43.
[123] Howlett and Browne 77132/40.
[124] Schaffenburg and Selye B3478/48, Selye B3142/47, B1433/48.
[125] Winter and Selye 82219/42.
[126] Selye and Dosne 95371/39-40.
[127] Selye A9804/38.
[128] Leaf and Couter B39085/49.

Significantly great excesses of exogenous NaCl are poorly tolerated and may lead to dangerous water and salt retention during the postoperative period in man.[128a]

Potassium

The metabolism of potassium is closely related to that of Na and Cl; hence, reference has already been made to it in the preceding chapter. Let us re-emphasize, however, that K is the chief cation in the intracellular fluid, but only little of it is present in the intercellular spaces, the plasma and the lymph. Plants which possess no extensive intercellular fluid system contain much more K than the tissues of vertebrates.

The absorption of K from the diet occurs almost exclusively in the small intestine, while the excess is eliminated through the kidneys.

Systemic Stress

Hyperkalemia and hyperkaluria are **characteristic** A-R changes,[129] presumably occasioned by the liberation of much K from disintegrating cell-bodies at the time of the catabolic impulse. This response is very constant, indeed it has been said [130] that "in all the conditions given by Selye as suitable to produce an alarm-reaction there is a rise in the concentration of potassium in the serum". In the stage of resistance blood- and urine-potassium values return to normal,[131] but data concerning K metabolism in the stage of exhaustion are not yet sufficiently conclusive to permit any generalization.

Studies on tissue slices (salivary glands, liver, etc.) led to the conclusion that K is neither discharged nor absorbed by resting cells, but "stimulation" and various "damaging influences" cause this cation to be discharged from the protoplasm "independently of the agent which caused the stimulation or damage".[132]

Following **traumatic** injuries, the characteristic discharge of K into the plasma, with subsequent elimination through the urine, has repeatedly been observed. The resulting post-traumatic urinary-K loss runs approximately parallel with the N loss during the catabolic impulse.[133] There is a corresponding K loss from the tissues.[134]

It has been emphasized that these changes in K metabolism are accompanied by typical signs of the A-R and that they are most reminiscent of the hyperkalemia of adrenal insufficiency.[135] However, in very acute and severe post-traumatic alarm-reactions, as in the fulminating type of adrenal insufficiency, the hyperkalemia is accompanied by a decreased urinary excretion of K. It has been assumed that defective filtration of K through the glomeruli, due to impaired renal circulation, may further increase the plasma-K level in both these conditions.[136]

[128a] Homburger et al. B30372/47.
[129] Selye 73232/38, B1204/46.
[130] Kendall and Ingle 68707/37.
[131] Selye 35935/ND.
[132] Brock et al. 81458/39.
[133] Berry et al. B46086/48, Blixenkrone-Moller B45328/49, Clarke and Cleghorn A56192/42, Cremer B19806/42, B19807/42, Cuthbertson and Robertson A6664/37, Gutman et al. 81881/41, Howard and Bigham B3015/45, Manery and Solandt B26178/43, Scudder A32530/40, Zwemer and Scudder B26180/38.
[134] Clarke and Cleghorn A56192/42, Fuhrman and Crismon 98509/47.
[135] Feyel and Varangot 99211/42.
[136] Feyel and Varangot 99211/42.

Apparently damage during the shock-phase causes discharge of this element from disintegrating cells, hyperkalemia and hyperkaluria, but K elimination is insufficient to clear the plasma of the excess and — in the event of renal damage — there may even be hypokaluria. During countershock, as a result of defensive corticoid secretion (see below) K returns from the plasma into the cells, but simultaneously so much of it is lost through the urine that dangerous K deficiency may ensue, unless much K is ingested.

Recent investigations show that the syndrome of post-operative alkalosis with K deficiency is accompanied by electrocardiographic changes characteristic of a lack in K and that both these cardiac manifestations and other clinical signs of the syndrome improve upon intravenous administration of KCl. Furthermore ACTH can produce a similar alkalosis and K deficiency in man. "These results suggest that the pathogenesis of this syndrome in post-operative patients is due to the alarm-reaction producing hyperfunction of the adrenal cortex, with loss of potassium and chloride (or retention of sodium) in the urine associated with a low intake of potassium".[137] The hypokalemia, elicited by DCA in the rat, is not inhibited by ACTH.[137a]

Essentially similar derangements in K metabolism have been observed both in animals and in man after a variety of systemic stresses, for instance, after **hemorrhage,**[138] **burns,**[139] **x-irradiation,**[140] exposure to **cold,**[141] **nervous** and **emotional stress,**[142] forced **muscular exercise,**[143] **anoxia,**[144] acute **infections,** e.g., toxic diphtheria,[145] malaria,[146] or experimental pneumococcus-infection,[147] intoxication with **vesicants,**[148] **starvation,**[149] **intestinal obstruction** [150] and **gravity shock.**[151]

It is interesting that under the influence of acute stress (e.g., forced muscular exercise) the K liberated from the muscles is temporarily taken up by the liver, while during recovery, much of it returns to the muscles. Thus a "potassium cycle" develops, comparable to the well-known "carbohydrate cycle" which occurs under similar conditions. Perhaps here K is transported into the liver as the lactate.[152]

Stimuli Influencing Potassium Metabolism During the G-A-S

Hypophysectomy causes no pronounced and consistent change in serum, tissue, or urine-K concentration. This may be an indication of some remaining adreno-cortical function after ablation of the anterior-lobe.[153]

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[137] Pearson and Eliel B33432/49.
[137a] Woodbury et al. B46344/50.
[138] Borst 99102/38.
[139] Hilgenfeldt 38008/36, McLean et al. B38602/47, Moore and Langohr B4487/46, Roos et al. B38603/47, Stenger A31097/38.
[140] Jüngling B26806/38, Weichert A56943/42.
[141] Di Macco A2920/36.
[142] Gavrilescu and Ionescu A2912/37, Hoagland B4975/47.
[143] Fenn A3071/39, Hoagland B4975/47, Hoagland and Stone B19300/48, B17688/48. Keys B23163/40.
[144] Burrill et al. B678/45, Bryan and Richetts B10396/44, van Liere B26199/42.
[145] Nitschke and Krätshell B20000/38, Stenger A32003/39.
[146] Overman B28216/48.
[147] Fox and Ashwell B32743/49.
[148] Philips et al. B29996/48.
[149] Howard and Bigham B3015/45, Howard and Carey B38343/49, Lorusso and Postiglione B31602/44, Wellers and Waitz B46013/47.
[150] Bellet et al. B45327/49, Jorgensen et al. A31857/40.
[151] Cole et al. 84978/44.
[152] Fenn A30371/39.
[153] Selye **94572/49.**

ACTH produces hypokalemia and severe losses of K through the urine, as shown by observations in man [154] and in the rat.[155]

Adrenalectomy increases the K-concentration in the serum [156] as well as in brain and muscle.[157] These changes are readily corrected, not only by mineralo-corticoids, but also by simple cortical extracts.[158]

In commenting upon the similarity of the A-R and the condition of acute adrenal insufficiency, it has been emphasized that if rats are previously adapted to high-K diets they tolerate elevated blood-K levels even after subsequent adrenalectomy. Since we had envisaged the possibility that toxic metabolites may play a rôle in the pathogenesis of the A-R, it was suggested "that potassium should be included as at least one of the toxic metabolites postulated by Selye".[159]

Adrenaline (or intense sympathetic stimulation) discharges K from the liver, simultaneously with glycogen; insulin has opposite effects. The adrenaline discharge, which occurs during the A-R, may therefore add to the hyperkalemia typical of this stage.[160]

The **mineralo-corticoids** appear to be most specifically concerned with K metabolism. Their leading representative, DCA, causes marked K-excretion in the urine and depresses the K concentration in the blood [161] and muscle.[162] The resulting hypokalemia may be so severe that the excitability of the musculature is diminished and a syndrome ensues which simulates familial periodic paralysis.[163] The decrease in muscle-K occasioned by muscular exercise (swimming) is further augmented by DCA.[164] Allegedly the drop in plasma-K caused by DCA is merely due to a K-shift from plasma to erythrocytes,[165] but this requires confirmation. Yet there are other data which also support the view that DCA does not influence K-metabolism solely by regulating its elimination through the kidney; the hormone apparently also affects K-distribution between cells and the surrounding intercellular spaces.[165a]

Certain **gluco-corticoids,** e.g. 17-hydroxy-corticosterone (cpd. F), likewise cause marked hyperkaluria. It was concluded that this compound reproduces the changes caused by ACTH. "So there is no reason to postulate that a separate Doca- (DCA) like substance is secreted when the adrenals are stimulated by ACTH. If carbohydrate-active steroids are liberated in the alarm-reaction, then the K deficiency may not simply be due to diminished intake. A high K intake would, however, help restore K".[166] Cortisone also increases K elimination [167] in man, and this tends to be associated with a hypokalemic, hypochloremic alkalosis,[167a] very similar to that caused by DCA in the rat (cf. above).

In summary, it may be said that corticoids tend to counteract those changes in K metabolism which we consider to be characteristic of the shock-phase.

[154] Forsham et al. B17987/48. Hoffman et al. B23331/48. Luft et al. B45270/49, Prunty et al. B36504/48, Sayers et al. B37710/49, Sprague et al. B46430/50.
[155] Ingle et al. B2709/47.
[156] Selye **94572/49.**
[157] Hoagland and Stone B19300/48.
[158] Selye **94572/49.**
[159] Kendall and Ingle 68707/37.
[160] Selye 94572/49.
[161] Forsham et al. B17987/48, Sposito A63750/42, Selye **94572/49.**
[162] Hoagland and Stone B19300/48, Muntwyler et al. B28066/44, Parviainen et al. B46923/50.
[163] Selye **94572/49.**
[164] Hoagland and Stone B19300/48.
[165] Decourt and Bastine B26874/42.
[165a] Barnett and McNamara B43396/49.
[166] Fourman et al. B39685/49.
[167] Perera et al. B36595/49, Sprague and Power B46979/50.
[167a] Sprague et al. B46430/50.

The kidney naturally plays an important rôle in the regulation of K metabolism during the G-A-S, since it is the only important route of K elimination. Consequently, in nephrectomized animals the blood-K concentration rapidly rises to extraordinarily high levels. Curiously, even this rise is somewhat delayed by DCA.[168] Thus it appears that the mineralo-corticoids do not affect K metabolism exclusively through their influence upon the renal excretion of this element.

The kidney does not appear to produce any hormones which influence the blood-K concentration. Even if fatal nephrosclerosis, hypertension and hyalinosis is produced in rats by the "endocrine-kidney" technique, the kalemia remains normal. Hence it was concluded that, if hypertension and hyalinosis are really produced by DCA through its effect upon the kidney, the hypokalemic action of this corticoid is probably of no great importance in their pathogenesis.[169]

Dietary **potassium** complements have been recommended for the treatment of intestinal obstruction,[169a] traumatic shock [169b] and of various diseases (e.g., infantile diarrhea, diabetic acidosis, chronic malnutrition, cardiac decompensation) which can cause severe losses of this element, at least partly through their non-specific stress effect, perhaps by way of excess mineralo-corticoid production.[169c]

Calcium and Phosphorus

Calcium and phosphates are absorbed chiefly in the upper part of the small intestine. Large amounts of calcium, magnesium or fatty acids tend to inhibit phosphate absorption, presumably due to the formation of insoluble salts and soaps respectively. A marked decrease in the normal alkaline reaction of the upper intestine improves phosphate and calcium absorption.

Calcium and inorganic phosphates are excreted by the kidneys, the liver and the large intestine, but the participation of the liver in phosphate excretion is negligible. The renal threshold for calcium lies between 6.5-8.5 mg., that for phosphorus between 2-3 mg./100 cc. of plasma. Below these blood levels the renal excretion of calcium and phosphate is insignificant.

The skeleton contains the most important stores of calcium and inorganic phosphate. When needed these elements are readily mobilized from the bones, for instance, by parathyroid hormone. The soft tissues contain comparatively little calcium and inorganic phosphate but they are rich in organic phosphorus.

Phosphatases (see p. 252) play an important rôle in liberating phosphates from organic phosphorus compounds (e.g., for discharge into the plasma or urine); they also participate in the introduction of phosphate into organic molecules (e.g., synthesis of nucleoproteins, lecithin).[170]

The changes in blood-phosphate concentration most **characteristic** of the G-A-S are an immediate increase during the A-R, followed by a decrease to, or below, normal levels during the stage of resistance and finally, a terminal second period of hyperphosphatemia during the stage of exhaustion. Such changes have been observed for instance, in rats exposed to the systemic stress of daily formaldehyde injections, muscular exercise or cold.[171] Phosphat-

[168] Selye 35935/ND.
[169] Schaffenburg and Selye B3478/48, Selye B1433/48. B3142/47
[169a] Bellet et al. B45327/49.
[169b] Blixenkrone-Moller B45328/49.
[169c] Howard and Carey B38343/49.
[170] Cantarow and Trumper **B776/45.**
[171] Masson and Selye A19256/39.

uria is a good indication of the general tissue catabolism characteristic of the stages of alarm and exhaustion, because during the hyperphosphatemic periods of the G-A-S, the urinary elimination of phosphates is likewise increased, unless the systemic damage is so severe that it seriously interferes with renal function. During these catabolic periods the urinary phosphates come partly from the degradation of organic phosphorus compounds (e.g., nucleoproteins, phosphoric esters of carbohydrates, phosphocreatine, phospholipids) and partly from the inorganic phosphorus stores of the skeleton. Under the influence of systemic stress, both calcium and phosphate are discharged from bones mainly as a result of the dissolution of the organic matrix during the catabolic periods of the alarm and exhaustion stages.[172] Hence — unlike the urinary phosphate derived from soft tissues — that discharged from bones is accompanied by much calcium, because in the skeleton, phosphate is held in combination with calcium.

After **traumatic injuries** a large increase in the phosphate content of the plasma has repeatedly been observed, both in animals and in man.[173] This increase in plasma inorganic phosphorus is directly proportional to the increase in the organic phosphorus content of the erythrocytes.[174] The hyperphosphatemia of the A-R is not accompanied by any significant or constant change in blood-calcium,[175] but this is perhaps largely due to the fact that plasma calcium is relatively insoluble in the presence of large amounts of phosphate. In any event, following trauma, the great increase in the urinary elimination of inorganic phosphates is accompanied by a rise in the calcium content of the urine.[176] This is understandable since osteoporosis ensues during the catabolic phase of the A-R (see below), and much of the eliminated phosphate must be derived from bone. Indeed Albright[177] states that "what in the past we have called atrophy of disuse of bone (osteoporosis) after a damaging event, may be, in part, a manifestation of the alarm reaction, and not entirely due to the loss of stresses and strain through immobilization..."

Hemorrhage likewise raises the plasma inorganic phosphate content.[178] Here again a direct proportionality was observed between the plasma inorganic phosphorus, the organic phosphorus of the red-cells and the concomitant fall in the blood pH;[179] as judged by observations on the dog, this rise in blood-phosphate is accompanied by a rise in the blood-calcium.[180]

During intense **muscular work** the inorganic P of the blood varies in inverse proportion to the blood-sugar, presumably because it is utilized for the formation of hexosephosphate in the course of the intense carbohydrate metabolism which accompanies exercise.[181]

Several other stressors cause hyperphosphatemia, for instance, **injection of toxic defibrinated blood,**[182] **gravity shock** in the rabbit[183] or **electrically induced seizures** in the rat.[184]

[172] Selye 35935/ND.
[173] Allison et al. B4739/47. Bollman and Flock B25577/44. Duncan B25580/43. Green B26010/43, Mylon et al. 84205/43, Neufeld et al. A63529/43, Wilhelmi B18793/48.
[174] Allison et al. B4739/47.
[175] Mylon et al. 84205/43, Neufeld et al. A63529/43.
[176] Beattie B18456/47, Cuthbertson A56384/42.
[177] B309/43.
[178] Wilhelmi B18793/48.
[179] Allison et al. B4739/47.
[180] Nitzescu and Runceanu A32665/27.
[181] Moruzzi B31389/38.
[182] Nitzescu and Benetato 18668/28.
[183] Allison and Cole B20411/44. Nastuk B26184/47.
[184] Ward and Call B27708/49.

Additional observations concerning decalcification of the skeleton under the influence of stress will be reported later (cf. chapter: Bones). Suffice it to point out here that administration of calcium, particularly in combination with calciferol, is claimed to help the anabolism of bone minerals, especially in the so-called "**famine osteopathy**".[185] Normally, chronic starvation decreases the calcium content of the skeleton and tends to cause some degree of hypocalcemia in man.[185a]

Even large doses (12 mg/day) of **ACTH** caused no significant change in the phosphorus excretion of the rat in one experiment,[186] but in another small amounts (3 mg/day) elicited a definite phosphaturia.[187] Certain impure corticotrophin preparations increase the phosphate and decrease the Ca content of the plasma. In rats, this humoral change stimulates parathyroid growth and it was held responsible for the parathyroid hyperplasia often occurring in Cushing's disease.[188] In man, ACTH tends to increase the urinary elimination of Ca and P [188a] presumably due to the osteoporotic action of gluco-corticoids, so manifest in Cushing's disease. Much of this Ca is also lost through the feces.[188b]

Adrenocortical extracts likewise cause hypocalcemia and hyperphosphatemia in the rat.[189]

In man *cortisone* tends to decrease phosphate elimination, at least at the time when the blood-sugar rises,[190] but long-continued treatment with this hormone renders the phosphate and calcium balances negative.[190a]

Sulfur

The dietary sulfur is derived partly from inorganic salts and partly from organic compounds, especially the amino-acids cystine and methionine. It enters into the molecules of many biologically important substances, e.g., thiamine, glutathione, anterior-lobe hormones, insulin and the above-mentioned sulfur containing amino-acids.

Both the organic and inorganic sulfur compounds are absorbed chiefly in the small intestine. Upon reaching the liver the major part of the organic sulfur is oxidized to the inorganic form, although some organic compounds, especially the sulfur-containing amino-acids, tend to escape oxidation.

In the serum, S is found as inorganic sulfate (0.5-1.0 mg %) ethereal sulfate (0.1-1.0 mg %) and neutral S (2.0-3.5 mg %). A marked increase in serum inorganic sulfate occurs in renal disease (glomerular nephritis), intestinal obstruction and leukemia.

Sulfur is excreted in the urine in all three forms in which it exists in the blood. Most of the urinary S is in the form of inorganic sulfate (about 90%); some as ethereal sulfate (10%), e.g., indoxyl, indican, and a trace as neutral S, e.g., cystine, urochrome, taurine, thiocyanate, thiosulfate, etc. Sulfur participates in the detoxification of certain toxic compounds, such as monobrombenzene, which upon conjugation with cysteine (derived from cystine) forms

[185] Lamy et al. B26867/48.
[185a] Klotzbücher B45392/48, Mellinghoff B46542/49, Mellinghoff and van Lessen B46547/49, Wellers and Waitz B46013/47.
[186] Bergner and Deane B23875/48.
[187] Li et al. B34773/49.
[188] Törnblom B39104/49.
[188a] Luft et al. B45270/49, Sprague et al. B46430/50.
[188b] Kinsell et al. B46958/50.
[189] Törnblom B39104/49.
[190] Forsham et al. B35919/49.
[190a] Sprague et al. B46430/50.

mercapturic acid. Phenol derivatives such as indol, which are formed in the intestine through bacterial action, are also excreted after combination with sulfates.[191]

Little is known about the changes in sulfur metabolism **characteristic** of non-specific systemic stress. It is a well established fact, however, that together with the increased elimination of nitrogen, phosphate and other protein split-products during the catabolic phase of the A-R, the urinary elimination of inorganic sulfate also rises, for instance, in fever [192] and after bone fractures.[193]

Experiments in rabbits indicate that the increase in general resistance seen after the production of a sterile abscess may be due to the liberation of detoxifying sulfur compounds from protein. It was found that the amount of mercapturic-acid-S excreted by the rabbit following oral administration of monobrombenzene is raised in the presence of a sterile abscess. Sulfur partitions showed that the abscess increases neutral sulfur elimination through the urine and it was concluded that "this neutral sulfur may be utilized by the animal in forming mercapturic acid. These data indicate that a specific metabolic reaction can utilize the tissue breakdown products resulting from the formation of a sterile abscess", a fact which was considered of significance in interpreting the protective action of such abscesses.[194] (Cf. Glutathione).

In man **ACTH** increases the urinary elimination of inorganic and organic (mainly methionine and cystine) S.[194b]

Iron

Up to now no systematic studies of iron metabolism have been made during the G-A-S, although scattered pertinent observations suggest that they would be most rewarding. (Cf. also Hemoglobin and its derivatives, p. 259.)

The claim that **muscular exercise** decreases the iron content of the serum has not been confirmed.[194a] However, various types of non-specific damage tend to decrease the plasma-iron concentration in man. This was shown to be the case especially in **tuberculosis** [195] as well as in other **infections** and in **carcinomatosis.**[196]

From a series of studies on the pathogenesis of the **"anemia of infection"** it was concluded that here a concomitant disturbance in the intermediate metabolism of iron is of pathogenic importance. In dogs, under the influence of staphylococcus or turpentine injections, the plasma iron concentration falls to progressively low levels.[197] Here the absorption of administered iron was apparently adequate but the metal was rapidly removed from the plasma. Experiments with radio-iron in pigs showed that during various types of inflammations and infections, anemia does not appear at once but only when the outworn red corpuscles must be replaced. In spite of the pronounced iron avidity of the tissues, the utilization of this element for hemoglobin synthesis is impaired in the presence of turpentine or staphylococcus abscesses, as well as after burns. Apparently, under the influence of inflammations and other conditions causing catabolism (e.g., neoplasms, malnutrition), injected iron is rapidly diverted from the plasma.[198] Intravenous iron-tolerance tests in patients suffering from acute and subacute infections likewise showed a more rapid disappearance of the metal from the blood due to its fixation in the tissues.[199] Some investigators ascribe this unusually rapid disposal of exogenous iron to an increased avidity of the reticulo-endothelial system in which its increased deposition during infections is directly demonstrable; [200] others believe that iron is attracted by the inflamed tissues themselves.[201] Analyses of the spleen and liver from human autopsy specimens in chronic disease revealed large accumulations of iron in these organs, the amounts deposited being out of proportion with the degree of anemia.[202]

Recent studies with radio-iron demonstrated the deposition of this metal in the liver and spleen of rats and dogs with acute inflammations, but no significant quantity of iron was diverted into the inflamed area itself. Apparently "the major diversion of plasma iron in infection is to the ordinary storage tissues, mainly the liver". The degree of this diversion is related to the hypoferremia.[203] However, other experiments on dogs revealed no acceleration of the disappearance of radio-iron from the plasma following turpentine abscess formation.[204] Perhaps here again the response depends upon the "conditioning" effect of intermediate metabolism.

Interesting correlations appear to exist between iron and *ascorbic acid* metabolism. During the hypoferremia of infection, ascorbic acid administration tends to raise the serum iron concentration, while in true iron deficiency it exerts an opposite effect.[205]

Fasting tends to raise the plasma iron in man. As judged by observations on the rabbit this may be at the expense of the hepatic iron stores.[206]

As shown by experiments on **adrenalectomized** and **cortical extract** treated rats, the suprarenal does not affect the normal plasma-iron level, nor the hypoferremia produced by turpentine injection. It may, however, be essential for rapid recovery from such hypoferremia.[206a]

Other Ions

Copper tends to accumulate in the spleen and liver of man under the influence of various chronic diseases and this is usually accompanied by anemia.[207] The exact relationship between such changes and resistance to systemic stress has not yet been studied, but interestingly, the hypoferremia of infection is often accompanied by hypercupremia.[208]

Several workers have reported increases in plasma **magnesium** during traumatic shock and burns.[209] It is also well known that the plasma magnesium increases in renal failure, but apparently only if the kidney lesion is severe and of long standing.[210]

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191 Cantarow and Trumper **B776/45.**
192 Cantarow and Trumper B776/45.
193 Cuthbertson A56384/42.
194 Schultz B18183/48.
194a Björck B29351/48.
194b Kinsell et al. B46958/50.
195 Reginster B26631/41, B26634/42.
196 Heilmeyer and Plötner B26951/37, Lederer et al. B26796/47, Neukomm **B40257/49.** Vannotti and Delachaux B27056/42.
197 Cartwright et al. 93254/46, 93255/46.
198 Cartwright et al. 93254/46, Greenberg et al. 96955/47, Wintrobe et al. 96954/47, B37960/47.
199 Hoet and Lederer B26304/46, B26306/47, Renaer and Lederer B26626/46.
200 Heilmeyer and Plötner B26951/37, Schäfer B26952/43.
201 Menkin B26953/30.
202 Gross et al. B26955/42, Rechenberger and Schairer B42396/48, Sandberg et al. B26954/42.
203 Greenberg et al. 96956/47.
204 Yuile et al. 98692/47.
205 Albers B31800/41.
206 Eser B38538/47.
206a Majumder and Wintrobe B42808/48.
207 Gross et al. B26955/42, Sandberg et al. B26954/42.
208 Cartwright et al. 93254/46.
209 Stoner and Green **B38488/49.**
210 Cantarow and Trumper **B776/45.**

In patients who suffer from severe inanition the total plasma-magnesium is often low and the Mg-balance becomes negative. The ultrafiltrable plasma-Mg, on the other hand, rises above normal; presumably in preparation for renal elimination.[210a]

ACTH increases the urinary elimination of Mg. in man.[210b]

DCA reduces the plasma magnesium level in the rat; allegedly this is inhibited by ACTH.[210c]

Acid-Base Balance

It is obviously not within the scope of this monograph to discuss the numerous factors which influence the acid-base balance of the organism. Na, K, Ca and Mg among the cations; Cl, protein, H_2CO_3, HPO_4 and SO_4 among the anions are (in this order) most important as regulators of the actual and potential pH in body fluids and tissues.

The actual pH or "hydrogen ion concentration" cannot deviate much from neutrality without causing death. On the other hand the potential pH, that is, the buffering ability of the body fluids, is subject to great fluctuations. These are not particularly injurious in themselves, but they exhaust the neutralizing reserve and hence reduce the possibility of adjustment to any stimulus, tending further to displace the pH in the same direction. Blood-CO_2 is readily eliminated through the *lungs* by respiration hence the plasma-bicarbonate represents a supply of neutralized base which is immediately available for the neutralization of any excess acid; we therefore refer to it as the "alkali reserve".[211]

It is customary to distinguish between "respiratory" and "metabolic" acidosis or alkalosis respectively. The former is primarily due to anomalies in the CO_2 (more properly H_2CO_3) content of the body fluids; the latter to disturbances in the "fixed ion" content, which changes the alkali reserve. It must be kept in mind, however, that the terms metabolic alkalosis or acidosis are not quite correct since the underlying change does not necessarily result from primary metabolic derangements (e.g., ketosis), but sometimes from impairment of the regulatory organs, for instance, the kidney.[212]

All those ions which play an important rôle in the regulation of the acid-base balance are primarily under *renal* control, except for CO_2 and protein; hence interference with kidney function — so commonly occasioned by systemic stress — can seriously derange the ability of the body to maintain its normal pH.

The *gastric mucosa* secretes a very large amount of HCl but since most of this is re-absorbed after neutralization in the small intestine, alkalosis does not ensue, except in case of pyloric obstruction and persistent vomiting. Intense diarrhea likewise places acid-base regulation under considerable strain because of the accompanying loss of electrolytes and water through the *intestine*.

The abnormal accumulation in the *extracellular fluid* of organic acids (lactic, pyruvic, acetoacetic, hydroxybutyric) has already been mentioned as characteristic of severe systemic stress. It occurs especially during the initial (A-R)

[210a] Mellinghoff B46544/48, B46543/48, B46542/49, Mellinghoff and van Lessen B46547/49.
[210b] Kinsell et al. B46958/50.
[210c] Woodbury et al. B46344/50.
[211] Cantarow and Trumper **B776/45**, Gamble **B2332/47**.
[212] Cantarow and Trumper **B776/45**, Gamble **B2332/47**, Verain and Chamette A32672/30.

and final (exhaustion) catabolic phases of the G-A-S, when large quantities of organic acids are formed as degradation products of proteins and fat. Concurrently, tissue anoxia tends to develop at times of extreme stress. Hence, the alkali reserve cannot be utilized readily for the neutralization of accumulated organic acids, because the displacement of CO_2 by the latter is impeded. During systemic stress the depletion of the carbohydrate reserves further aggravates this condition, since complete oxidation of organic acids and fat is largely dependent upon simultaneous carbohydrate combustion.

The changes in acid-base balance which are strictly **characteristic** of the G-A-S, have received comparatively little attention. It is a well established fact, however, that during the A-R stage many systemic stressors cause an acidosis, which is usually compensated; it manifests itself mainly by a reduction of the alkali reserve. Subsequently, during the counter-shock phase and the onset of the stage of resistance, overcompensation with an "alkaline wave" tends to ensue.[213] No systematic studies have been carried through to the stage of exhaustion, but scattered data — gathered from the literature on the humoral effects of chronic infections, intoxications, etc. — suggest that during the terminal phase of the G-A-S, a second period of acidosis ensues. Premortal renal failure, tissue anoxia and ketosis presumably play an important rôle during this late stage.

After **traumatic injuries** there is a fall in the alkali reserve, and sometimes even in the actual pH of the plasma.[214] This is so constant that it was considered to be a characteristic manifestation of the "post-operative disease".[215] The initial acidosis is usually compensated within 24 hours after the operation and is sometimes followed by an alkaline wave during the subsequent days.[216] This secondary post-operative alkalosis is often associated with hypokalemia and since similar changes have also been produced with ACTH, the syndrome has been ascribed to increased ACTH production as a result of the ensuing A-R.[217] Allegedly continuous infusion of sodium bicarbonate prevents the development of irreversible traumatic shock in dogs,[218] hence this response is presumably useful.

An essentially similar transitory acidosis has been observed both in animals and in man following exposure to a variety of systemic stressors such as **hemorrhage,**[219] **burns,**[220] **x-irradiation,**[221] **ultra-violet-irradiation,**[222] **heat-stroke,**[223] forced **muscular exercise,**[224] **anoxia,**[225] **electro-shock,**[226] **"gravity shock",**[227]

[213] Selye **B1204/46**, Wilhelmi **B18793/48**.
[214] Cannon and Cattell 13334/22, Crile A32669/15, Henderson 47094/10, 47095/10, 47096/10, Henderson et al. 59823/17, Richards B26109/44, Verain and Chaumette A32672/30, Wright A32670/17.
[215] Lambret and Driessens A2914/37, Leriche B18459/34.
[216] Roscher B25560/33.
[217] Pearson and Eliel B33432/49.
[218] Wiggers and Ingraham 95649/46.
[219] Aggazzotti B19554/39, Frank and Fine B26173/43, Milroy B26885/897, Penfield B26886/19, Price et al. B26011/41.
[220] Ficarra and Naclerio B808/44, Simonart 63360/30.
[221] Guthmann and Wirtz A32673/30, Hirsch and Petersen A32674/23, Hussey 51259/22, Kroetz A16087/24, Lacassagne and Loiseleur 53672/33.
[222] Kroetz A16087/24.
[223] Malamud et al. B18019/46.
[224] Peters et al. 25379/26, Turrell and Robinson B19683/42.
[225] Herber B19880/48, van Liere B26199/42.
[226] Delmas-Marsalet B26881/46, Ward and Call B27708/49.
[227] Allison and Cole B20411/44, Allison et al. B26108/43, Cole et al. 84978/44.

"medical shock",[228] acute **infections**,[229] as well as after treatment with various **drugs**, tissue **extracts** and especially **anesthetics**.[230]

It is noteworthy that in many of these observations, during the acute stage of exposure, there was an actual fall in the pH in addition to the decline of the alkali reserve, while later a characteristic compensatory alkaline wave ensued. Indeed, upon continued exposure, for instance, to x-irradiation, a condition of uncompensated alkali excess has allegedly been observed in the rabbit. As an illustration of the applicability of the G-A-S concept to this type of study, let us point out that in this latter experimental series sodium bicarbonate was injected into the peritoneal cavity of rabbits and since this was followed by systemic effects similar to those produced by x-irradiation, it was concluded that alkalosis may play a specific rôle in the mechanism of x-ray sickness.[231] In view of what we have learned since about the non-specificity of the G-A-S, such an interpretation appears highly improbable, because similar responses can also be produced with acids or any other toxic agents.

Acapnia (CO_2-depletion of the blood) is also a frequent accompaniment of acute systemic stress. It occurs, for instance, after traumatic injuries or in nervous shock [232] and allegedly often plays an important rôle in the genesis of the shock-syndrome. Acapnia appears to be largely the result of hyperventilation; while it may in itself be a stressor, it cannot be regarded as an indispensable prerequisite for the development of the G-A-S. Since pronounced acapnia is associated with alkalosis, it may participate in the production of the alkaline wave of the late counter-shock phase.

The factors regulating the acid-base balance during the G-A-S have received so little attention up to now that it would not be profitable to discuss them in detail. Let us merely point out that, a large single dose of **ACTH** caused no significant change in plasma-pH or CO_2 in man.[233] On the other hand, both severe **DCA** overdosage [234] and the **"endocrine kidney"** [235] induce severe hypochloremic alkalosis in the rat.

Water Balance

In reviewing the G-A-S changes in water balance, it is well to recall first some of the pertinent fundamental facts.

Water is *absorbed* mainly from the small intestine.

Normally *the water content of the body* corresponds to about 70% of the total weight. It is kept in three distinct compartments: (1) the plasma (5% of body weight) which is rich in protein and Na, (2) the interstitial fluid (15% body weight) which contains only traces of protein but as much Na as the plasma, (3) the intracellular fluid (50% body weight) which is rich in protein but practically free of Na. These differences in the distribution of protein and Na are of the greatest importance in the regulation of water metabolism.

[228] Davidson et al. 87543/46.
[229] Wright A32670/17.
[230] Dautrebande A32671/30, Lacassagne and Loiseleur 53671/33, Roscher B25560/33, Wright A32670/17.
[231] Hussey 51259/22.
[232] Henderson 47093/09, 47094/10, 47095/10, 47096/10, Roger A32642/16.
[233] Sayers et al. B37710/49.
[234] Selye B1204/46, **B1433/48.**
[235] Schaffenburg and Selye B3478/48, Selye B3142/47, B1433/48.

The walls of the capillaries and cells act as semipermeable membranes, which do not permit the free passage of the large protein molecules from either plasma or cells into the interstitial fluid. The smaller Na molecules migrate freely across capillary walls from plasma into interstitial fluid and vice versa — but, as previously stated — they cannot pass readily across cell membranes. Inside the cell K almost completely replaces Na.

Since Na, the chief basic ion in the extracellular fluid cannot readily enter the cell, both the osmotic pressure and the pH of the extracellular fluid depend almost entirely upon this cation. The CO_2-content of tissues is easily adjusted through respiration, hence variations in the "fixed" anions (e.g., Cl) of the fluids, rarely cause pH disturbances, which could not be counteracted by changes in the alkali reserve. This further emphasizes the importance of Na in regulating the body pH. It should also be kept in mind that there is a close correlation between pH and water balance. Acidosis tends to cause dehydration due to diuresis and transfer of water from plasma to cells with swelling of the latter, while alkalosis exerts opposite effects.

To maintain blood homeostasis during stress, the organism uses its intercellular fluid reservoir as a buffer system. When excess amounts of water are introduced into the circulation (by ingestion or intravenous infusion) this is rapidly deposited in the intercellular spaces. From here it is gradually taken up for renal elimination. Since diffusion into the intercellular spaces occurs much more rapidly than renal elimination, the former is a more effective means of maintaining the constancy of plasma volume and concentration in the event of sudden flooding with water. Conversely, when much plasma or plasma-water is lost, the body draws upon its intercellular tissue-fluid reserves to re-establish the normalcy of plasma structure.

Most of the water is *excreted* through the kidney, although under certain conditions, an equivalent or even greater amount may be eliminated through the skin (perspiration) and lung (respiration). Almost all the water secreted into the intestinal lumen (pancreatic bile, intestinal secretion, etc.) is normally reabsorbed, but large amounts of fluid may be lost through the intestinal tract in the case of profuse diarrhea or vomiting. About 180 liters — an amount of water corresponding to almost three times the average body weight — is filtered through the glomeruli during 24 hours, but approximately 99% of this is reabsorbed; hence the daily urine volume usually varies between 1.5 and 2 liters. This is about 1/7 of the total extracellular fluid of the body (14 liters). A nearly equal degree of concentration occurs in the tubules as regards the Na and Cl content of the filtrate, while K, HPO_4 and SO_4 are less intensely reabsorbed (93, 83, 74% respectively).

It should be kept in mind that in an infant of 7 Kg. the daily urine output corresponds to 700 cc. This equals about half the total extracellular fluid (1400 cc.) at this age. Thus the safety margin in the defense against dehydration is small and there is a great tendency towards exsiccosis among infants in the event of sudden fluid losses.[235a]

The changes in water balance **characteristic** of the G-A-S are largely secondary to the derangements in protein catabolism, capillary permeability and electrolyte balance, which are typical of the three stages of this syndrome.

[235a] Cantarow and Trumper **B776/45.**

The greatest attention has been devoted to changes in blood-volume and concentration. In rats in which a typical G-A-S was elicited by various stressors (formaldehyde injections, exposure to cold, excessive muscular exercise) it was observed that during the stage of alarm the *blood-volume* decreases while the hematocrit and hemoglobin values increase as a result of hemoconcentration; all these changes are reversed within 2-24 hours after discontinuation of exposure. During the stage of resistance there was blood dilution, with an increase in total blood-volume, even if exposure to stress had been continued, while in the stage of exhaustion, a second period of hemoconcentration and oligemia was usually observed.[236]

Our earliest studies on the A-R had clearly shown that during the shock phase there is *edema* due to loss of water into the intercellular spaces, even at a distance from the site of direct injury. The formation of edema in the thymus, pancreas and stomach, as well as the transudation of fluid into the pleural and peritoneal cavities, was usually very pronounced in rats exposed to a variety of systemic stressors (e.g., formaldehyde, cold, muscular exercise, spinal shock). Here it is obviously impossible to ascribe the edema to increased permeability of the capillary walls caused by direct damage. It is noteworthy, however, that edema is particularly frequent in the organs (thymus, pancreas, stomach) which are undergoing acute, degenerative processes during the A-R.[237] It may be postulated therefore that tissues, at a distance from the primary injury, become predisposed to edema formation due to capillary damage in areas which are selectively injured by the A-R itself (e.g., acute thymus involution, pancreas involution, gastric ulcers).

It has also been emphasized that during the stages of alarm and exhaustion, *urine* output is diminished, while in the stage of resistance, it is usually at or above normal levels.[238] Significantly, "in the alarm-reaction (especially after such damaging agents as muscular exercise and cold) retention of water may occur without clinical evidence of shock".[239]

If immediately following exposure to a first alarming stimulus (during the counter-shock phase) a rat is again exposed to either the same or any other mild stressor, this second exposure fails to cause water retention and may actually increase diuresis.[240] This observation was interpreted as showing that two typical alarm-reactions cannot be elicited in rapid succession and that some "crossed resistance" is manifested in the period immediately following the first exposure.[241]

During **traumatic shock** hemoconcentration is usually very pronounced and accompanied by a decrease in total blood-volume.[242] In the pertinent investigations the hemoconcentration and oligemia were demonstrated with a variety of techniques including: hematocrit, hemoglobin, plasma water, plasma

[236] Karády et al. 74590/39, A31125/39.
[237] Selye 36031/36, 38798/37, Selye et al. 38815/36.
[238] Birnie and Eversole B44553/49, Browne et al. A18203/39, Karády et al. A8194/38.
[239] Howlett and Browne 77132/40.
[240] Karády et al. A8194/38.
[241] Selye B1204/46.
[242] Blalock and Beard 8726/32, Cleghorn and McKelvey 84886/44, Cournand et al. B26894/43, Evans et al. B26892/44, Gregersen B26890/43, B26891/42-44, Holmes and Painter B38210/47, Keith B26887/19, Lawson et al. B2080/45, Mills and Gordon 93421/46. Noble and Gregersen 93259/46. 93260/46, Robertson and Bock B26888/19, B26889/18, Warren et al. B26893/44.

protein and total plasma volume determinations by the dye and other methods. Hence, it is almost unanimously agreed that oligemia is an important manifestation during the shock phase of the systemic response to trauma. It is still a much debated question, however (cf. capillary permeability, below), whether this oligemia is due to loss of plasma throughout the organism or only in directly injured areas. The relative importance of incidental hemorrhage during trauma is also quite differently assessed by the various authors.

Direct examination of venous blood, coming from a limb damaged by the tourniquet technique, indicates that important losses of fluid into damaged tissues do occur even in the absence of hemorrhage. Such observations show furthermore, that systemic manifestations of shock appear before any important quantity of fluid is lost into the damaged tissue.[243] Since hemoconcentration during shock considerably raises the blood viscosity, severe cardiovascular disturbances can ensue. Hence irreversibility in tourniquet-shock develops at higher blood-pressure levels than in hemorrhagic shock, because in the latter, blood dilution nullifies the tendency of the stressor to raise blood viscosity.[244] Measurements of the total circulating erythrocyte and plasma volume in the dog (by the "Evans blue", radio-iron and radio-iodine techniques) revealed that there is always a greater reduction in circulating red-cells and plasma than can be accounted for by measurable external hemorrhage. This is partly due to internal blood loss, but largely also to stagnation of blood "trapped" in the capillaries of all organs.[245]

Many investigators examined the conditions influencing the leakage of fluid from the plasma into the intercellular spaces.[246] The interstitial fluid in the damaged area was found to be unusually rich in protein, thus resembling blood-plasma.[247] Furthermore, following release of tourniquets in the frog, the gain of sodium allegedly so much exceeds the gain of water in the gastrocnemius that penetration of Na into the intracellular compartment has been suspected.[248]

After traumatic injuries, oliguria or even anuria develops with great regularity, during the "secondary shock" phase. Since this usually coincides with hypotension, it is — at least in part — probably dependent upon a disturbance in renal circulation. Nevertheless, experiments on guinea-pigs showed that oliguria can ensue after trauma, at a time when the systemic blood-pressure is still high. This is true even if the kidney has been previously denervated. Hence, it was concluded that hormones, or toxic substances, may directly affect the kidney and thus cause post-traumatic anuria.[249] As we shall see below (cf. G-A-S → Kidney), degenerative renal lesions may accompany this decrease in urine output; however, the anuria of the counter-shock phase must not be confused with the "crush syndrome", which does not develop until several days after the trauma.[250]

[243] Selye and Dosne A35802/41
[244] Seligman et al. 93251/46.
[245] Gibson et al. B26950/47.
[246] Fox and Baer B4517/47, Friedberg and Katz 88843/45, Scott 93258/46.
[247] Aikawa B26907/34, Harkins B26900/34, Harkins and Harmon B26902/37, Harkins and Hudson B26901/34, Harkins et al. B26903/36, Harmon and Harkins B26904/37, B26905/37, Herbst B26895/33, B26896/34, Holt B26897/35, Holt and MacDonald B26898/34, Roome and Wilson 30672/34.
[248] Fuhrman and Crismon 98509/47.
[249] Jourdan et al. 93172/44.
[250] Moon B26013/47.

Following severe **hemorrhage**, the loss in plasma volume is rapidly compensated by the uptake of intercellular fluid into the blood. This markedly decreases the intracellular fluid compartment, unless the latter is replaced by exogenous water. Therefore patients and animals experience great thirst and make every effort to obtain water after extensive hemorrhages. The hematocrit, hemoglobin, and blood protein values indicate hemodilution after hemorrhage, rather than the usual hemoconcentration of the A-R, because the formed elements and the proteins of the blood cannot be as rapidly replaced as the water.[251]

The increased tendency to form edema and the diminution in the urine output characteristic of the stages of alarm and exhaustion, are usually very evident after hemorrhage, since these changes are not counteracted by the specific effects of this stressor. In fact, the loss of blood-protein, with the resulting diminution in osmotic pressure, increase the edema tendency, while the (at least temporary) diminution in plasma volume and blood-pressure, as well as the great need for water preservation, tend to further augment the anti-diuretic effect of systemic stress.

Cardiac edema does not occur in dogs in which irreversible hemorrhagic shock is produced, unless they are given massive infusions of saline. Hence, cardiac edema can not explain the deterioration of the heart in such experiments.[252]

The decreased volume-flow of blood through the tissues has been responsible for the decreased alkali reserve and increased blood-N.P.N. which occur after severe blood losses.[253] The reduced bleeding-volume (total amount of blood obtainable by unrestricted bleeding), noted during hemorrhagic shock, is not abolished by re-infusion of the lost blood. Hence it was ascribed to a redistribution of the blood into the splanchnic area where it is trapped during shock.[254]

Exposure to **cold** causes marked polyuria during the resistance stage of the G-A-S, in the rat. This is particularly obvious in animals sensitized by partial nephrectomy and a high NaCl intake. The diuretic effect of cold (as its hyalinosis producing action) is greater than that of most other stressors.[254a]

Extensive **burns** cause a particularly pronounced loss of water, because, in addition to their very intense systemic stress effect, they occasion a profuse seepage of fluid on the entire affected surface area.[255] Consequently, after widespread skin burns in man, the plasma-volume may fall 50% below normal within two hours.[256] It must be kept in mind, however, that in burned patients, the measurement of plasma-volume with dyes or radioactive proteins, gives rather inaccurate results, because the capillaries become permeable for such

[251] Blalock and Beard 8726/32, Borst 99102/38, Noble et al. 93260/46.
[252] Rodes et al. B37245/49.
[253] Rukstinat A32657/32.
[254] Foreman B38175/47.
[254a] Selye B1204/46, Stutinsky B46553/49.
[255] Hilgenfeldt 38008/36, Kabat and Hedin 83643/42, Lambret et al. A8119/37, Mills and Gordon 93421/46, Moon B26013/47, Moore and Langohr B4487/46, Noble et al. 93260/46, Rossiter B26840/43, Stenger A31097/39.
[256] Colebrook et al. B26911/45.

substances, at least in the directly injured area.[257] This also explains the extraordinarily high protein content of the fluid lost from the burned surface.[258]

Experiments on rats showed that after the initial phase of hemoconcentration the blood-volume tends to rise significantly above normal after burns.[259] This may well correspond to the stage of resistance.

Among the factors invoked to explain the genesis of the anuria following burns, the most important are: hypoproteinemia, increased blood viscosity and density, decreased plasma-volume, hypotension and the stimulation of nerves which act directly upon the kidney.[260]

During **electro-shock** therapy in man, the plasma-volume decreases slightly.[261] There also tends to be a transitory inhibition of diuresis, which has tentatively been ascribed to an increased vasopressin production by the posterior-lobe.[262]

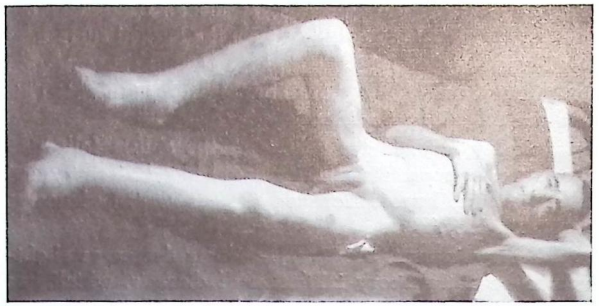
Systematic studies in the dog showed that the elimination of exogenous water is greatly inhibited by **emotional stress.**[263] Similarly, in the rabbit, emotional disturbances and painful stimuli cause antidiuresis, presumably by decreasing the renal blood-flow and filtration rate. Here, tubular reabsorption of water appears to be of minor importance. Since adrenaline, in large doses, causes renal ischemia similar to that observed during emotional oliguria and since denervation of the kidneys does not change this renal response to nervous stimulation, the reaction may be mediated through a discharge of adrenaline.[264]

Conversely, in aviators, the emotional stress of flying tends to increase diuresis. Simultaneously the excretion of steroids (presumably of adrenocortical origin) rises, hence it was suggested that the diuresis may be due to adrenal cortical stimulation such as occurs in the counter-shock phase of the A-R.[265]

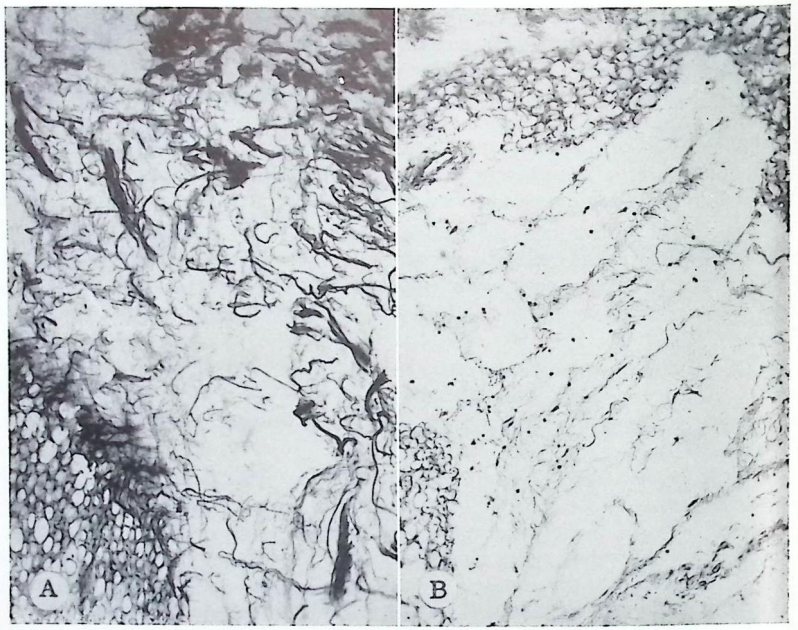
Perhaps the diuresis observed in **anoxia** [266] is governed by a similar mechanism. It must be kept in mind, however, that — apart from the production of diuretic steroids — stressors cause many other changes which could account for this polyuria.

During **fever** an increase in the total water content of the body had been observed as early as 1869.[267] The blood-volume also tends to rise during fever,[268] but only if the resulting systemic stress is not too grave and acute. Fulminating **infections** cause hemoconcentration and oliguria,[269] as do other stressors which elicit a marked shock-phase. Thus, here again, increased hydration may correspond to the counter-shock or early resistant phase of the G-A-S.

[257] Cope and Moore B26912/44.
[258] Harkins B26899/35, B26900/34, Underhill et al. B26906/23.
[259] Bergman et al. B37980/48.
[260] Barac B38654/47, B26093/47, B24074/46, B24080/46, B23974/48, B23975/48.
[261] Altschule and Cline B28589/48.
[262] Kreienberg and Ehrhardt B38182/48.
[263] Verney B18117/47.
[264] Brod and Sirota B36853/49.
[265] Hoagland B4975/47.
[266] Burrill et al. B678/45, Kleinschmidt B46632/48, van Liere B26199/42, van Middlesworth et al. B28285/48, Stickney B26636/46, Stickney et al. B26638/46.
[267] Leyden B26815/869.
[268] Soule et al. B26820/28.
[269] Moon A33122/39, Nitschke and Krätschell B20000/38, Penner and Bernheim B37656/42, Stenger A31097/39.



Hunger edema. Undernourished concentration-camp inmate after four years of forced labor. Note enormous swelling of the lower extremities as well as loss of pubic hair. The latter probably represents part of the hypogonadal syndrome characteristic of prolonged stress. (Courtesy of Salzmann and Hottinger B27607/48).



Hunger edema. Section through subcutaneous tissue of buttocks **(A)** and of pelvis region **(B)** in two undernourished concentration-camp inmates, who developed marked water retention. Note the intense water infiltration, which separates the adipose tissue lobules from each other. (Courtesy of E. Uehlinger B27612/48).

Changes in the water balance caused by chronic **undernutrition** have been studied with especial care in an effort to explain the important syndrome of *"famine edema"*.[270]

[270] Brull et al. B3026/45, Dumont B3027/45, Gsell **B27611/48**, Henschel et al. B23151/47, Keys **B37797/48**, Lamy et al. **B26867/48**, Uehlinger B27612/48, **B24304/47**.

Lack of food, and especially lack of protein, has long been known to cause edema. It has been emphasized in this connection[271] that 2300 years ago Diogenes Laertius described the experience of Hercules who retired into the mountains and lived only on herbs and legumes, upon which he became hydropic and died. Of course he may have suffered from renal disease or cardiac decompensation — and indeed he may not have existed at all — but let us not enter upon any more detailed discussion of the many G-A-S problems raised by Greek mythology.

The occurrence of hunger edema has been mentioned as a characteristic manifestation of famines in the descriptions of the Peloponnesian wars (430 B.C.), during the Russian campaign of Napoleon (1812) and ever since.[272] It is often accompanied by the formation of pleural and peritoneal transudates, and may lead to acute lung or brain edema with delirium and confusion.[273]

During the recent World War, among the inmates of concentration camps, severe exsiccosis often alternated with periods of generalized tissue edema. When moderate amounts of physiologic saline solution were administered to dehydrated starving men, almost the entire fluid was immediately deposited in the extracellular space. This often caused acute lung edema and "flooding" of the serous cavities as well as of the subcutaneous tissue. Such manifestations are allegedly due to an essential inability of the undernourished patient to keep normal amounts of water in the vascular system. Polyuria is likewise frequent among severely undernourished men.[274]

A decreased osmotic pressure of the plasma (due to hypoproteinemia) and impaired renal function are probably the most important factors in the production of famine edema and the associated derangements.[275] Yet starvation may cause edema even if the protein-osmotic pressure of the plasma remain within normal limits,[275a] presumably as a result of increased capillary permeability.[275b]

Exposure to *cold* may be a contributing factor. In the undernourished it may suddenly elicit edema and cause an almost elephantiasis-like swelling of the legs, transudation into the serous cavities, etc. In some cases, exsiccosis and edema co-existed; the mucous membranes were dry, and the patient suffered from intense thirst, although the subcutaneous tissue was edematous.[276]

Studies concerning changes in water balance and distribution induced by other stressors have not been very systematic and were largely limited to the A-R stage. However, generally speaking, the disturbances so far observed support the view that most stressors tend to elicit derangements essentially similar to those outlined above as being typical of the G-A-S. One or more of these manifestations have been noted following exposure to **nuclear fission products,**[277] **x-irradiation,**[278] **heat,**[279] excessive **muscular exercise,**[280] intraperi-

[271] Lamy et al. B26867/48.
[272] Justin-Besançon B26913/43.
[273] Lamy et al. B26867/48.
[274] Lamy et al. **B26867/48.**
[275] Brull B26141/42, Brull and Lambrechts B26140/45, Brull et al. **B3026/45,** Heller and Dicker B37604/47, Klotzbücher B45392/48, Kurnick B45782/48, Lamy et al. **B26867/48,** Lloyd et al. B44877/48, Wellers and Waitz B46013/47.
[275a] Beattie et al. B45482/48, Berkman et al. B46014/47, Pallister B45658/47.
[275b] Lamy et al. B45139/48.
[276] Lamy et al. B26867/48.
[277] Prosser et al. B26618/47.
[278] Moon et al. A31861/40, Prosser B26618/47.
[279] Barac B23119/46.
[280] Rakestraw A7856/21.

toneal injection of **glucose,**[281] toxic doses of histamine [282] or **adrenaline,**[283] heavy overdosage with **folliculoids,**[284] deep ether anesthesia,[285] **constriction of the hepatic veins** [286] and a variety of severe diseases conducive to **"medical shock"** [287] and **circulatory collapse.**[288]

Stimuli Influencing Water Balance During the G-A-S

Complete **hypophysectomy** does not produce as pronounced a disturbance in water metabolism as isolated removal of the posterior-lobe or transection of the pituitary stalk. These latter operations induce the experimental equivalent of diabetes insipidus. They interfere with the production of the antidiuretic posterior-lobe hormone, which is presumably identical with vasopressin. It is perhaps for this reason that the administration of diuretic steroid hormones, such as *DCA* [289] and *progesterone* [290] causes especially marked polyuria after hypophysectomy.

Thyrotrophin or thyroid hormone can elicit diabetes insipidus in completely hypophysectomized animals. Hence, lack of thyrotrophic stimulation probably plays a part in the prevention of the development of polyuria after ablation of the entire hypophysis.[291]

The diuretic effect of exposure to *cold* appears to be abolished by hypophysectomy, in the rat.[291a]

In the intact organism, treatment with impure preparations of **anterior-lobe hormones** rarely causes any significant change in water balance until severe secondary changes occur, for instance, nephrosclerosis or adrenocortical hypertrophy. Then polyuria ensues due to renal damage.[292] Short term treatment with purified *corticotrophin* causes water retention in man.[293]

Among the **posterior-lobe hormones,** vasopressin plays an especially important rôle, because of its previously mentioned stimulating effects upon the reabsorption of water in the proximal convoluted tubules. A good deal of evidence has been adduced to show that *emotional strain* [294] *burns* [295] and *other types of severe stress,*[296] increase the secretion of vasopressin and that this humoral mechanism plays an important part in the genesis of oliguria during the shock phase.

The well-known diuretic effect of *cold* resembles water diuresis in many respects and in both these instances vasopressin exerts a pronounced antidiuretic action. This "constitutes suggestive evidence that cold-diuresis is controlled by the posterior pituitary gland".[297] Similarly the *"acceleratory polyuria"* (seen in rats placed in a centrifuge) is reversed or inhibited by posterior-pituitary extract.[298] A diminution of vasopressin secretion may thus occur during the polyuria of the stage of resistance, but the evidence for this later assumption is inconclusive.

[281] Lawson et al. B2080/45.
[282] Blalock and Beard 8726/32.
[283] Lawson et al. B2080/45.
[284] Selye et al. 38815/36.
[285] MacAllister and Thorn A33119/37.
[286] Hepler and Simonds A15174/38.
[287] Herbut 93650/46, Moon A33122/39.
[288] Brun et al. 93248/46.
[289] Selye and Bassett A32813/40, A33566/40.
[290] Selye and Bassett A32813/40, Winter and Selye 82219/42.
[291] Selye **94572/49.**
[291a] Stutinsky B46553/49.
[292] Selye **94572/49.**
[293] Hoffman et al. B23331/48, Prunty et al. B36504/48, Spies and Stone B45101/50.
[294] Verney B30123/46, B18117/47.
[295] Barac B26093/47.
[296] Brun et al. B19617/45.
[297] Bader et al. B32706/49, Eliot et al. B32737/49.
[298] Silvette and Britton B29985/48.

Adrenalectomy causes dehydration of the tissues, probably accompanied by a decrease in the extracellular and an increase in intracellular water. These derangements are readily corrected by pure mineralo-corticoids, gluco-corticoids or cortical extracts, but not by adrenaline.[299] The diuresis noted during the counter-shock phase of the A-R produced by various stressors is prevented by adrenalectomy in the rat. This was ascribed to the resulting elimination of the usual excess corticoid production during stress.[299a]

Adrenalectomy increases the edema-producing and antidiuretic effect of various systemic stressors during the stages of alarm and exhaustion; it inhibits the development of the inverse phenomena characteristic of the stage of resistance.[300] *Trauma and histamine* injections, for instance, cause much more pronounced water retention in adrenalectomized than in intact control rats. Suitable cortical-extract treatment improves diuresis and diminishes the edema tendency during the A-R. This beneficial action is especially obvious after adrenalectomy when the corticoid deficiency is maximal.[301] The diuretic action of parenterally administered *glucose* solutions is greatly diminished by adrenalectomy in the rat, but adrenal transplants restore it towards normal.[302]

Adrenaline tends to cause diuresis, due to constriction of the efferent glomerular vessels. It also counteracts the antidiuretic action of vasopressin.[303] In the dog toxic doses of adrenaline often cause edema of the heart with pericardial effusions.[304] In view of the hyperadrenalinemia of stress these effects must not be neglected.

The water retaining effect of **corticoids** runs roughly parallel with their ability to retain Na and Cl (cf. Adrenalectomy p. 191, and Corticoids pp. 192-195). Like other mineralo-corticoid actions, the effect upon water metabolism is largely dependent upon conditioning factors (e.g., length of treatment, condition of kidney, NaCl and water intake). Various corticoids, especially DCA, can cause pronounced diuresis both in experimental animals and in man. However, marked polyuria occurs only on a high *NaCl* intake and after prolonged treatment, at a time when histologic changes begin to appear in the proximal convoluted tubules. It is probable therefore that the diuretic action of mineralo-corticoids is secondary to their damaging effect upon that part of the nephron in which water reabsorption takes place. Although among the steroids so far examined DCA possesses the greatest diuretic effect, other mineralo-corticoids (e.g., desoxocortisone),[304a] cortical extracts [304b] and even gluco-corticoids (e.g., cortisone), can stimulate diuresis to some extent on very high Na-intakes.[304c]

After still more prolonged treatment, DCA may cause water retention, with generalized edema, especially in certain species such as the chick [305] but also in the rat,[306] dog, monkey [307] and in man.[308] This manifests itself by an increase in blood-volume with water accumulation in the pleura, pericardium, perito-

[299] Selye **94572/49.**
[299a] Birnie and Eversole B44553/49.
[300] Barac B25621/47, Selye 35935/ND.
[301] Howlett and Browne 77132/40.
[302] Wyman and Tum Suden A55093/42.
[303] Verney B30123/46, B18117/47.
[304] Scholz B28087/45.
[304a] Selye B43385/50.
[304b] Birnie and Eversole B44553/49.
[304c] Selye 35935/ND.
[305] Selye A55847/42, A56426/43, Selye and Stone A56585/43.
[306] Green et al. B29398/48, Selye and Friedman A33118/40, Skahen and Green B29995/48.
[307] Selye and Hall A56584/43, A56583/43.
[308] Bock and Meinrenken B40815/47, Bricaire et al. **B32043/48,** Gülzow B29425/48, Sarradon B33935/47, Selye **94572/49.**

neum, subcutaneous tissue, brain and, to a lesser extent, in other tissues. At the same time, the body weight rises considerably due to water retention, but as a result of a sustained increase in water turnover the polyuria may continue. The pathogenesis of the edema is not yet fully understood; in part it is secondary to the renal changes, disturbances in osmotic pressure and increased capillary permeability. The rise in blood-volume induced by DCA (e.g., in the rat) may well play a rôle in the pathogenesis of the hypertension caused by this mineralo-corticoid.[308a]

Even brief treatment with corticoids may cause some water retention. This has been observed in man not only with DCA, but also with cortisone [309] and 17-hydroxy-corticosterone (Kendall's cpd. F).[310] Obviously here again we are dealing with conditioning factors which determine whether a corticoid will augment or diminish water retention. The nature of these factors is not known, but the NaCl reserves and the osmotic pressure of the body fluids are likely to be involved.

Various investigators examined the effect of corticoids in individuals exposed to diverse types of systemic stress. Thus, it was found that in patients with *renal diseases,*[311] *non tropical sprue* [312] as well as in simply *undernourished patients* [313] DCA tends to cause especially pronounced edema. Presumably here water retention by DCA is facilitated as a result of protein depletion. The elimination of water through perspiration in patients exposed to *heat* [314] and the decrease in plasma-volume during *ether anesthesia* [315] are allegedly also inhibited by corticoids.

Our investigations concerning the value of corticoid therapy in combatting dehydration during the A-R showed that gluco-corticoids and cortical extracts are particularly effective, while DCA is of comparatively little value in preventing the hemoconcentration during the shock phase after *traumatic interventions, partial hepatectomy,* etc.[316] The general tissue-edema formation, often observed in rats during an A-R (e.g., after histamine or trauma) can be counteracted by adequate doses of cortical extract.[317]

Curiously **progesterone** also stimulates diuresis, in intact (and especially in hypophysectomized) rats, although this steroid does not cause nephrosclerosis in mammals.[318]

The rôle of the **kidney,** as the main portal of water elimination, has been briefly touched upon above. A detailed discussion of the enormous pertinent literature is not within the scope of the present study. It should be mentioned, however, that under certain experimental conditions, an A-R (produced by cold, muscular exercise, trauma, or histamine administration) counteracts the formation of pleural transudates and lung edema even in the *absence of the kidneys.* This was shown in experiments in which completely nephrectomized rats were intravenously injected with 1% NaCl solution in amounts which normally always cause death from lung edema and pleural water accumulation.[319] These

[308a] Braun-Menéndez and Martinez B46379/49.
[309] Perera et al. B36595/49
[310] Fourman et al. B39685/49.
[311] Luft and Sjögren B39101/49.
[312] Kraft A72513/42.
[313] Decourt and Bastin B26874/42, Gülzow B29425/48.
[314] Schlegel A56984/41.
[315] McAllister and Thorn A33119/37.
[316] Selye and Dosne A30702/40, Selye et al. A32768/40.
[317] Howlett and Browne 77132/40.
[318] Selye and Bassett A32813/40, Winter A36510/42.
[319] Selye A8050/38.

observations indicate that the effect of the A-R upon water metabolism is not merely secondary to changes in renal function.

Experimental *perinephritis* increases the extracellular fluid- and blood-volume in the rat. Part of the pressor effect of this intervention may depend upon these changes.[319a]

Renal hormones can influence water metabolism in various ways. Experiments with the "endocrine kidney" lend themselves particularly well to this type of study, since here urine formation is completely abolished in one kidney. In this respect a rat bearing an "endocrine kidney" corresponds to one in which a unilateral nephrectomy has been performed. In the rat, removal of one kidney does not significantly influence diuresis, or any other aspect of water metabolism, because the safety margin of the remaining kidney is adequate to compensate for this degree of functional loss. Conversely, the bearer of an "endocrine kidney" develops pronounced diuresis, simultaneously with nephrosclerotic changes in the contralateral organ. These lesions resemble those produced by DCA. We may therefore surmise that the diabetes-insipidus-like polyuria produced by the "endocrine kidney", is due to a derangement in the reabsorption capacity of the tubules similar to that caused by DCA overdosage. The rise in glomerular filtration pressure, caused by the hypertensive effect of the "endocrine kidney", presumably also plays a rôle. It is noteworthy that unlike the diuresis induced by DCA, that elicited by the "endocrine kidney" is not significantly augmented by NaCl administration.[320]

Injection of *renin* causes marked polyuria in the rabbit; allegedly due to inhibition of water reabsorption in the convoluted tubules.[321]

Nervous and emotional factors can also significantly influence the water balance during the G-A-S. The relevant literature has already been discussed above. Let us merely add a few pertinent facts.

After section of the supraoptico-hypophyseal tracts, a greatly reduced amount of antidiuretic substance is released from the neuro-hypophysis of the dog during emotional stress, as shown by an almost complete abolition of the usual "slow type" of inhibition of water diuresis.[322]

Normally the diuretic effect of orally administered water is greatly delayed by exposure to *heat.* In the dog this delay is abolished by transection of the pituitary stalk. Hence it has been concluded that a discharge of vasopressin is involved in this adaptive response to heat.[323]

Conversely the antidiuretic effect of *burns* is largely independent of the hypophysis since it remains obvious after decapitation, even in dogs whose blood-pressure is maintained at a normal level. Here the response is ascribed to stimuli reaching the kidneys directly through the renal nerves.[324] Although the gross pathology (gastrointestinal ulcers, subendocardial hemorrhages, etc.) was the same in a series of observations on burned intact and burned "spinal" cats, the latter developed less severe hemoconcentration. It was concluded that: "filtration of fluid into the burned skin is apparently decreased by functional deafferentation".[325]

In relation with the pathogenesis of hormonal hypertension it is interesting that partial **pancreatectomy,** as well as **high-protein diets,** which notoriously

[319a] Braun-Menéndez and Martinez B46379/49.
[320] Selye B1433/48.
[321] Brandt and Gruhn B23361/48.
[322] O'Connor B36165/46.
[323] Bonvalet et al. B36580/48.
[324] Barac B23975/48.
[325] Kabat and Hedin 83643/42.

sensitize the rat to vasopressor and hyalinosis producing stimuli, greatly augment the blood-volume.[325a]

Many **other factors** are capable of influencing the water balance during the G-A-S. Several of these have been discussed in connection with the various stressors affecting water exchange during this syndrome. Thus, it became apparent that a decreased *colloid osmotic pressure* of the blood (due to protein catabolism), increased *capillary permeability*, interference with *renal function* (due to toxic or humoral agents affecting the kidney and to a fall in the filtration pressure) play important rôles in this respect. It may be added that the prevention of *fluid loss* in the directly damaged tissue, for instance by the application of *pressure bandages* or plasters to burned areas, decreases hemoconcentration both in animals [326] and in man.[327] This procedure has even been recommended for the prophylaxis of shock, although its practical efficacy is still the subject of debate.

[325a] Braun-Menéndez and Martinez B46379/49.

[326] Cameron et al. B26839/45.

[327] Rossiter B26840/43.

HORMONES AND HORMONE-LIKE SUBSTANCES

In the present section we shall limit our discussion largely to observations in which derangements in hormone metabolism during the G-A-S, were studied by actual hormone determinations (bioassays, chemical estimations) in the body-fluids and tissues. For additional pertinent findings, the reader is referred to other sections of this book where the more indirect relevant data are surveyed, for instance: morphologic changes in endocrine glands, renal and cardiovascular lesions suggestive of excessive hormone production, etc.

Conjointly with the hormone-content of tissues and body-fluids we also propose to include concise statements concerning the behavior of some hormone-like, pharmacodynamically active metabolites (e.g., histamine, acetylcholine, "Frühgift", "Spätgift") whose possible participation in the G-A-S should be considered.

A critical summary of this subject is attempted in the section concerned with the theoretic interpretation of the metabolic changes which occur during the G-A-S.

Anterior-pituitary Hormones.

It has been claimed that, in the rat, the **thyrotrophin**-content of the serum and urine increases upon exposure to *cold*.[1] Since cold has a rather specific influence upon the thyroid, this response is not necessarily characteristic of the G-A-S.

The elimination of **gonadotrophin** in the urine of *burned* patients remained within normal limits during the first twenty days, according to one group of investigators.[2] This is surprising in view of the well-known gonad-atrophy-producing effect of systemic stress (cf. gonads).

The cachexia caused by *carcinomatosis* considerably diminishes gonadotrophin excretion in man.[3] The same is true of anorexia nervosa.[3a]

The gonadotrophin content of the hypophysis was found to be unchanged [4] or even elevated [5] in rats whose ovaries became atrophic as a result of *starvation*. This was ascribed to a failure of hormone-discharge.

The **luteotrophin** (prolactin) content of the anterior-pituitary is greatly reduced by starvation in the rat.[6]

The usual pure **ACTH** preparations now on the market are homogeneous proteins of small molecular weight,[6a] but it has been possible to prepare a corticotrophic material of even greater potency with the characteristics of the still smaller polypeptides; this is generally designated as ACTP.[6b]

The **corticotrophin**-content of the blood allegedly rises in intact, but not in hypophysectomized rats during an A-R produced by *trauma*.[7] In clinical

[1] Brolin 91168/45.
[2] Glendenning et al. 84678/44.
[3] Segaloff and Coppedge B33436/49.
[3a] Berkman et al. B46014/47.
[4] Meites and Reed B27700/49.
[5] Maddock and Heller B17565/47, Rinaldini B36690/49
[6] Meites and Reed B27700/49.
[6a] Selye **94572/49.**
[6b] Morris and Morris **B46149/50.**

hypertension the corticotrophin-content of the serum has also been reported to be frequently above normal.[8] All these data are in accordance with current concepts concerning the hormonal mechanism of the G-A-S, but since the biossay-methods used were not entirely specific, further data would be desirable. Authors who employed more reliable assay techniques failed to detect significant amounts of ACTH in the urine of normal or diseased persons; [8a] indeed even after the intravenous administration of large amounts of ACTH, the hormone rapidly disappeared from the blood and only traces could be recovered from the urine.[8b] Both *trauma* and *burns* decrease the corticotrophin-content of the hypophysis due to their stressor action. *Adrenalectomy* is even more effective in this respect.[9]

Posterior-pituitary Hormones.

There is no evidence that **oxytocin** participates in the G-A-S, but **vasopressin,** currently assumed to be identical with the anti-diuretic hormone,[10] appears to play a rôle.

The release of anti-diuretic hormones, under the influence of *emotional stimuli* in the dog,[11] has already been mentioned. This response is almost completely abolished by severance of the supraoptico-hypophyseal tract, an operation which causes atrophy of the posterior-hypophysis.[12] Conversely, stimulation of the neurohypophysis of conscious rabbits by the "remote control" method, causes an elimination of antidiuretic hormone through the urine.[13]

It may be relevant that, after *hemorrhage,* the antidiuretic potency of the urine was claimed to rise especially in patients who fainted.[14] Significantly, the manifestations of vasopressin-overdosage (pallor, nausea, desire to defecate, headache) strikingly resemble those of subjects who faint after venesection.[15]

The antidiuretic potency of the urine increases in the dog after *burns.*[16] It is not known whether the responsible urinary product is in any way related to the vasoconstrictor substance which appears in the blood after trauma, hemorrhage and burns,[17] although this possibility has been considered.[18]

Observations on normal man in whom circulatory collapse was produced on a tilt-table, lead to the conclusion that probably post-syncopal oliguria is due to an increased secretion of the antidiuretic posterior-pituitary hormone.[18a]

All these observations support the often suspected participation of the posterior-pituitary in the vasomotor phenomena of the A-R.

In connection with the concept of the diseases of adaptation, let us mention that patients suffering from *cardiac decompensation* (hypertensive, rheumatic, arteriosclerotic) often eliminate considerable amounts of antidiuretic-material in the urine. However, the characteristics of this principle differ from those of commercial pituitrin.[19]

[7] Ungar 85462/44, B1173/45.
[8] Miller de Paiva B18845/47, Sievert A99491/38.
[8a] Locke et al. B43455/49.
[8b] Sayers et al. B37710/49.
[9] Cheng B35910/49, Cheng et al. B32722/49, Sayers and Cheng B31736/49.
[10] Selye **94572/49.**
[11] Verney B30123/46, B18117/47.
[12] O'Connor B36165/46.
[13] Harris B36557/48.
[14] Taylor and Noble B23337/48, B32837/49.
[15] Sunahara et al. B32835/49.
[16] Barac B24074/46, B24080/46, Brull B23116/47, Humblet and Barac B24102/46.
[17] Abel and Page 84395/43, Page A59852/43.
[18] Humblet and Barac B24102/46.
[18a] Brun et al. 93248/46.
[19] Bercu et al. B36360/49.

The blood of rats contains a chloruretic and antidiuretic substance whose plasma-concentration increases after *adrenalectomy.* Like vasopressin, this principle presumably stimulates renal reabsorption of water and, significantly, it disappears from the blood after *hypophysectomy.*[20]

DCA increases the output of antidiuretic material through the urine in rats. Since NaCl exerts a similar action "the evocation of the anti-diuretic excretion factor by desoxycorticosterone would appear to be a consequence of the disturbance in fluid exchange".[20a] Perhaps lack of this compensatory reaction may explain the great increase in the diuretic effect of DCA after hypophysectomy. (Cf. p. 214.)

Adrenergic Hormones

That **adrenaline** is discharged from the adrenal-medulla during various types of systemic stress is too well known to deserve much discussion. It has been proven, by numerous bioassays and analytic determinations, that the adrenaline-concentration simultaneously falls in the medulla and rises in the serum, following emotions, burns, anoxia, cold, muscular fatigue, electronarcosis, insulin-overdosage and many other alarming stimuli.[21]

A discharge of **sympathin** (presumably a mixture of adrenaline and noradrenaline) [22] from adrenergic nerve-endings, has also been proven to accompany systemic stress. The increased pulse-rate of the denervated heart and the dilatation of the denervated iris in adrenalectomized animals, are but two examples of the many experiments by which such an extra-adrenal production of adrenergic substances was demonstrated after exposure to stressors.[23]

Nor-adrenaline-like activity is likewise detectable in the blood [23a] and presumably this also participates in the adrenergic response to stress.

It is especially pertinent to our problem that recently — using a highly sensitive fluorometric method — it could be shown that, after adrenalectomy, stress (pain, hemorrhage, muscular exertion) actually decreases the blood-adrenaline content of the rat. Indeed adrenalectomy alone suffices to cause a fall in the adrenaline-level of the blood. Both at rest, and after stress, DCA or cortical extracts restore the adrenalinemic curve after adrenalectomy. Presumably the extraadrenal sources of adrenergic substances suffice, even during emergencies, but their hormone production depends upon the action of corticoids.[23b]

An **adrenaline-like urinary compound** is normally excreted by the dog, but the claim that its elimination rises after trauma has not been confirmed.[24]

It has been asserted that some, not clearly identified, **sympathomimetic amines** may appear **in the heart** (*sympathin?*) and **brain** (*"encephalin"?*) as a result of postganglionic neurosecretion. Their relationship to stress, the blood-corticoid level and cardiovascular disease has been much discussed,[25] but the possibility of their identity with known pressor amines cannot be dismissed until these substances are chemically identified. (Cf. p. 230, 237.)

[20] Birnie et al. B31722/49.
[20a] Skahen and Green B29995/48.
[21] Bacq 99225/47, Cannon B14905/39, Diethelm B29023/45, Jourdan et al. B39545/48, Milhorat and Diethelm 98560/47, Morin B36539/48, Selye **94572/49,** Tietz and Van Harreveld B27706/49.
[22] Bacq and Fischer B23245/47.
[23] Bacq **99225/47,** Cannon **B14905/39,** Selye **94572/49.**
[23a] Page et al. B45617/49.
[23b] Lehmann and Kinzius B46548/49, B46549/49, Michaelis and Straub B46550/49.
[24] Konzett and Verney B38184/48.
[25] Raab A36730/41, 98574/47, B23181/48.

Corticoids

There is considerable evidence showing that the elimination of **corticoids in the urine** rises far above the normal level (both in experimental animals and in man), during the A-R. That this can occur even under the influence of physiologic stressors, has first been suggested by observations on race horses, whose urine contained considerable quantities of corticoid material following intense muscular exercise.[26] Numerous subsequent investigators, using a variety of bioassay (cold-resistance-test, glycogen-deposition-test) and chemical (neutral-reducing-lipid-, formaldehydogenic-material-determination, infra-red-spectrophotometry, etc.) techniques, definitely established that this increased corticoid-elimination is really *characteristic* of the systemic response to stressors. Pronounced rises — sometimes up to ten times the normal value — were found in man exposed to a variety of alarming stimuli (e.g., surgical interventions, crush injuries, acute infections, anoxia, burns, emotional stimuli, intense muscular exercise).[27] Even "the adrenal of the newborn is capable of responding to trauma with an increased output of gluco-corticoids".[27a]

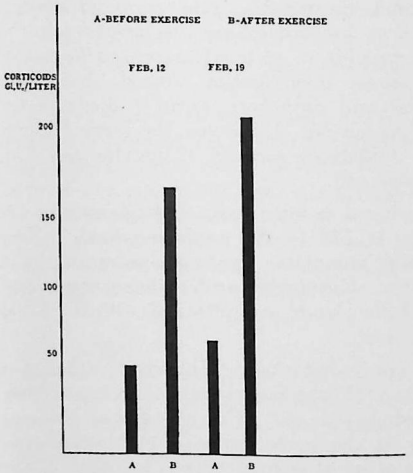
These observations have subsequently been confirmed, with improved techniques, using many alarming stimuli. Thus it was shown that urinary corticoid-excretion is augmented by *ionizing radiations*,[28] *trauma*,[29] *burns*,[29a] *muscular work*,[30] *mercurial intoxication* [30a] and *infections* [31] in man and during *potassium-intoxication* [32] in the rat.

Increased corticoid-formation also occurs in men as a response to the requirement to conserve *sodium* during acclimatization to humid heat.[32a] From indirect evidence it was concluded, furthermore, that in man "a very low-sodium intake is met by increased adrenal cortical activity of a desoxy-corticosterone-like hormone, accompanied by increase in the activity of adrenal protein catabolic hormone". The authors conclude that "the work of Selye on the general adaptation syndrome suggests that our observations might simply cover an adaptation to sodium restriction as the stress, but this would only further describe rather than explain our results".[32b]

Even the comparatively slight stress of normal daily activities appears to cause a rise in corticoid-elimination, as judged by the *diurnal* rhythm of the latter. Most subjects show minimal corticoid-excretion during sleep and maximal output after the initiation of the day's activities in the morning; the evening values tend to be intermediate.[33] 17-KS-elimination roughly parallels this excretion-curve (see below).

[26] Selye and Dosne A33299/40.
[27] Browne B352/43, Browne et al. B347/45, Cope B348/45, Hartman and Brownell **B36274/49**, Heard et al. 93691/46, Pincus 98426/47, B37780/49, Robinson **B46201/49**, Shipley et al. 93284/46, Sprechler **B32336/49**, Talbot et al. B4496/46, 98831/47, Tompsett and Oastler B19057/47, Tronchetti **B38477/49**, Venning and Browne 85883/45, B4498/46, 98463/47, B2216/47, Venning and Kazmin 93048/46, Venning et al. 84677/44, Weil and Browne 76887/39, 77788/40.
[27a] Venning et al. B43546/49.
[28] Schwartz B33435/49.
[29] Browne et al. B46960/50, Mason B46740/50, Shipley and Dorfman B29086/45, Venning and Browne **B37779/49**.
[29a] Browne et al. B46960/50.
[30] Venning and Browne B37779/49.
[30a] Richet et al. B36282/49.
[31] Ceresa and Cravetto B38764/49. Shipley and Dorfman B29086/45.
[32] Jarpa and Croxatto B33757/48.
[32a] Conn B39549/49.
[32b] Leaf and Couter B39085/49.
[33] Pincus 98426/47, Pincus et al. B25094/48, Romanoff et al. B37718/49.

In one such study, bioassays on previously healthy and chronically ill patients were compared. It was found that *in well-nourished* individuals the urinary elimination of gluco-corticoids rises very markedly following a sudden systemic stress (trauma, bone fracture, burn, etc.) from the normal value of 60, to about 400 gluco-corticoid units per 24 hours (1 unit is equivalent in biologic activity to 1 γ of cortisone). On the other hand, *in chronically ill, undernourished* individuals subjected to similar stresses, the rise in gluco-corticoid-elimination is slight or absent.[34] In healthy persons a sudden systemic stress also causes a more pronounced catabolic response than in the chronically ill; hence the above difference in corticoid-elimination may be due to the well-known stimulating effect of catabolism upon corticotrophin-production. It is possible, however, that the condition of the chronically ill patients corresponds to the stage of resistance in which corticoid-secretion is probably less intense than during the stage of alarm. Unfortunately, up to now, no systematic investigations have been published concerning the urinary elimination of corticoids throughout the three stages of the G-A-S. Indirect evidence (morphologic studies of adrenal structure, quantitative determinations of corticoid-requirements) suggests, however, that the greatest discharge of corticoids from the adrenal occurs during the A-R, although overproduction continues throughout the stage of resistance. Presumably, in the stage of exhaustion, the adrenal function becomes deficient when the structure of the gland breaks down.



Effect of strenuous exercise on the excretion of corticoids in a group of 14 army recruits.
(After E.-H. Venning and V. Kazmin: Endocrinology 39, 131, 1946.)

It has been shown by observations in man that purified *corticotrophin* greatly augments the renal elimination of corticoids.[35] Since, conversely, *destruction of the pituitary* (e.g., Simmond's disease) diminishes corticoid-excretion, such hormone-determinations confirm (the now generally accepted view) that the stimulation of cortical function is mediated by the hypophysis.[36]

Under the influence of ACTH, "compound F" appears in the urine of patients with rheumatoid arthritis. Even after *cortisone* treatment only traces of this hormone are excreted unchanged. There is some evidence that the 11-ketone is normally reduced to a hydroxyl group.[36a]

As judged by colorimetric determinations, the **corticoid-content of the blood and adrenals** of rats kept

[34] Dobriner et al. B46963/50, Venning and Browne B2216/47, B37779/49.
[35] Dobriner et al. B46963/50, Forsham et al. B17987/48, Hoffman et al. B23331/48, Sayers et al. B37710/49, Sprague et al. B46430/50, Talbot et al. B46954/50, Venning et al. B23339/48.
[36] Selye **94572/49**.
[36a] Mason B46740/50, B46964/50.

in the *cold* (6°C) is also above normal; the rise in the blood beginning to be demonstrable after 19 hours, in the adrenals 70 hours, after the initiation of treatment.[37]

Bioassays (cold-resistance-test) performed on adrenal-vein-blood suggested that one suprarenal of a dog produces as much corticoid hormone per minute as can be extracted from 13.5 gm. of adrenal tissue, "since the adrenal weighed 0.72 gm. it had secreted, during one minute, 19 times as much as could have been extracted from it".[38] Essentially similar findings were obtained with a chemical test for corticoids.[39] Since the operative intervention incident to the insertion of the venous cannula represents a stress, it is probable that such amounts are greatly in excess of the normal, basal corticoid-production.

Comparable experiments on unanesthetized normal dogs (in which adrenal-vein-blood was obtained with the angiostomy-method) were required to evaluate the influence of stress in the above experiments. These revealed that corticoid-secretion is augmented by a *variety of alarming stimuli* (e.g., formaldehyde, trauma, insulin). An attempt was made to examine whether adrenergic blocking agents, such as dibenamine, would prevent this response, since it had previously been suggested that corticotrophin-production during the A-R depends upon adrenergic stimuli. However, it was found that "dibenamine itself is an alarming stimulus".[40]

It will be remembered that during the A-R there is a sudden discharge of stored lipids and corticoids from the adrenal cortex; during the stage of resistance, however, lipid-deposition, and presumably also corticoid-storage, appears to surpass the rate at which these substances are discharged into the blood. Thus storage or discharge are possible in spite of increased hormone-secretion. This could explain why some investigators found that acute stressors, such as *trauma,*[41] or *tetanus-* and *diphtheria-toxin,*[42] diminish the corticoid-content of the adrenals in the guinea-pig. However, the latter findings must be interpreted with caution since a bioassay method of questionable specificity (fish-melanophore-test) was employed.

In cattle-, dog- or sheep-adrenals perfused in vitro, corticoid-production can be considerably augmented by adding *ACTH* to the perfusion-fluid.[43] This observation confirms that corticotrophin stimulates corticoid-secretion by a direct, peripheral action upon the cortex. Curiously, under these conditions, some corticoid-secretion persists even if the glands are perfused with the blood of a *hypophysectomized* donor.[44]

Using this same technique, it was concluded that: "Intravenous infusion of *adrenaline* causes a strong, immediate and long-lasting stimulation of suprarenal cortical activity in the eviscerated dog or cat. The effect was obtained with doses of adrenaline which occur in the body under physiological conditions. The increased yield was of the order of several times the basal output. The action is independent of blood-pressure or blood-flow and "is not mediated by hormones from the pituitary".[45] This latter conclusion was arrived at on the basis of a single experiment on a decapitated dog and being contrary to

[37] Hemphill and Reiss B1406/47.
[38] Vogt B17483/47.
[39] Corcoran and Page B35555/48.
[40] Paschkis et al. B32805/49, B35916/49.
[41] Lambret et al. 96167/41.
[42] Giroud et al. 93596/41.
[43] Hechter B32765/49, Vogt B32938/49.
[44] Vogt B32938/49.
[45] Vogt B897/44.

all we know about the mechanism of corticoid-secretion, it requires confirmation.

The rise in corticoid-secretion was confirmed, by chemical determination, in the adrenal-vein-blood obtained by cannulation before and after adrenaline-injection.[46] On the other hand, "in vitro" observations failed to reveal any release of corticoids into the adrenal vein after intra-arterial injection of adrenaline.[47]

In support of the concept that adrenaline could stimulate corticoid-production by a direct action upon the adrenals, it was mentioned that: "electrical-stimulation of the left *splanchnics,* provided reflex activity of the nerves on both sides had been avoided, caused an increase in cortical secretion in half of the experiments".[48] This claim likewise awaits confirmation.

Using the perfused adrenal as a test-object, it has also been noted that intra-arterial injection of *acetylcholine* increases corticoid-production. Adrenaline-liberation by the suprarenal-medulla is dependent upon cholinergic stimulation; hence this observation was interpreted as further evidence suggesting that adrenaline can directly stimulate the cortex to produce corticoids.[49]

Among many other metabolites tested only *creatine-phosphate, ATP* and *potassium* proved capable of increasing the corticoid-production of the isolated, perfused adrenal.[50] Further work will be necessary, however, to determine whether these substances can exert a direct corticotrophic action (that is one not mediated by the pituitary) under physiologic conditions.

Sweat induced by muscular exercise or heat also contains a significant amount of corticoid material as judged by chemical determinations (Heard-Sobel's method) in man.[51]

It must be kept in mind that most of the work mentioned in this section was done with bioassay methods based upon gluco-corticoid activity (e.g., glycogen-deposition) or upon "corticoid activity in general" (e.g., cold-resistance) without any possibility of distinguishing between the various types of corticoids. The chemical determinations also fail to make this distinction. Studies concerned specifically with the excretion of mineralo-corticoids during the G-A-S would be very informative and could be performed with the radio-sodium [52] or radio-potassium [53] technique.

17-Ketosteroids

The 17-KS-elimination through the urine is **characteristically** increased during the first one or two days following exposure to systemic stress, while upon continued exposure, the values fall considerably below normal. In one such study, the average initial values in males were 12-13 mg./24 hrs. and rose to 18 mg./24 hrs, one day after exposure; they reached approximately normal values following two or three days and declined to as low as 4-8 mg./24 hrs. after three weeks of exposure to various stressors.[54] In normal females, the initial increase was usually absent, but a fall from a pre-exposure average

[46] Corcoran and Page B35555/48.
[47] Hechter B32765/49.
[48] Vogt B897/44.
[49] Vogt B897/44.
[50] Vogt B32938/49.
[51] Nichols and Miller B28608/48.
[52] Dorfman et al. B4910/47.
[53] Dorfman B34764/49.
[54] Forbes B358/43.

of 8 mg./24 hrs, to about 4 mg./24 hrs, occurred within 5 to 6 days of stress. Interestingly, the initial peak was frequently very marked in hirsute women [55] Essentially similar observations have been made in patients following exposure to *trauma, infections, bacterial toxins, nervous and emotional stimuli, burns, etc.*[56]

Upon brief exposure to **cold** or heat no significant change in 17-KS excretion was observed in man,[56a] but here presumably the resulting stress situation was not sufficiently severe to elicit a marked G-A-S.

X-irradiation causes a marked increase followed by a relative decrease in 17-KS excretion, in patients with ankylosing spondylarthritis. In connection with the concept of the diseases of adaptation it is also noteworthy that normally, both male and female subjects suffering from this disease have a high urinary 17-KS titer.[57]

Studies on dogs exposed to x-irradiation revealed an initial rise with a secondary fall of urinary 17-KS elimination; it was pointed out that "this hormonal excretion pattern is observed in adaptation of the organism to stress as described by Selye".[57a]

Electro-shock is another stressor which elicits a characteristic G-A-S-type of 17-KS excretion-curve in man.[58]

In **psychotic** patients, the initial increase in 17-KS-excretion during stress (e.g., cold) is diminished or absent.[59] From these and other studies, it was concluded that "this failure of fundamental stress-mechanisms in psychotic patients is especially interesting since psychotics are persons who have broken under the stresses of daily life and have developed bizarre and socially inadequate behaviour-patterns to cope with their environment".[60]

It has been emphasized that (e.g., during **emotional stress**) the 17-KS-excretion-curves tend to run inversely parallel with the lymphocyte-count.[61]

The urine of men performing intense **muscular exercise** allegedly contains large amounts of a hitherto unidentified chromogenic steroid, which may be Δ^5-androstene-3(β),17(α)-diol.[62]

Drugs, having marked systemic stress-effects, likewise produce a characteristic 17-KS excretion pattern. Recent experiments in the rabbit have shown that *nitrogen-mustards* exert this effect simultaneously with other manifestations of the A-R. Previous exposure to another stressor (e.g., hemorrhage) inhibits this action. It was concluded that "this toxic drug thus acts as a stress eliciting the alarm-reaction and its effect is inhibited by another, previously applied, stress (intense bleeding)".[63] This was interpreted as an additional example of "crossed resistance", but of course it must be kept in mind that if these 17-KS represent the adrenal stores, they could obviously not be discharged into the urine twice in rapid succession.

[55] Forbes B358/43.
[56] Browne et al. B46960/50, Bryan and Ricketts 84665/44, del Castillo et al. 99086/47, Ceresa and Cravetto B38764/49, Forbes 83226/42, Freeman et al. 84664/44, Glendenning et al. 84678/44, Hoagland B4975/47, Hoagland et al. A95861/46, Stevenson et al. 84666/44, Tronchetti B38477/49, Venning and Browne B2216/47.
[56a] Stein et al. B37251/49.
[57] Davison et al. B30925/49.
[57a] Lawrence B39174/49, B43542/49.
[58] Hoagland et al. B34447/46.
[59] Freeman et al. 84664/44, Hoagland B4975/47.
[60] Hoagland B4975/47, Pincus **B37780/49.**
[61] Hoagland et al. A95861/46.
[62] Guterman and Kraus B32760/49.
[63] Heusghem et al. B31783/48.

A single observation in a patient with *sublimate* poisoning led to the suggestion that here again an increased 17-KS elimination is due to the A-R.[63a]

In Holland, under the influence of chronic **malnutrition** during the last World War, the average elimination of 17-KS fell considerably below normal.[64] A similar fall was noted among badly undernourished prisoners-of-war.[65] Observations on normal male and female subjects showed that starvation for 4 days can reduce 17-KS excretion by 50%.[66] Similar changes occur in anorexia nervosa.[66a]

An extensive series of investigations on 66 persons who went through some type of medical or surgical injury led to the conclusion that "...urinary 17-KS excretion usually rises for a brief period (one to three days) and almost always falls for a longer period which lasts until convalescence is achieved, when it gradually returns to normal. In *chronically ill* or *debilitated* individuals on the other hand, the initial level is subnormal and the response to injury usually small or absent. It is believed that these findings are further evidence that alterations in adrenal-cortical function are an integral part of the adaptation-syndrome of Selye and a link in our understanding of the part this syndrome plays in clinical medicine".[67] In patients who became cachectic due to carcinomatosis, 17-KS-elimination is usually low.[68] These findings recall the fact that corticoid-elimination is also subnormal in debilitated patients exposed to systemic stress (see above).

The **diurnal** variations in corticoid-excretion (see above) are accompanied by 17-KS-elimination curves of an essentially similar pattern.[69]

The rise in 17-KS-elimination during the A-R may be due to a mere discharge of stored steroids from the adrenal-cortex, or to an actual increase in their production. On the other hand, their decreased elimination during the stage of resistance suggests diminished testoid-production, both by the adrenal-cortex and (in the male) by the testis, as a result of the "shift in pituitary hormone production" elicited by chronic systemic stress.

Presumably **corticoid** production also declines during the stage of resistance, since these (e.g., cortisone) would likewise be partly eliminated as 17-KS.[69a]

It has been shown in man that not only **gonadotrophin** (LH) [70] but even pure **corticotrophin** increases the renal elimination of 17-KS [71] even in females,[72] and children. Since 17-KS may result during the metabolic degradation of corticoids, this does not prove that ACTH stimulates testoid secretion.

The literature concerning hormone-elimination in the various **"diseases of adaptation"** will be discussed in the sections specifically devoted to the latter. Let us merely mention here that Δ^9-etiocholenolone, a 17-KS rarely found in normal urine, is frequently excreted by patients suffering from cancer, hypertension or Cushing's disease.[73] It is too early to attempt an interpretation of this finding.

[63a] Richet et al. B36282/49.
[64] Dingemanse et al. 99081/46.
[65] Salter et al. B24286/46.
[66] Landau et al. B18637/48.
[66a] Berkman et al. B46014/47.
[67] Forbes et al. 98825/47.
[68] Segaloff and Coppedge B33436/49.
[69] Pincus 98426/47, Pincus et al. B25094/48.
[69a] Sprague et al. B46430/50.
[70] Selye **94572/49.**
[71] Hoffman et al. B23331/48, Luft et al. B45270/49, Sayers et al. B37710/49, Venning et al. B23339/48.
[72] Forsham et al. B17987/47.
[72a] Talbot et al. B46954/50.
[73] Dobriner B37852/48.

Renal Hormones and Related Substances

It is well known that interference with the renal circulation (e.g., by the Goldblatt-clamp) raises the production of renin by the kidney; consequently increased amounts of this enzyme appear in the blood.[74] Renin itself has no effect upon the blood-pressure, but it transforms hypertensinogen (an inert blood-globulin) into the intensely pressor compound hypertensin (see below). The chemical properties of renin suggest that it belongs to the glycoproteins.[75] In dogs with experimental renal hypertension it was noted that the blood-renin-concentration tends to return to normal after an initial rise.[75a] Since in such animals the hypertension nevertheless persists, some authors assume that a hypersensitivity to renin has developed; others believe that after the initial humoral phase the blood-pressure continues to be maintained at a high level, because secondarily a sympathetic, vasopressor mechanism is brought into play.[76] Several additional facts have come to light which make it unlikely that increased renin-production is the sole cause of renal hypertension,[77] but it must be remembered that the kidney probably produces other pressor substances as well as renin (cf. below).

Since the hypotension of the shock-phase also interferes with renal blood-supply, it is in agreement with current theory that *hemorrhage* increases the renin-concentration. This was shown to be the case not only in the blood coming directly from the kidney, but even in that of the systemic circulation. It was concluded that renal hormones participate in blood-pressure-homeostasis.[78] The renin content of the kidney-tissue itself is not demonstrably altered during hemorrhagic shock.[79]

Injection of *cobra venom* into the renal artery of the cat produces a renin discharge from the kidney (even after adrenalectomy and evisceration). Since the venom does not cause renal vasoconstriction it has been concluded that ischemia of the kidney is not a necessary prerequisite for renin secretion.[79a] Of course it is possible that the venom accomplished, by chemical means, those same alterations in the metabolism of the kidney which the constriction of the renal artery produces through a derangement in circulation.

Adrenalectomy does not prevent the rise in the blood-renin-concentration after hemorrhage, unless a *nephrectomy* is simultaneously performed.[80] This shows that the pressor substance is of renal origin and that its production is not necessarily dependent upon stimulation of renal incretion by the adrenal.

Adrenalectomy fails to influence the usual disappearance of renin from the contralateral kidney following unilateral clamping of the renal artery; however it accelerates the rate at which renin reappears in this kidney.[81]

In normal dogs, the renin-content of the kidney is significantly diminished by *DCA*-treatment. In renal hypertensive dogs DCA diminishes the renin-content of the constricted kidney, but fails to influence the low-renin-concentration in the contralateral organ.[82] This also suggests that mineralocorticoids can influence the renal pressor mechanism.

[74] Dexter **91416/46**, Goldblatt **B29301/48.**
[75] Marshall and Wakerlin B32788/49.
[75a] Taquini and Fasciolo B46006/47.
[76] Ogden B29650/47.
[77] Mylon et al. **B19299/48.**
[78] Dexter **91416/46**, Dexter et al. 84409/43, Hamilton and Collins B26983/41, A55526/42, Houssay et al. B26984/42, Huidobro and Braun-Menendez A55775/42, Sapirstein et al. A37036/41.
[79] Wakerlin and Chobot A35072/39.
[79a] Reid and Jenkins B44156/48.
[80] Collins and Hamilton 81946/42.
[81] Bessinger and Wakerlin B33092/48.

After unilateral *renal-artery-constriction*, renin soon disappears from the contralateral kidney of dogs, but curiously it reappears rapidly if the animals contract an infection (e.g., distemper, pneumonia),[83] or if their adrenals are removed.[84]

If renin is injected intravenously in doses sufficient to raise the blood-pressure of a dog, its concentration in the systemic blood is demonstrably increased. Yet, using the same bioassay technique, no increase in blood-renin is noted in patients with *essential hypertension*. On the other hand, in *acute hypertension* (e.g., glomerulonephritis or eclampsia) the systemic blood does contain a definitely high renin-concentration.[85] Perhaps in man also only the initial acute stage of renal hypertension is due to renin, while later, other renal-pressor-substances or sympathetic stimuli take over.

The **hypertensinogen** (or "renin-substrate") content of the blood diminishes during *hemorrhagic* shock.[86] This may be preceded by a sharp rise.[87] The diminution has been ascribed to the simultaneously increased renin-formation, which must result in a greater utilization of its substrate. The development of refractoriness ("tachyphylaxis") to renin, following severe hemorrhagic hypotension,[88] also finds its explanation in this interaction since renin cannot act in the absence of hypertensinogen.[89]

Corticotrophin increases the hypertensinogen-content of the peripheral blood in the intact, but not in the adrenalectomized dog.[90] Here again there is evidence of an adrenal regulation of the renin-hypertensin mechanism.

The **hypertensin** content of the systemic blood rises in dogs with *experimental renal hypertension*.[90a] A similar rise occurs in dogs subjected to *hemorrhage*. This also agrees with the concept that increased amounts of renin (while depleting hypertensinogen) form an excess of hypertensin from this precursor.[91] It must be admitted, however, that other experiments failed to reveal vasoconstrictor properties (rabbit's ear preparation) in the renal-vein-blood of dogs after hemorrhage or *carotid-sinus-stimulation*. Hence, it is still debated whether the renal pressor-mechanism is of physiologic significance.[92]

Hypertensinase is an enzyme which destroys hypertensin. It is present in various tissues; the intestine, kidney, pancreas, spleen and erythrocytes (enumerated here in decreasing order of activity) are the richest, while the plasma is very poor in this enzyme.[93] Its possible rôle during the G-A-S has not been studied.

The enzymatic production of hypertensin-like vasopressor substances from proteins is not entirely specific. It has been shown[94] that, upon digestion with pepsin, both hypertensinogen, and even several other proteins (egg albumen, washed fibrin, hypertensinogen-free beef serum, etc.), are rapidly

[82] Bessinger and Wakerlin B33092/48.
[83] Wakerlin et al. B27070/48, B32844/49.
[84] Bessinger and Wakerlin B33092/49.
[85] Haynes et al. 99996/47.
[86] Dexter 91416/46, Dexter et al. 84409/43, Huidobro and Braun-Menendez A55775/42, Sapirstein et al. A37036/41.
[87] Rau B36677/49.
[88] Hamilton and Collins A55526/42.
[89] Collins and Hamilton A71604/44.
[90] Haynes et al. B32764/49.
[90a] Gollan et al. B39302/48.
[91] Collins and Hamilton 81946/42. A71604/44.
[92] De Landsheere B24540/47.
[93] Dexter **91416/46.**
[94] Croxatto and Croxatto 83448/41. A37520/42.

transformed into an intensely vasoconstrictor and hypertensive substance: **pepsitensin.** These observations have been confirmed and extended by numerous subsequent studies.[95] Some investigators claim to have detected minor differences in the chemical behaviour (especially the resistance to the hypertensinase of erythrocytes) of hypertensin and pepsitensin,[96] but these are so slight that they may well be due to accompanying impurities or some slight modification of the chemical structure. Hence, it is now generally agreed that pepsitensin is essentially similar to, if not identical with, hypertensin.

Several investigators reported pressor substances in **enzymatic digests of kidney-tissue.** There is some reason to believe that these vasopressors were amines, perhaps iso-amylamine, tyramine, phenylethylamine, hydroxytyramine or mixtures of such compounds.[97]

Since **tyramine** possesses a definite pressor action and is chemically related to adrenaline, it has been suggested that this amine may play a rôle in the pathogenesis of hypertension. Chronic treatment with tyramine may cause arterial and renal hyalinosis.[98] The possibility of a transformation into more active pressor amines (e.g., hydroxytyramine, nor-adrenaline or adrenaline) and of mutual potentiation between tyramine and related adrenaline-like compounds cannot be excluded (cf. below). It is especially interesting that tyramine (and probably other vasopressors) can be formed from the amino-acid tyrosine in vitro, upon incubation of renal tissue or renal extracts.[99] Indeed, it has been claimed that the tyramine so formed can subsequently be oxidized to adrenaline by adrenal tissue.[100] However, the claim that the blood-tyramine concentration is increased in experimental and clinical hypertension has not been uniformly confirmed.[101] The participation of this amine in the genesis of the G-A-S or the diseases of adaptation remains to be proven.

It is especially noteworthy that **allylamine** has been identified as a toxic substance present in the tissues of animals dying from experimental paratyphoid infection. Since allylamine given intravenously greatly increases capillary permeability it has been claimed that this may be one of the metabolites involved in the genesis of "serous inflammation".[102] (Cf. also effect of this compound under: G-A-S → Vessels.)

Upon anaerobic incubation of kidney-extracts with the amino-acid dihydroxyphenylalanine (DOPA), **hydroxytyramine** is formed in vitro, due to the action of a decarboxylase.[103] Under aerobic conditions however, hydroxytyramine is rapidly oxidized to dihydroxyphenylacetaldehyde by the action of an amine-oxidase. The amine has a pressor action (which, like that of the

[95] Alonso B27011/42.
Alonso et al. A54809/43, 92406/42-43,
Braun-Menendez et al. A33948/40,
Croxatto and Rioseco B17476/44,
B17477/45, B4952/45,
Helmer and Page A37746/42.
Weber et al. B27018/42.
[96] Braun-Menendez et al. A33948/40,
A64898/43,
Dexter **91416/46,**
Dexter et al. B981/45,
Plentl and Page 88266/44.
[97] Drill B27013/42,
Hartwich and Hessel B27014/32,
Victor et al. B27017/40,
Williams and Crossman A16861/38,
Williams et al. A14679/38.
[98] Duff et al. A30190/39,
Enger and Lampas B27049/40.
[99] Holtz A9214/37, B27015/38,
Holtz and Janisch B27016/37,
Schuler and Wiedeman 54170/35,
Schuler et al. 38745/36,
Werle and Mennicken B27019/37.
[100] Schuler and Wiedeman 54170/35.
[101] Dexter **91416/46,**
Loeper et al. **B19724/44.**
[102] Eppinger **B37085/49,**
Eppinger et al. B26941/34.
[103] Holtz et al. 74003/38.

related adrenaline, is increased by cocaine), while the aldehyde has a depressor action.[104] These observations have subsequently been confirmed and it was shown, furthermore, that similar reactions occur if whole kidneys are perfused with DOPA. Indeed it appears that renal ischemia increases the formation of pressor substances from DOPA, even in vitro.[105] Perhaps decarboxylation of DOPA is a type of reaction which can occur in ischemic kidney and thus may lead to the production of pressor amines. Even in vivo, intravenous injection of DOPA produces a marked blood-pressure-rise in renal-hypertensive cats [106] and hypertensive patients,[107] but little or no change in normal individuals. This was again taken to suggest that ischemic kidney-tissue is more than normally active in transforming DOPA into pressor substances. Yet, some workers [108] obtained essentially similar pressor responses from DOPA in normal and hypertensive rats, indeed complete nephrectomy enhanced the effect. Hence, apparently, the transformation can also occur outside the kidney and perhaps, during uremia, the pressor effect is increased by the accumulation of protein-catabolites (competing substrates ?).

Interestingly, *adrenalectomy* abolished the pressor action of DOPA while *DCA* restored it, even in the absence of the adrenals.[109]

Extrarenal formation of **pressor tissue-degradation-products** has been postulated to explain the occasional development of hypertension after complete nephrectomy, as well as the greater degree of hypertension occurring in the nephrectomized partner of a pair of parabiotic rats, in which only one twin is deprived of its kidneys.[110] However, here the possible rôle of increased blood-volume must not be disregarded. It has also been possible to isolate extrarenal **pressor substances from putrified muscle-tissue.**[111]

Certain protein-catabolites, which in themselves have little or no vasopressor effect, can perhaps be enzymatically activated by various tissues, though especially readily by ischemic kidney-cells. The blood-concentration in such catabolites may rise as a result of systemic stress, multiple thromboses (cf. serotonin and "Spätgift", below), or uremia. The actual rise in blood-pressure may then depend upon: (1) the availability of potentially vasopressor protein-catabolites (mainly extrarenal in origin), (2) their enzymatic activation (mainly in ischemic kidney-tissue) and (3) potentiation by adrenaline or allied compounds. The latter could result for instance through substrate-competition. In this phenomenon, enzymes, which can destroy the active vasopressors, are largely monopolized by pharmacologically less active, but structurally related, chemical analogues.

About forty years ago the term **urohypertensin** had been proposed [111a] to designate an ether-soluble pressor substance found in urine. However, both isoamylamine [112] and nicotine [113] can be isolated from human urine and since these are vasopressor compounds, they were held responsible at least for part of the "urohypertensin effect".

[104] Holtz et al. 74003/38.
[105] Bing 79776/41,
Bing and Zucker A35785/41,
Blaschko B27012/42,
Croxatto and Croxatto B27025/41.
[106] Oster and Sorkin A55995/42.
[107] Bing and Zucker A35785/41, 81420/41.
[108] Page and Reed B905/45,
Schroeder 83491/42.
[109] Page and Reed B905/45.
[110] Grollman 98433/47, B4352/47,
Halpert and Grollman B4222/47.
[111] Abelous et al. 37856/06,
Barger and Walpole 50205/09.
[111a] Abelous and Bardier 37777/08,
37778/09.
[112] Bain B27031/09, B27032/14.
v. Euler and Sjöstrand B27034/43.
[113] Page 53307/34,
Helmer et al. B27035/39.

The claim that the pressor action of urine (urosympathin ?) is greater in *hypertensives* than in normal individuals [114] has not been uniformly confirmed.[115] Indeed, the total amine excretion is subnormal in certain hypertensives.[115a]

Recently, Holtz et al.[116] succeeded in demonstrating the constant presence of some pressor material in every human urine. Its action is augmented by cocaine and decreased or reversed by ergotoxine or yohimbine. Polyphenoloxidase destroys the substance with brown discoloration. Pharmacologic and chemical analysis suggests that the material which they termed **"urosympathin"** represents a mixture of hydroxytyramine, adrenaline (sympathin-I) and nor-adrenaline (sympathin-E). The same investigators emphasized that the adrenals normally produce both adrenaline and nor-adrenaline. It is assumed that DOPA is physiologically transformed into hydroxytyramine, then into nor-adrenaline and finally into adrenaline. All three of the last mentioned compounds are allegedly eliminated into the urine, in quantities which (as regards their pressor effect) are equivalent to 100-150 γ per day. The urosympathin content of the urine is significantly increased following *muscular work* and in *essential hypertension;* [117] this suggests that excessive production of such compounds may play a rôle in the G-A-S.

Urohypotensin was a name suggested [118] for a depressor material found in the urine, but this is believed to be identical with the subsequently prepared kallikrein.[119]

Nephrin is the name suggested for a hypertensive substance extractable from kidney-tissue with sublimate-alcohol. It allegedly differs from renin, adrenaline, tyramine, hydroxytyramine and vasopressin. Small amounts of this substance are also demonstrable in the blood and urine where its concentration increases during experimental, renal hypertension in the dog, as well as in hypertensive glomerular nephritis and eclampsia in man. Allegedly, nephrin raises the blood-pressure through a complex action involving constriction of the peripheral vessels, increase in the minute-volume of the heart and a direct effect upon the central nervous system.[120] There is much to suggest that nephrin is identical with hypertensin.[121]

Nephrohormone is a pressor substance which accelerates the transformation of indol into indican. This compound has been isolated from the blood of the renal vein, as well as from urine. It is claimed to differ from all known pharmacologically active renal principles, being a sterol-derivative formed in the renal tubules.[122]

In rabbits, in which hypertension had been induced by transection of the depressor nerves, nephrohormone allegedly disappears from the renal vein blood if the plexus renalis is destroyed.[123]

Nephrolipin is the name suggested for a principle which can be extracted from the kidney, and which allegedly regulates the blood-lipid-concentration.

[114] Bohn and Hahn B27033/33.
[115] Granger A21284/12.
Leathem A15439/38.
[115a] Edinger and Olsen B47126/50.
[116] B18862/47.
[117] Holtz et al. B18862/47.
[118] Abelous and Bardier B27030/09, A50310/09.
[119] Dale 16500/33.
[120] Enger A72764/42, B19358/47, Enger and Dölp A39117/41, Enger and Jellinghoff A39118/41.
[121] Volhard B29452/48.
[122] Atsumi A39377/39, A32186/39, A39378/39, Masuda A39379/39 A32192/39.
[123] Atsumi A32186/39, A39378/39.

Nephrectomy causes a rise in the total lipid, phospholipid, neutral fat, fatty acid and cholesterol content of the blood in the dog. This lipemia can be prevented by kidney-extracts, allegedly because they contain nephrolipin.[124]

The hypertension caused by stimulation of the central stump of the vagus, is not inhibited by hypophysectomy, adrenalectomy or nephrectomy. Hence, it was concluded that here the pituitary-adrenal-kidney-system is not involved. Yet, as shown by cross-transfusion experiments, the blood acquires pressor properties during this hypertension. The causative pressor principle could not be identified with any known adrenergic factor. On the basis of indirect evidence, it was assumed to be produced by the arteries themselves and was merely designated as an **"arterial pressor substance"**.[125]

A depressor substance, **contranephrohormone** (apparently a protein) is claimed to be secreted in large quantities into the blood after transection of the depressor nerves in rabbits. This presumably represents a compensatory mechanism against the hypertensive effect of depressor transection.[126] Contranephrohormone has also been prepared from the renal cortex and is claimed to be present both in the albumin- and in the globulin-fractions of renal-vein-blood. It allegedly acts through the intermediary of the brain-stem.[127]

Renipressin is the name suggested for a pressor agent, present in deproteinated renal extracts, which exhibits no tachyphylactogenic properties.[128]

Tubulin is an antipressor substance extracted from kidney-tissue. It antagonizes the vasopressor actions of renin, hypertensin, renipressin [129] and adrenaline.[130] The depressor antirenin effects resemble those obtained with other. not specially named, kidney-extracts (see above).[131]

During grave systemic stress conducive to prolonged hypotension (e.g., hemorrhage, crude renal extracts, spontaneous diseases, toxic drugs) the plasma of various animals (cat, dog, rat, etc.), acquires the ability to cause a sustained elevation of blood-pressure. This is demonstrable upon intravenous injection of extracts from such blood into previously nephrectomized animals.[132] The effect has been attributed to the discharge into the blood of a special, **sustained pressor principle (SPP).** The latter is presumably produced by the kidney, since it does not appear in the blood of animals exposed to stress after nephrectomy. SPP differs from renin, hypertensin, pepsitensin, hydroxytyramine and tyramine in that its effect is much more prolonged.[133]

Antirenin [134] is a principle which appears in the blood of animals injected with crude kidney-extracts. It causes hypotension after nephrectomy and neutralizes both renin and SPP.[135] This latter observation, the renal origin of both renin and SPP, as well as the fact that both these substances are discharged in response to hypotension, suggest some close relationship between

[124] Diaz and Castro-Mendoza B38179/48.
[125] de la Barreda et al. B37537/47.
[126] Kin A32185/39.
[127] Tokumitsu A39646/39.
[128] Jablons 90684/45.
[129] Jablons and Cope 85853/45.
[130] Cope and Jablons 98495/47, Jablons B25737/47.
[131] Jablons 64924/35, 80839/41, Jablons and Cope 85853/45.
[132] Shipley and Helmer B17753/48.
[133] Helmer **B27074/48.** Helmer et al. 98535/47, Shipley **B27073/48.** Shipley and Helmer B17552/47, B17753/48, B25987/48, Shipley et al. B4734/47.
[134] Wakerlin B4363/47, Wakerlin et al. B17768/48, Wolf 90685/45.
[135] Helmer et al. B17684/48.

these pressor agents, in spite of certain differences in their pharmacologic actions.

It is well known that normal, functional kidney-tissue counteracts hypertension produced in various ways (e.g., Goldblatt-clamp, endocrine kidney, hypertensin, renin, SPP, VEM); that is why renal pressor-substances are usually assayed on nephrectomized animals.[136] It is interesting therefore that certain kidney-extracts have anti-pressor properties, although it is not yet known to what extent antirenin-formation is responsible for this action.[137]

Yet another substance, which might be involved in the mechanism of renal hypertension, is the **"peripheral vasoconstrictor substance" (PVC)**. This is allegedly a non-diffusible, relatively stable vasoconstrictor whose concentration in the blood is high in dogs after infusion of renin, and in dogs or human beings with chronic hypertension.[138] The substance is assayed by the vasoconstriction which it elicits in the isolated perfused rabbit's ear, but there is nothing to indicate that it is a blood-pressure raising substance.[139] Some of the properties of this PVC are similar to those of the SPP mentioned above.[140]

Certain blood-borne vaso-active principles, which appear to play an important rôle during shock have been assayed by their effect upon the terminal blood-vessels in the "mesoappendix", that is, the cecal mesentery of the rat.[141] In the initial stages of hemorrhagic shock, the blood contains a **vaso-excitor material (VEM)**, which is detected by its adrenaline-potentiating effect. Under its influence, the reactivity of the terminal arterioles to adrenaline may increase up to twenty times above normal.[142]

Conversely, during prolonged, profound hypotension, VEM gradually disappears from the blood while a **vaso-depressor material (VDM)** becomes demonstrable in high concentration. The latter substance is assayed by its ability to render the terminal arterioles of the rat-mesoappendix refractory to adrenaline.[143] VDM has been claimed to be identical with **ferritin** or its protein moiety.[144] Ferritin does not consistently change the systemic blood-pressure of rats rendered hypertensive by the "endocrine kidney" technique, or by injection of adrenaline. Hence it was concluded that the terminal arterioles of the mesoappendix, on which VEM- and VDM-effects are usually studied, "...do not participate significantly in the pressor response to intravenous adrenaline" and available data fail to support the view that "...responsiveness to adrenaline in this segment is closely related to the level of arterial pressure".[145] Ferritin has been isolated from the kidney and spleen of animals after the intraperitoneal injection of hemoglobin, and it was considered possible that abnormal ferritin accumulation in the kidney may be the cause of tubular necrosis in hemoglobinuria.[145a]

Humoral responses, essentially similar to those caused by VDM, were obtained in various species of animals after the production of shock by *hemorrhage, tourniquet or crushing injuries*.[146]

[136] Dexter Kahn 48.
[137] Wilhelmi et al. B2204/47, B17768/48.
[138] Page 98559/48.
[139] Corcoran B29530/48.
[140] Corcoran B29530/48.
[141] Chambers et al. 85155/44.
[142] Shorr et al. B18009/47, B19255/48, Zweifach et al. B17785/48.
[143] Shorr et al. B18009/47, B19255/48, Zweifach et al. B17785/48.
[144] Mazur and Shorr B29486/48, B46732/50.
[145] Corcoran et al. B32725/48.
[145a] Hampton and Mayerson B46211/50.
[146] Chambers and Zweifach B1731/47.

It is now assumed that the liver and the kidney possess enzymatic mechanisms for the inactivation of VEM and that both the formation and inactivation of these vasotropic substances play an important rôle in the mechanism of blood-pressure-homeostasis during conditions of shock.[147]

Since rats maintained on low-protein *diets* do not tolerate surgical procedures well, attempts have been made to show whether they suffer from some disturbance in VEM- and VDM-production. Relevant studies suggest that here the significant lesion is the failure of the liver to inactivate VDM (tested under aerobic conditions, in vitro). This is perhaps due to the hepatic cirrhosis which such animals develop. The renal VEM-mechanism is also impaired since abnormally little VEM is produced by the kidneys of these animals, upon anaerobic incubation in vitro. "These derangements in the VDM-VEM mechanisms, because of their significance for compensatory vascular reactions to shock, are believed to contribute to the predisposition of the cirrhotic rat to shock".[148] Yet, even in acute experiments on rats, fasting and low-protein-diets inhibit or abolish renal VEM-formation.[148a] Here, of course, there is no question of hepatic cirrhosis.

In connection with the relationship between the *adrenal-cortex* and the renal pressor system, it is interesting that adrenalectomy allegedly interferes with VEM-formation by the kidney.[149] DCA restores this defect in the adrenalectomized rat,[150] but curiously, DCA hypertension is unassociated with a rise in VEM-formation.[150a]

For further details concerning the properties of VEM and VDM the reader is referred to the original publications.[151] It must be pointed out, however, that re-examination of this problem, on *hepatectomized* and *nephrectomized-hepatectomized* dogs, led to the conclusion that hemorrhagic shock develops essentially in the same manner in intact animals and in those deprived of both liver and kidney. Indeed, restoration of their own blood after shock had developed, resulted in a return of the blood-pressure to the normal level for 2-3 hours. These and similar experiments led to the conclusion that: "the absence of the liver does not change significantly the response of dogs to hemorrhagic shock".[152] Further work is required to clarify the cause of these discrepancies.

Assays performed on the blood of dogs with experimental *renal hypertension* and patients with *essential hypertension* led to the conclusion that the VEM-VDM-mechanism participates in the pathogenesis of both these derangements.[153] There is, allegedly, much evidence to suggest that the same is true of normotensive subjects with chronic *congestive-heart-failure* due to rheumatic lesions.[153a] In connection with the pathogenesis of the *"crush syndrome"* it has been pointed out, furthermore, that in animals injected with hemoglobin, the kidney stores large amounts of ferritin.[154]

As we shall see later, a number of substances, some vasoactive (e.g., hypertensin and renin) others not (e.g., liver extracts, cocaine) possess the

[147] Shorr et al. B19255/48.
[148] Shorr and Zweifach B17756/48.
[148a] Payne and Shorr B32808/49.
[149] Zweifach et al. 98747/47.
[150] Payne and Shorr B32808/49.
[150a] Zweifach and Shorr B46973/50, B47203/50.
[151] Baez et al. 96957/47, Furchgott and Schorr 98510/47, Schroeder et al. B17750/48, Shorr B18010/48, Shorr et al. 98584/47, B18009/47, B4353/47, B17755/48, B19255/48, Zweifach et al. 98605/47, 98606/47, B17785/48.
[152] Reinhard et al. B17738/48.
[153] Shorr and Zweifach B27646/48, B32831/49, Zweifach and Shorr B27072/48.
[153a] Escher et al. B36361/49.
[154] Hampton B32763/49, Hampton and Mayerson B36364/49.

ability to potentiate the pressor action of sub-threshold doses of adrenaline and allied compounds (e.g., tyrosine, tyramine).[155] Hence the possible relationship between VEM, hypertensin, SPP and other pressor agents deserves further study.

Since plasma normally contains traces of adrenaline,[156] and of structurally related compounds,[157] even the activation of *renin* by plasma [158] is not necessarily due to enzymatic hypertensin-formation.[159]

It is especially noteworthy that according to Mylon and Heller [160] purified *hypertensin* itself is not vasoconstrictive when tested on the perfused rabbit-ear-preparation unless adrenaline or tyrosine is added to the perfusate.

It has been postulated that some compounds of the *"vitamin-P"*- group, especially certain catechins, have an "adrenaline-sparing" action inasmuch as they inhibit the oxidation of this hormone in the blood.[161] When tested on the rat meso-appendix preparation, various catechins of the vitamin-P group exert pronounced vaso-constrictor effects even by themselves, that is without the addition of adrenaline [162]. We must not forget that, through their possession of the pyrocatechol-ring, the catechins are related to adrenaline.

It has also been claimed that the oxidative deamination of adrenaline is inhibited by *ephedrine*. In view of the structural similarity between ephedrine and adrenaline, the former may perhaps compete with the latter for the amine-oxidase which can destroy either of these substances.[163]

All these observations show that the power to potentiate the vasopressor action of adrenaline is not specific to any one hormone, but is shared by a number of compounds, some of which could be formed during the catabolic phase from the cleavage-products of protein.

Freund [164] introduced the terms "Frühgift" (see below) and **"Spätgift"** to designate certain vaso-active compounds which appear in the blood during the process of clotting or defibrination. The first, the "early poison" appears almost immediately and has vaso-dilator properties which may play a rôle during the shock-phase; the latter, the "late poison" is formed subsequently and exerts predominantly vasopressor actions.[165]

The terms "vasotonine",[166] "vasoconstrictine",[167] "β-thrombovasine" [168] and "serotonine" [169] have been suggested for preparations whose active principle was most probably identical with the Spätgift.

Considerable work has been done in an effort to identify these compounds by chemical and pharmacologic means,[170] but this has not yet been accomplished with certainty.

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155 Mylon and Heller B17999/48, B18584/47, Mylon et al. B4338/47, B4337/47.
156 Shaw A15002/38.
157 Bain et al. 71548/37, Bloor and Bullen A36230/41, Raab A71733/44, Whitehorn 31473/35.
158 Page and Hellmer A32851/40.
159 Mylon and Heller B17999/48.
160 B17999/48.
161 Galmiche B27020/45, Javillier and Lavollay B27024/46, Lavollay B27021/45, Paraf B27023/44, Parrot B1229/46, Parrot and Galmiche B27022/45.
162 Haley et al. B1866/47.
163 Gaddum and Kwiatkowski A17451/38.
164 12058/20, 40038/20, B27028/21.
165 Dexter **91416/46**, Goldberger **10580/31**, Landis **B27043/44**, Reid and Bick **A55692/42**, Rigler **A17047/38.**
166 Heymans et al. 8290/32, 59885/32.
167 Dexter 91416/46.
168 Simon 75043/38, A15485/38.
169 Rapport et al. B26837/48.
170 Borgert and Keitel B26988/26, Clark 58185/20, B27039/13, Haake 21562/30, Heymann B26987/27, O'Connor 35493/11, 49936/12, Handovsky and Pick B26986/13, Simon and Komlós 75044/38, Trendelenburg 46313/11, 49110/15.

The fact that defibrinated blood acquires vasoconstrictor properties has long been known,[171] however, this was described mainly as a nuisance disturbing organ-perfusion experiments. Subsequently, it was shown that the responsible pressor-compound differs from *adrenaline*.[172] Nevertheless, the "Spätgift-action" is inhibited or reversed following administration of ergotamine, ergotoxine [173] or potassium-cyanide [174] and is increased by cocaine [175] In these and in many other respects [176] it imitates the pharmacologic properties of adrenaline.

The possibility has been considered that the "Spätgift" could be identical with *tyramine*,[177] but this seems rather unlikely.[178] The "Spätgift" also differs in many of its pharmacologic and chemical properties from *renin*.[179]

Recent investigations led to the isolation of a crystalline (m.p. 212-214°C) nitrogenous substance from defibrinated beef-blood. This compound contains the indole-nucleus and may be the sulfate of an aromatic amine. It is twice as active as adrenaline in causing vasoconstriction in the isolated rabbit-ear. This principle has been termed *"serotonin"* and is presumably identical with the Spätgift.[180] "It may play a rôle as a hemostatic agent in intravascular clotting and in cases, such as myocardial infarctions following coronary thrombosis, where the prevention of spread of hemorrhage into tissues is important".[181]

Observations on traumatized vessels in the mesentery of the rat revealed that local vasoconstriction occurs whenever a platelet-plug is formed at the site of injury. It was concluded that "the vasoconstrictor substances released from the platelet-plug doubtless contribute to this contraction and, in addition, produce constriction of adjacent uninjured blood vessels".[182] During systemic stress the widespread formation of platelet-plugs in injured tissues could perhaps even produce sufficient amounts of such vasoconstrictor substances to counteract the characteristic hypotension of shock.

The "Spätgift" is probably *derived from the formed blood-elements* and, in particular, from the platelets of the blood,[183] but perhaps also from erythrocytes as a by-product of hemolysis (see below). It is interesting that a smooth-muscle-stimulating principle, found in serum and platelets, causes a discharge of adrenaline and a rise in blood-pressure in cats.[184]

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171 Batelli B26999/05, Bernstein B26995/877, Brodie B26997/03, Ludwig and Schmidt B26993/868, Mosso B26994/874, Pfaff and Vejnx-Tyrode B26996/03, Stevens and Lee B26998/884.
172 Janeway and Park 35642/12, Kahn 6861/12, Kaufmann B27001/13, O'Connor 35493/11, 49936/12, Rothlin 12119/20, 12120/20, 12121/20, Schultz B27000/12, Stewart and Harvey A2247/12, Stewart and Zucker 35683/13, Trendelenburg 46313/11, 49110/15.
173 Bayliss and Ogden B27036/33, Bing B27037/41, Heymans et al. 8290/32, 59885/32, Simon 71998/37.
174 v. Euler and Sjöstrand A63566/41.
175 Simon 71998/37, 74347/38.
176 Rassers 10484/20.
177 Freund B26991/36.
178 Enger and Arnold B26990/37, Müller B26992/36.
179 Braun-Menendez and Fasciolo 78267/39, A34000/40, v. Euler and Sjöstrand A63566/41.
180 Rapport et al. B35593/48, B35594/48, B24840/48, B23908/48.
181 Rapport et al. B26837/48.
182 Zucker B27046/48.
183 Freund 40038/20, Hirose B27002/18, Janeway et al. B26985/18, Kashiwabara 27849/34, O'Connor 35493/11, 49936/12, Stewart and Zucker 35682/13, A487/14, Zucker and Stewart A25888/13.
184 Reid B38508/47, B29740/48.

Defibrinated blood loses its vasoconstrictor activity during in vitro *perfusion through certain organs*, such as the lung,[185] liver [186] and spleen; [187] perfusion through the kidneys [188] or placenta [189] does not inactivate it. The especially marked loss of activity during perfusion through the lung is not due to oxygenation; [190] it is probably an enzymatic process.

Prevention of blood-clotting by *heparinization* largely prevents the formation of "Spätgift", although some vasoconstrictor activity may still develop as a result of mechanical damage to the formed elements.[191] (Cf. by-products of hemolysis, below.)

It has often been noted that mechanical damage to the blood also produces vaso-active substances, which may arise as a by-product of **hemolysis.**[192] Some of these cause vasoconstriction,[193] others, vasodilatation.[194] It is not known whether the former are identical with the "Spätgift", but, in any case, is of great importance in connection with the G-A-S-concept, that hemolysis can produce vasoconstrictor substances, since various stressors (e.g., burns, crush-injuries, drugs) cause hemolysis in vivo and could form vasopressor materials as a result of this.

It appears that the vasodilator substance liberated from hemolyzed erythrocytes differs from acetylcholine, histamine, adenosine, adenylic-acid, the "substance P" of v. Euler and Gaddum and from kallikrein. It may be identical with adenosine-triphosphoric acid or adenosine-triphosphate [195] and hence with the frühgift (see below).

Pressor properties have also been detected in human plasma, ascitic fluid and cerebro-spinal fluid. The active substance was thought to be an organic base, bound to plasma-colloids, since the activity is not demonstrable in ultrafiltrates, but is liberated on coagulation of the colloids by alcohol. Blood-coagulation alone does not produce this principle. Here we are apparently dealing with a **pressor substance acting through the central nervous system,** since its hypertensive effect is not demonstrable after pithing and is greatly diminished by anesthesia. The material also appears to augment the carotid-sinus-reflex.[196] It differs from "Spätgift" in that its action is mediated by the central nervous system, and from renin, in that it causes no tachyphylaxis upon repeated injections.[197]

The **"Frühgift"** of Freund [198] or α-thrombovasine [199] is a blood-pressure-decreasing principle(s), which appears in clotted or defibrinated blood before the "Spätgift" is formed.[200] Its depressor effect is probably due to adenine-nucleotide and other adenosine-compounds.[201]

185 Bayliss and Ogden B27036/33, Braun-Menendez and Fasciolo 78267/39, A34000/40, Eichholtz and Verney B27040/40, Hemingway B27041/31, Herrick and Markowitz B27042/29, Rapport et al. B23908/48, Starling and Verney 39570/24.
186 Bing B27037/41, Bornstein B27038/26.
187 Bing B27037/41.
188 Bayliss and Ogden B27036/33.
189 Budelmann 22480/29.
190 Bayliss and Ogden B27036/33, Hemingway B27041/31, B27003/31.
191 Best and Jaques B19249/48, Landis B27043/44, Landis et al. B27044/43.
192 Hemingway B27003/31, Phemister and Handy B27004/27.
193 Hirschfeld and Modrakowski 50027/11. Studer et al. A18122/38.
194 Fleisch 70057/37, Fleisch and Weger 70052/37, Studer et al. A18122/38.
195 Barsoum and Gaddum 55948/35, Fleisch and Weger 70052/37, Studer et al. A18122/38, Zipf B27008/30, 9952/31, 9491/31.
196 Page 30859/35.
197 Page 30859/35.
198 12058/20, 40038/20, B27028/21.
199 Simon 75043/38, 74347/38, A15485/38.

Adenosine-triphosphoric-acid has been demonstrated in the blood,[202] and three nucleotides were prepared from erythrocytes, namely: diphosphopyridinucleotide (the co-zymase of v. Euler), triphosphopyridinucleotide (the co-ferment of Warburg) and adenosine-triphosphate.[203] The adenosine-content of the erythrocytes is higher than that of the plasma and when blood clots, or when citrated blood is shaken, its adenosine-equivalent increases although the histamine-equivalent remains unaffected.[204] It is very probable, therefore, that the formation of adenosine-compounds during clotting, and their liberation from erythrocytes during hemolysis, can contribute to the development of hypotension during intense systemic stress.

Several of the blood-borne vasodilators (e.g., histamine, choline, adenosine) are more active in causing hypotension than in eliciting the decrease in kidney-volume which often accompanies a fall in blood-pressure. The reverse is true of adenylic-acid. Some depressor substances, which appear in human plasma, ascitic fluid and spinal fluid (when they are allowed to stand), resemble adenylic acid in that their constrictor effect on the kidneys is particularly pronounced.[205] They may be identical with "Frühgift".

Even re-injection into the same animal of its own defibrinated blood can cause fatal hypotension. This does not occur if blood-clotting is prevented by heparin or dicumarin; [205a] hence the damage has been ascribed to some process incident to blood-clotting.[206] The causative vasodilator substance is extremely labile; if the blood is re-injected 30 minutes after defibrination, it no longer exerts its fatal effect.[207] It has been assumed that thrombin is formed during the process of defibrination and causes multiple emboli, but after some time thrombin is transformed into inactive derivatives and hence the blood loses its toxicity. These experiments led to the view that the "Frühgift" is identical with thrombin and that death from this substance is the result of multiple thromboses.[208] This concept remains to be proven.

Splenic Hormones

According to Ungar [209] the spleen produces two hormonal substances which have even been extracted from splenic tissue. The first, **splenine-A** can allegedly be formed, even in vitro, from ascorbic-acid by splenic enzymes. It is apparently an esterified aliphatic compound ($C_{18}H_{36}O_5$) containing a lactone-linkage. The compound exerts "vitamin-P"-like actions, inasmuch as it augments capillary-resistance and decreases capillary-permeability as well as the bleeding-time. It has been claimed that splenine-A is secreted by the spleen under the influence of the *hypophysis* (corticotrophin) and the *adrenal-cortex* (corticoids). "The substance is assumed to play a rôle during the course of the G-A-S, probably by accelerating the neutralization of the protease, which

200 Gaddum **33164/36.** Rigler **A17047/38.**
201 Zipf B27027/30, B27008/30, 9491/31, 9952/31, 8390/32. Zipf and Wagenfeld 21561/30, 21560/30.
202 Fiske 18251/34.
203 Warburg and Christian B27026/36.
204 Barsoum and Gaddum 55948/35.
205 Page 30859/35.
205a Bayerle and Marx B40925/45.
206 Freund B26991/36.
207 Freund B26991/36.
208 Lenggenhager 37812/36.
209 85459/44, 85460/44, 85461/44, B1173/45, B4968/47, B4934/47, B2263/47, B4934/47.

is discharged under the influence of diverse noxious agents; thus it protects the capillary endothelium".[210]

While splenine-A occurs only in spleen and blood, **splenine-B** (which is allegedly formed from glycogen) occurs both in the spleen and in the bone-marrow. Its pharmacologic actions are essentially opposite to those of splenine-A and it is presumably identical with *"thrombocytopen"*,[211] which decreases the platelet-count and increases the bleeding-time.

Acetylcholine

There is very suggestive evidence that during systemic stress both the adrenergic (cf. above) and the cholinergic humoral mechanisms are hyperactive. This is somewhat reminiscent of the simultaneous contraction of both agonists and antagonists, among skeletal muscles, in preparation for a fight, to increase resistance against a blow, no matter where it comes from.

Allegedly **traumatic** injuries and **anaphylaxis** liberate more acetylcholine than can be inactivated by cholinesterase at the nerve endings. The resulting discharge of acetylcholine into the blood is claimed to produce systemic actions, which participate in the genesis of the shock-syndrome.[212] However, this hypothesis still lacks confirmation. It has been noted that in various species the parasympathetically denervated iris contracts during anaphylaxis, but since this response is not blocked by atropine "it is doubtful whether acetylcholine is a factor" in this phenomenon.[213]

Following denervation of the facial and ocular muscles of rhesus monkeys (by transection of the facial, oculomotor and trochlear nerves) the paralytic muscle fibers become hypersensitive to acetylcholine and contract during **emotional excitation,** e.g., whenever the animal is angered or frightened. This has been called the *"fright reaction"*. The contraction so elicited is exactly simulated by small doses of injected acetylcholine.[214] "It is suggested that during fright there occurs a general discharge of the autonomic nervous system with a secretion not only of sympathetic-adrenergic hormone, but also of parasympathetic-cholinergic substance, acetylcholine, both of which enter in the rôle of body defense mechanisms in time of emergency".[215] Samples of blood, withdraw from patients during intense emotional upsets, allegedly contain both adrenergic and cholinergic substances.[216] It contains abnormally high amounts of an adrenaline-like compound when the predominating emotion is "anxiety" and acetylcholine-like substance "during states of emotional tension".[217]

The acetylcholine content of the brain also depends upon stress factors. Thus in the rat, under anesthesia or during sleep, it is increased, while emotional excitement, electric stimulation and convulsions reduce it. Thus the acetylcholine content of the brain appears to vary inversely with the degree of activity.[217a]

[210] Ungar B4968/47.
[211] Cronkite A71791/44, Rose and Boyer B27047/41, Troland and Lee B27048/38, Watson A36306/41.
[212] Laborit and Morand B37565/47
[213] Bender B24440/43.
[214] Bender B24439/38, A34107/38, B27005/38.
[215] Bender A34107/38.
[216] Diethelm et al. B29023/45.
[217] Milhorat and Diethelm 98560/47.
[217a] Richter and Crossland B43567/49.

It has also been claimed — without confirmation — that cholinergic substances are discharged during papain-shock.[218]

The miosis noted after intravenous injection of **laked blood, lecithin-** or **cephalin**-preparations in the denervated iris of the cat, is not blocked by atropine nor is it potentiated by eserine.[219]

Corticotrophin apparently exerts a rather important action on acetylcholine-metabolism. In the presence of blood from patients affected by myasthenia gravis, the synthesis of acetylcholine (which normally occurs upon addition of choline-acetylase) is inhibited. Corticotrophin-treatment restores the ability of such serum to support acetylcholine synthesis.[220]

Hypophysectomy inhibits acetylcholine synthesis in the rat; *ACTH* restores it to normal.[220a]

Histamine

The view has repeatedly been expressed that injured cells release histamine into the blood, irrespective of the nature of the damaging agent to which they have been exposed. The subsequent flooding of the organism with histamine, or "histamine-like" compounds is considered by some investigators as at least one of the factors responsible for the effects that localized injuries exert upon distant organs.[221] It is claimed that the histamine-like toxic compounds are enzymatically liberated from directly injured cells and can secondarily cause systemic damage. (Cf. histamine theory of shock, pp. 88-89.)

In this connection it should also be remembered that certain nerves are very rich in histamine-like compounds. There is much evidence to suggest that "histaminergic" nerves exist; they could produce this substance during excitation, just as acetylcholine or sympathin is elaborated.[222]

Several investigators expressed the opinion that histamine-liberation from the tissues may be a **characteristic** and fundamental feature of the A-R-syndrome.[223]

Traumatic injuries may slightly raise the histamine content of the blood and many investigators believe this to play an important rôle during the catabolic phase.[223a] The pertinent literature has been mentioned elsewhere (cf. Histamine in Shock, pp. 88-89). Suffice it to repeat here that the rise in blood-histamine is not sufficiently pronounced and constant to account entirely for the manifestations of traumatic shock.[224] However, this does not mean that here histamine-liberation does not occur, or is of no pathogenic significance.

It has been claimed that in the dog, during **experimental ileus** large amounts of histamine are formed in the intestinal contents.[225] This is of special importance in connection with the histamine-theory of the A-R since we showed that in alarmed guinea-pigs, oral administration of histamine leads to severe intoxication. Presumably the gastric mucosa, which normally is not permeable

[218] Zacco and Pratesi B37559/47.
[219] Shwartzman et al. B24871/41.
[220] Torda and Wolff B37750/49, B39092/49.
[220a] Torda and Wolff B47187/50.
[221] Barsoum and Gaddum **A43/36,** Barsoum and Smirk **A32676/36,** Best and McHenry **57442/31,** Dale **16500/33,** Delherm et al. **B26979/35,** Lewis and Grant **B26949/25,** Loeper et al. **B19724/44,** Rocha e Silva **86646/44, B1280/46.**
[222] v. Euler B37520/48.
[223] Karády and Kovács B40495/48, MacKay and Clark A15541/38, Rose and Browne A36113/41, Rózsa and Karády B44551/50, Ungar 85462/44, B4934/47, Zacco B39571/48.
[223a] Schovanec B45186/47.
[224] Chambon et al. B36392/43, Vernetti B41445/46.
[225] Urabe 35816/36.

to histamine, absorbs this compound during the A-R at the sites of ulcer-formation.[226].

Following **burns** an increase in the blood-histamine level was reported in man [227] and in animals.[228] The initial rise is almost invariably followed by a decrease to or below normal levels. In view of this biphasic response, it is understandable that, depending upon the time of the determination and other experimental conditions, stress may also cause a decrease in blood-histamine.[229]

It has been especially emphasized that the appearance of blisters in burned skin may be related to local histamine liberation [230] and animal experiments showed that moderate burns increase, while severe burns diminish, the histamine-content in the directly damaged skin.[231]

During exposure to extreme **cold** an increase in the plasma-histamine content was allegedly observed in the cat. This was ascribed to the ensuing tissue anoxia.[232]

The systemic manifestations of radiation sickness have been ascribed to the liberation of histamine or similar compounds by the **x-rays** but this view is chiefly based on inferential evidence.[233]

During **anoxia** the blood-histamine-level first rises and then declines again, in spite of continued exposure.[234] This biphasic response is very reminiscent of other metabolic changes occurring during the first two stages of the G-A-S. Significantly the hyperhistaminemia, elicited immediately following treatment with other stressors (e.g., cold, morphine), has been ascribed to the resultant tissue-anoxia.[235]

In **anaphylactic and peptone-shock** the liberation of histamine has been clearly demonstrated in animals [236] as well as in man.[237] It is probable that here, as in various other catabolic reactions, protein-bound (inactive) histamine is liberated from cell-protoplasm and thus becomes active.[238]

In the dog, the discharge of large amounts of histamine from the liver during peptone-shock could also be confirmed "in vitro".[239] On the basis of observations in man it has even been suggested "that physical allergy may represent a perversion of the alarm-reaction of Selye for which the release of histamine is the normal response to physical and emotional stimuli".[240]

Toxic doses of various **drugs**, e.g. *morphine*,[241] *papain* [242] or *atropine* [242a] allegedly also raise the blood-histamine content, roughly in proportion to their stressor action.

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[226] Selye A8052/38.
[227] Barsoum and Gaddum A43/36, Code and MacDonald A14572/37, Rose and Browne 83061/42.
[228] Behrmann et al. B4278/46, Kisima A15119/38.
[229] Rose and Browne A32980/40.
[230] Peters 89884/45.
[231] Dekanski B2586/47.
[232] Eichler and Speda A39576/40.
[233] Ellinger B24015/48, 68685/35.
[234] Burkardt et al. B32714/49, Fabinyi and Szebehelyi B39222/48, B39223/49.
[235] Eichler and Speda A39576/40.
[236] Bartosch et al. 8940/32, Chambon and Lavaud B36394/43, Chambon et al. B36393/43, Code 70503/38, Dragstedt and Gebauer-Fuelnegg 8393/32, B26917/32, Dragstedt and Mead 38786/36, 38784/36, Ungar and Parrot 71829/37, Watanabe 10452/30, 9611/31.
[237] Bray B26922/32, Horton et al. B26919/39, Lewis and Grant 20304/24, Millet B26921/31, Yates B26920/40.
[238] Rocha e Silva 86646/44, B28507/47.
[239] Jaques et al. 98542/47, Rocha e Silva B2174/47, Rocha e Silva and Teixeira B2058/46.
[240] Williams B1184/45, B1187/45.
[241] Eichler and Speda A39576/40.
[242] Zacco and Pratesi B37559/47.
[242a] Burstein and Parrot B44892/49.

ACTH raises the urinary elimination of histamine (and histidine) in man.[242b] This may be related to the anti-allergic and anti-asthmatic effect of this hormone. (Cf. Histidine, p. 261.)

In rats, **adrenalectomy** is claimed to cause a considerable reduction in the histamine-content of some tissues with a concurrent rise in others. Allegedly this is associated with a diminution in the amount of histamine that can be discharged into the blood by a subsequent A-R.[243]

Continuous intravenous infusion of very large amounts of **adrenaline** caused a considerable rise in the plasma-histamine of cats; [244] however, this led to lung edema, hence the specificity of the reaction was in doubt. In man, adrenaline rapidly increases the plasma-histamine-concentration, as judged by direct estimations,[245] and this can be inhibited by anti-histaminics, such as "antistin".[246] Since adrenaline-discharge is a very characteristic feature of the A-R, histamine-liberation at this time may, at least partly, be due to the resulting hyperadrenalinemia itself.

Following intravenous infusion of **histamine**, large amounts of this substance are demonstrable in the blood, but almost none in the lymph. This has been ascribed to the great histaminolytic power of lymph.[246a]

Heparin

Allegedly, regular variations in the heparin content of the blood are quite characteristic of the G-A-S,[246b] but this has not yet been definitely proven.

In **anaphylactic and peptone-shock**, considerable amounts of heparin are discharged from the liver into the circulation. This is accompanied by histamine- and fibrinolysin-discharge.[247]

It is especially interesting in this connection that according to many investigators heparin pretreatment prevents or diminishes anaphylactic shock and the "Arthus phenomenon".[248] This is consonant with the theory [249] that anaphylactic manifestations are primarily due to endothelial damage by the antigen; this results secondarily in fibrin-deposition throughout the vascular tree, but especially in the capillaries of the responsive organ(s), and eventually blood-sludging due to increased stickiness of the fibrin-coated endothelium. It is probable that other alarming stimuli exert similar actions. Yet parallel studies with various other stressors would be required to establish whether we are dealing with one of the manifestations of the G-A-S.

A rise in the heparin (or "heparin-like substance") content of the blood has also been claimed to occur in animals exposed to the **ionizing radiations** of the atomic bomb in the Bikini-experiment.[250] Indeed, hyperheparinemia was considered to be the cause of the hemorrhagic disease produced by total-body exposure to any ionizing radiation.[251] These conclusions were based on the observation that, following addition of a standard amount of heparin in vitro, excessive quantities of protamine are required to restore the normal clotting

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[242b] Holbrook et al. B46980/50, Rose B46991/50, Rose et al. B45103/50.
[243] Rose and Browne **A36113/41**, Ungar **B4934/47.**
[244] Eichler and Barfuss B26923/40.
[245] Staub B26029/46.
[246] Staub B26065/46.
[246a] Carlsten et al. B46629/49.
[246b] Rózsa and Karády B44551/50.
[247] Jaques et al. 98542/47, Rocha e Silva B1280/46, 86646/44, **B2174/47. B28507/47.** Rocha e Silva and Teixeira B2058/46.
[248] Grégoire **B24136/46.**
[249] Nolf 48362/10.
[250] Cronkite B26982/47.
[251] Allen et al. B26981/46.

time in the blood of the irradiated individuals. It will be recalled, however, that total-body irradiation not only renders the blood incoagulable, but also renders it thrombocytopenic and lack of platelets augments susceptibility to heparin.[252] Hence, the available data do not prove that ionizing rays increase the plasma-heparin-level, but merely that the accompanying thrombocytopenia raises heparin-sensitivity.

Various Depressor Substances

Kallikrein or **padutin** [253] are synonymous terms used to designate a depressor substance found in the urine by Frey and Kraut.[254] It can also be extracted from the pancreas and disappears from the urine after pancreatectomy. On the basis of these observations it has therefore been assumed that kallikrein is a depressor hormone produced by the pancreas and eliminated in the urine. Its chemical structure and true hormonal nature have not yet been definitely established.[255]

Depressan (or "detonin") is a hypotensive metabolite present in urine, which unlike kallikrein is not destroyed by boiling. Its chemical structure and hormonal nature has not yet been established.[256]

Vagotonine is a name given by Santenoise [257] to an allegedly hormonal principle which can be prepared from pancreas; it stimulates the parasympathetic system and causes hypoglycemia even upon oral administration. Its specificity is very doubtful.[258]

Angioxyl is a hypotensive material extracted from the pancreas; it may represent a mixture of depressor substances, but differs from histamine and choline.[259]

The **"histamine-like substance" of Croxatto and de la Lastra** [260] is a depressor compound found in plasma or serum; it has not yet been identified.

"Resistine" is a hypothetic antihistaminic substance, which is allegedly produced during the G-A-S and is claimed to account for much of the non-specific resistance that develops under stress.[260a]

Lymphogangline is a depressor principle present especially in lymph-nodes. It is possibly a choline-ester.[261]

The "Substance-P" of v.Euler and Gaddum is a vasodilator found especially in the brain and intestine. It decreases the blood-pressure and increases intestinal peristalsis even after atropinization in the rabbit.[262] Its physiologic significance and chemical structure are not known.

Many **other vaso-active tissue extracts** have been prepared and some of them have even been given special names, but since their identity, and especially their participation in the G-A-S is dubious, it would not be rewarding to discuss them.[263]

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[252] Conley et al. B28262/48.
[253] Dale **16500/33**. Rigler **A17047/38**.
[254] B27029/26, 19328/28.
[255] Flliott and Nuzum 10605/31, Frey 14272/29, Gley and Kisthinios 6287/29, Kraut et al. 18550/28, 11096/30, 10379/30, 8627/32.
[256] Riqler **A17047/38**.
[257] 99295/37.
[258] Louyot 99436/30, Rigler A17047/38, Santenoise 99295/37.
[259] Gley and Kisthinios 34237/35, 24270/28, 22193/29.
[260] B31711/48.
[260a] Karády and Kovács B40495/48, Petri and Karády B45380/50.
[261] Marfori et al. 19828/34.
[262] Rigler **A17047/38**.
[263] Rigler **A17047/38**, Schmiterlöw **B37544/48**.

Leucotaxin and Allied Substances

Leucotaxin polypeptide can be extracted from the skin of burned rabbits. When injected into normal rabbits it causes marked local edema and hematologic changes similar to those elicited by scalding.[264] Other hypothetical metabolites which may influence the blood-count during the G-A-S, have been discussed elsewhere (cf. chapter: Blood-count).

Insulin

In patients who died from various debilitating diseases, the pancreas was found to contain subnormal amounts of insulin.[265] It remains to be shown whether this change is related to the G-A-S. The effect of stress upon the structure of the pancreas and the interpretation of diabetes as a disease of adaptation, will be considered elsewhere in this book.

Thyroid Hormone

The concentration of radio-iodine by the thyroid and its distribution in the serum are markedly affected by adrenaline, trauma and typhoid vaccine in the rat. Adrenaline and adreno-cortical extract decreases the quantity of protein-bound iodine in the serum, even after adrenalectomy. Fasting and exposure to cold or heat resulted in a sub-normal concentration of radio-iodine in the thyroid. All these data were considered to indicate that stress exerts an important effect upon the production and discharge of thyroid hormones.[266] Additional pertinent data will be discussed in the section specifically devoted to the thyroid.

Folliculoids

The urinary elimination of folliculoids is greatly diminished in patients with anorexia nervosa.[267] This corresponds to the fall in 17-KS and testoid production characteristic of the resistant stage (cf. p. 225). Many other stressors diminish the production of ovarian hormones; [268] this is hardly surprizing since stress causes pronounced ovarian atrophy (cf. below).

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[264] Cullumbine B38022/47, Cullumbine et al. B38021/47, Menkin **A57481/43**.
[265] Franklin and Lowell B37247/49.
[266] Williams et al. B43573/49.
[267] Berkman et al. B46014/47.
[268] Selye **94572/49**.

ENZYMES

Because of the dominant rôle played by enzymes in the regulation of all vital phenomena, many investigators examined the possible participation of enzymatic processes in the various phases of the G-A-S.

Proteases and Peptidases

It was natural to suspect that the intense catabolic phenomena which occur during the stages of alarm and exhaustion, are probably dependent upon the activity of proteases and peptidases.[1]

Experiments on the rabbit led to the view that under the influence of **burns** large amounts of proteolytic enzymes are liberated from the damaged skin into the blood, since actual determinations showed a considerable rise in the proteolytic and peptolytic activity of the serum.[2] The so-called "amino exopeptidase" is normally demonstrable in serum, muscle, subcutaneous tissue and erythrocytes; after burns or trauma to a dog's extremity this enzymatic activity rises abruptly in the lymph draining from the affected area. In other species (calf, rat) this peptidase activity was also demonstrably increased in the serum after burns. It has likewise been found in fluid collected from blisters of burned human skin.[3]

The blood-polypeptidase-content of human serum also rises after **trauma** and **infections** conducive to systemic stress.[4] In patients with bone-fractures the leucylglycylglycine-splitting amino-peptidase-activity of the serum increases rather consistently during the catabolic phase. Significantly the values return to normal when a positive N-balance is re-established.[5] Similar observations, made with this same substrate in dogs during tourniquet-shock, have been related to the A-R.[6]

An "anti-proteinase" of plasma can antagonize the activity of a certain amount of tissue-proteinase when the latter is liberated into the blood, but excessive quantities cause widespread, systemic damage;[7] this must be taken into account in pertinent studies.

The manifestations of **trypsin-shock** resemble those elicited by other stressors. This led to the supposition that liberation of endogenous trypsin into the blood may play a prominent rôle in the genesis of shock in general.[8] The tryptic activity of plasma is not necessarily of pancreatic origin (cf. Fibrinolysin, below). Nevertheless, it may be pertinent that the exocrine tissue of the pancreas disintegrates with extreme rapidity during the catabolic phases of the G-A-S (cf. G-A-S → Pancreas). This sudden extensive histolysis of the pancreatic parenchyme would most probably discharge trypsin into the blood, due to the activation of trypsinogen, by contact with necrotic cell-components. Thus the discharge of proteolytic enzymes, from a limited

[1] Ungar B4934/47.
[2] Pfeiffer 36311/14.
[3] Zamecnik et al. B669/45.
[4] Barger et al. B19844/48.
[5] Stern et al. B36343/49.
[6] Croxatto et al. B33751/48.
[7] Peters 89884/45.
[8] Mirsky and Freis B1167/44.

area of directly damaged cells, may participate in the spreading of injury to distant organs. (Cf. also Abderhalden's "protective enzymes" below.)

Following a single large dose of **ACTH,** certain serum peptidases underwent a slight increase in man; this was ascribed to adreno-cortical stimulation.[8a]

ACTH increases gastric *pepsin* (and decreases intestinal *lysozyme*) formation. It also raises *uropepsin* excretion, but the latter action is abolished by gastrectomy.[8b]

Fibrinolysin. — This enzyme is also known as "plasma trypsin",[9] "lytic factor",[10] "plasmin"[11] or "tryptase".[12] It has been given special attention in connection with the G-A-S because this protease becomes manifest in the blood under conditions of stress and causes complete dissolution of the fibrin-clots produced by coagulation of blood or plasma. The characteristics of this enzyme resemble, but are not identical with, those of pancreatic trypsin.[13] Presumably plasma contains an inactive precursor "plasminogen" or ("profibrinolysin") as well as active "plasmin" or ("fibrinolysin"). Both these compounds are associated with the globulin-fraction, but the active enzyme is normally neutralized by an inhibitor, antifibrinolysin ("antiplasmin") which is an albumin. Proteolytic activity may therefore result from various disturbances in the normal equilibrium between fibrinolysin and antifibrinolysin. These observations led to the discovery that the supposed fibrinolysin activity of certain strains of β-hemolytic streptococci is actually due to the elaboration of a plasmin-activator "streptokinase"; this activates the inert precursor "plasminogen" (present in normal blood) to the active form, namely plasmin (fibrinolysin). Thus the "fibrinolysin" of the bacteriologic terminology corresponds to the plasminogen-activator of the nomenclature used in blood-coagulation studies.[14] Here we shall use the term in this latter sense. We prefer it to other synonyms only because it clearly indicates the ability of this enzyme to dissolve fibrin, a phenomenon which — as we shall see — is especially important during the G-A-S.

In connection with the mechanism responsible for the rise in plasma-fibrinolysin activity during the A-R, it is noteworthy that the anti-fibrinolysin content of the plasma shows no change during tourniquet-shock in dogs[15] and is irregularly influenced, or actually increased, in various spontaneous diseases of man.[16] This suggests that lack of anti-fibrinolysin is not involved. Yet there is the clotting-defect often observed during conditions of stress. It is known that after the action of fibrinolysin, thrombin no longer causes the blood to clot because there is no more fibrinogen. When normal blood clots it does not undergo fibrinolysis; however, in a variety of conditions conducive to systemic stress, although the blood clots after shedding, it subsequently becomes liquid again due to the activity of this enzyme.

MacFarlane[17] concluded from his pertinent studies that: "spontaneous (fibrinolytic) activity occurs in the blood of human subjects following a variety of disturbing stimuli such as surgical operations, shock, trauma, anxiety, violent exercise and in some pathological states. It can also be reproduced by the injection of adrenaline, and this observation, coupled with the nature

[8a] Sayers et al. B37710/49.
[8b] Gray et al. B46965/50.
[9] Rocha e Silva and Andrade B26938/45.
[10] Milstone B26937/41.
[11] Christensen B26936/45.
[12] Ferguson B26935/43.
[13] Croxatto et al. B23955/48.
[14] Christensen B26936/45, Christensen and MacLeod B26944/45, MacFarlane and Biggs B38711/48, MacFarlane and Pilling B26945/46.
[15] Rosati et al. B33752/48.
[16] Guest et al. B29411/48.
[17] B2271/47.

of the other stimuli mentioned, suggests that activation of the proteolytic system of the blood is part of the alarm reaction".

Such fibrinolytic activity has been demonstrated after treatment with toxic doses of *peptone* ("peptone-shock"),[18] *kallikrein*,[19] *typhoid-vaccine*,[20] *adrenaline*,[21] *mercurial diuretics*,[22] during excessive *muscular exercise*,[23] *traumatic injuries*,[24] *hemorrhagic* shock and extensive *burns*,[25] *toxemias of pregnancy*,[26] *fear*[27] and *other stressors*.[28]

In the course of the recent World War efforts were made to prepare cadaver-blood for transfusion. Here it was noted that patients who died a sudden death (*hemorrhagic* or *traumatic shock, medical shock*, etc.) yielded blood which underwent rapid fibrinolysis, or was entirely incoagulable due to the absence of fibrinogen.[29] Conversely, men dying from *chronic diseases* showed no lysis of the clot.[30]

Allegedly, in anaphylactoid conditions, both histamine and heparin are released from cells due to the action of fibrinolysin.[31]

It is interesting to confront the incoagulability of the blood characteristically occasioned by certain types of systemic stress (e.g., peptone, anaphylaxis, x-irradiation, nuclear-fission products, the Waterhouse-Friderichsen syndrome) with the increased tendency towards the formation of fibrinous, "fibrinoid" and "hyalin" deposits in the cardiovascular system (post-operative thrombosis, coronary thrombosis in clinical medicine and widespread thrombosis and hyalinosis following DCA- or LAP-overdosage in animals). Perhaps during systemic stress the formation of fibrin and its dissolution by fibrinolysis plays a prominent rôle.[31a] It could lead to incoagulability or increased coagulability of the blood, depending upon the relative predominence of one or the other among these opposing factors. During fibrin-formation, vasopressor hypertensive substances ("serotonin") appear in the blood. Hence, the constant widespread formation of fibrin throughout the vascular tree (even though it occurs only in microscopic amounts and is immediately followed by fibrinolysis), may perhaps contribute to the genesis of hypertension during the G-A-S. Thus, in some cases, vasoconstriction and a rise in blood-pressure could be looked upon as a by-product of an "increased fibrin-turnover".

Hyaluronidase

Whether the G-A-S causes any characteristic changes in hyaluronidase (mesomucinase, Duran-Reynals' spreading factor) activity has not yet been definitely established, but several facts suggest this to be the case. (Cf. also: Absorption, Serous Cavities.)

Hyaluronidase has the property of depolymerizing *hyaluronic-acid*. The latter is an integral part of connective tissue and inter-cellular cement sub-

[18] Jaques et al. 98542/47, Nolf B26910/05, B26934/38, Rocha e Silva B2174/47, Rocha e Silva and Teixeira B2058/46, Scroggie et al. B4341/47.
[19] Westerfeld et al. B423/44.
[20] Ham B26909/46.
[21] Biggs et al. B26948/47, MacFarlane and Biggs B38711/48.
[22] Wexler and Ellis B26915/44.
[23] Biggs et al. B26948/47, MacFarlane and Biggs B38711/48.
[24] MacFarlane and Biggs B26947/46, Smith and Smith 86769/45.
[25] Tagnon et al. B2128/46.
[26] Smith B26914/45.
[27] MacFarlane and Biggs B38711/48.
[28] MacFarlane B26946/37, B2271/47.
[29] Tagnon et al. B2128/46.
[30] Yudin B26916/37.
[31] Rocha e Silva B28507/47, Rocha e Silva and Teixeira B2058/46.
[31a] Anonymous **B44433/49.**

stances. It occurs normally in significant quantities within synovial fluid, aqueous and vitreous humors, Wharton's jelly and skin. It is also found in the capsules of certain streptococci. Under pathologic conditions, hyaluronic-acid is initially present in fluids derived from inflammatory processes, but subsequently, it disappears, due to the action of hyaluronidase.[32] *Hyaluronidase* is believed to exist in an inactive form in the skin. It also occurs in the testis, eye, certain pathogenic bacteria, poisonous insects, leeches and snake-venoms. Owing to depolymerization of the gel-like hyaluronic-acid in connective tissue, this enzyme enhances the spread of intradermally injected particulate substances (e.g., India ink, dyes, bacteria, viruses).[33] Because of these properties, it has been considered possible to participate in the pathogenesis of so-called diffuse collagen-diseases (lupus erythematosus, scleroderma, rheumatic fever) and in the hyalinosis which we produced with stress, LAP, DCA or the endocrine kidney.[34] It is of special interest in connection with its effects upon the vascular system that hyaluronidase also increases capillary-fragility;[35] this is presumably again due to liquefaction of cement-substances.

Significantly, normal sera and those of individuals suffering from non-bacterial diseases inhibit the action of hyaluronidase, while those of patients with *infectious diseases* (rheumatic- or typhoid fever, streptococcus- or staphylococcus-infections, tuberculosis, pneumonia) augment its effect.[36]

Inflammatory and anaphylactic phenomena are characterized by the swelling of connective tissue. A similar effect can be produced in vitro by histamine, in concentrations which may occur in vivo. In therapeutically employed concentrations, **salicylates** do not prevent the swelling effect of histamine upon the collagen-fiber, but they induce the swollen fiber to discharge the absorbed liquid. From this it was assumed that sodium-salicylate would probably have an anti-histamine effect in rheumatic diseases. Yet hyaluronidase does not produce swelling of collagen-fibers and sodium-salicylate, histamine or anti-histaminics fail to influence the viscosity-decreasing effect of hyaluronidase.[37] The failure of in vitro inhibition of hyaluronidase by salicylates has been confirmed,[38] but it was pointed out that the enzyme reduces both the "spreading action" and vasotoxic effects of snake-venom, as well as the action of histamine on capillaries.[39]

With respect to the interpretation of the diseases of adaptation, it is interesting that antibodies to streptococcal hyaluronidase occur in the blood of patients suffering from **rheumatic fever.** Indeed "the anti-hyaluronidase titer showed better correlation with changes in the activity of the rheumatic infection than did other tests".[40]

Potent hyaluronidase-inhibitors (e.g., DOPA, sodium-gentisate) fail to influence the course of **x-irradiation**-sickness in dogs. "It is suggested that the spreading factor, hyaluronidase, plays little or no rôle in the evolution of this disorder".[41]

In the mouse exposure to **heat** inhibits the spreading of intradermally-injected India ink, whether the latter is or is not mixed with hyaluronidase. It has been

[32] Campani and Schlechter B37878/47.
[33] Boltraffio B39229/49.
[34] Anonymous **B2316/47.**
[35] Alburn et al. **B27057/48.** Chambers and Zweifach B26122/47, Duran-Reynals A57968/42.
[36] Tolentino and Vasallo B37501/48.
[37] Fabinyi et al. B37516/48.
[38] Swyer B37355/48.
[39] Swyer B37354/48.
[40] Harris and Harris B32979/49.
[41] Field and Rekers B37300/49.

suggested that heat "may play a rôle in stimulating the adrenals and thus cause a decrease of the permeability of the ground substance",[41a] since glucocorticoids exerted a similar inhibitory action (cf. below).

Morphine and **adrenaline** were found to restrict the spreading action of hyaluronidase in animals.[42]

Anterior-pituitary extracts exert a similar effect.[43] In order to examine the mechanism through which the G-A-S might influence this effect, an A-R was produced in rats with *formaldehyde*-injections in the usual manner. Here, the spread of India-ink mixed with hyaluronidase and injected intracutaneously, was also restricted by the stressor agent, but the response was not influenced by **adrenalectomy** "and consequently it did not depend on the adrenocortical-lymphatic tissue reaction to injury".[44] Yet, it could have been due to G-A-S-changes which are not mediated through the adrenals.

In the mouse, the intradermal spreading of India ink (mixed either with saline or with hyaluronidase) is inhibited by adreno-cortical extract. This inhibition is obtained both by intraperitoneal injection and by direct intradermal administration of the extract mixed with the India ink. Conversely, adrenalectomy greatly enhances the spreading of India ink and this effect is counteracted by intraperitoneal adreno-cortical extract treatment.[44a] Cortisone, and to a lesser extent, Kendall's compound A, exerted a similar effect while testosterone, estradiol benzoate, progesterone and pregnenolone were ineffective.[44b]

Essentially similar inhibition of spreading was observed in intact rabbits treated with **adreno-cortical extract.**[44c] It is noteworthy that a comparable, though less pronounced, inhibition of spreading by corticoids has also been obtained in the above experiments if the India ink was not mixed with hyaluronidase.

In vitro observations on the urinary bladder of the rabbit, showed that hyaluronidase increases osmosis through this membrane. This increase was further enhanced by *DCA*, but inhibited by *adreno-cortical extract* or exposure of the rabbits to an alarming stimulus (colchicine) before the test. "The products released in vivo during the alarm-reaction rendered bladder membranes impermeable even in the presence of hyaluronidase".[45] Cortical extract or *cortisone* also diminish the permeability of the rabbit's synovial membranes in an A-R-like fashion.[45a]

Amylases

The amylase activity of the plasma is likewise increased under the influence of systemic stress, for instance, after **burns** and **traumatic** injuries.[46] This has been considered to be of some importance in the genesis of the hyperglycemia during the A-R. Recent observations led to the suggestion that "in the liver damaged by toxins" the normal barrier, with excludes amylase, or the normal environment, which inhibits amylase activity, might be disturbed. In either case, liver glycogen would then be broken down through this abnormal

[41a] Opsahl B44854/49.
[42] Cahen and Granier B39019/44.
[43] Seifter et al. B43460/49, Weinstein A33940/40.
[44] Zeckwer B24198/47.
[44a] Opsahl B39548/49.
[44b] Opsahl B44946/49.
[44c] Opsahl B44855/49.
[45] Seifter et al. B39251/49.
[45a] Seifter et al. B43460/49.
[46] Lobello 36111/36, Stolfi A2340/36.

pathway as well as by phosphorolysis. Since only the normal portion of the combined glycogenolysis would be subject to control by insulin, this could account for the so-called insulin resistance which occurs in conditions of systemic stress".[47]

Cholinesterases

Because of the important rôle played by the vegetative nervous system during the G-A-S, studies concerning cholinesterase activity in systemic stress are of great interest. Unfortunately, up to now only few relevant observations have been made and even some of these are difficult to evaluate since, until quite recently, no distinction had been made between true- and pseuda-cholinesterase activity. However, although only the former attacks acetylcholine directly and in great dilution, even the latter may exert an important effect upon nervous activity. Thus it was found that drugs, which inhibit the action of pseudo-cholinesterases, diminish the effect of carotid-nerve-stimulation upon the blood-pressure.[47a] In evaluating early observations, it may be well also to keep in mind that only the pseudo-cholinesterase-content of the blood is subject to important variations during systemic stress.

It has been found in guinea-pigs that inoculation with cultures of **B.pestis** lowers the cholinesterase activity of the blood, but this returns to normal if the animals survive. In one additional experiment in man, a large dose of Haffkine's **plague vaccine** also lowered plasma-cholinesterase activity, with return to normal upon clinical recovery. The authors state: "there is no reason to suppose that the lowering of cholinesterase values of blood are specific to plague infection".[48] Experiments in the rat led to the conclusion that the "non-specific effect of operations, such as ovariectomy or even simple laparotomy, result in a rapid, immediate fall of serum cholinesterase activity".[49] These observations and the fact that in dogs during **traumatic shock** eserine causes a precipitous fall in blood-pressure, led to apparently successful attempts of treating traumatic shock by the intravenous injection of cholinesterase in the dog.[50] Incidentally, in other animals and in man, traumatic shock also diminishes the cholinesterase activity of the blood.[50a]

A fall in serum-cholinesterase has been noted, furthermore, as a result of exposure to **anoxia,**[50b] after injection of **ovalbumine,**[50c] and as a result of various **severe organic diseases** (cancer, tuberculosis).[50d] On the other hand, during **anaphylactic shock** and in certain experiments with shock-producing doses of **proteins** or **histamine,** the results were inconclusive or negative.[50e]

Forced **muscular exercise** has been variously reported to cause no change[51] or a sudden and pronounced increase in serum-cholinesterase.[52] Because of such discrepancies it is difficult to evaluate pertinent data, but they are sufficiently suggestive to warrant more systematic studies concerning the rôle of cholinesterase during the G-A-S.

Hypophysectomy causes an increase in the plasma pseudo-cholinesterase level in rats. Treatment with *thyroxine* results in a depression of the plasma

[47] Taubenhaus and Soskin 82817/42.
[47a] Heymans et al. B39577/48.
[48] Dikshit and Mahal A7932/37.
[49] Everett and Sawyer 95227/46.
[50] Schachter B929/45.
[50a] Aron and Herschberg B40807/47, Imperati et al. B44630/46, Schovanec B45186/47.
[50b] von Muralt and Stettler B45986/48.
[50c] Aron and Herschberg B40807/47.
[50d] Laborit et al. B44481/48.
[50e] Aron and Herschberg B40807/47.
[51] Watkins et al. B25880/47.
[52] Pecora B38525/47.

pseudo-cholinesterase level even in the absence of the hypophysis. Hence it was concluded that the pituitary is not an essential link in the characteristic diminution of plasma-pseudo-cholinesterase by thyroid-hormone.[53]

A comparative study of true- and pseudo-cholinesterase in the serum, brain and muscle of intact and **adrenalectomized** rats revealed no marked deviation from the normal in either group following intensive muscular work. Only in the muscle itself was there a slight increase in cholinesterase- activity in the adrenalectomized group. Although this change was not pronounced, it was felt that "it does suggest again that in some way or other neuromuscular transmission is impaired in these animals".[54] In a recent lecture concerning this subject, it was stated that in rats "the effect of adrenalectomy and stress, individually or combined, on brain-tissue does not consistently change either the choline-acetylase or co-enzyme levels".[55] The only published abstract of this work unfortunately does not mention the kind of stressor used.

Under various experimental conditions **adrenaline** can potentiate the action of acetylcholine; allegedly, the former may increase the synthesis of the latter. It has also been shown that adrenaline inhibits the hydrolysis of acetylcholine by true- and pseudo-cholinesterases in vitro.[56] The adrenergic discharge could thus influence cholinesterase-activity.

Further work will have to be done to establish definitely whether the hypophysis-adrenal-system is necessary for the normal regulation of cholinesterase-activity during the G-A-S.

The inactivation of cholinesterases by **D.F.P.** in dogs, resulted in no detectable abnormality in heart-rate, blood-pressure, peristalsis, salivation, etc., although sensitivity to injected acetylcholine was enormously increased.[57] It remains to be seen how D.F.P. influences the activity of the cholinesterase-mechanism during stress.

In patients with essential **hypertension,** the plasma-cholinesterase level is allegedly very high, there being a direct relationship between it and the arterial pressure itself. These patients are claimed to respond with a substantial fall in blood-pressure following prostigmine injections and this was attributed to the latter's inhibitory action upon cholinesterase.[58] Such observations are of great interest in connection with the interpretation of hypertension as a disease of adaptation, but they require confirmation on a larger clinical material.

Phosphatases

A detailed systematic study concerning the effect of the A-R upon the histologically demonstrable alkaline phosphatases led to the conclusion that these increase in many tissues of rats during systemic stress (cold, formaldehyde, muscular exercise). The most pronounced and characteristic rise was found in the liver, the lung and throughout the reticulo-endothelial system. The nuclei, nucleoli and cell-membranes become especially prominent in sections stained with methods for the demonstration of alkaline phosphatases. This response is apparently **characteristic** of the A-R, but its significance

[53] Hawkins and Nishikawara B37731/49.
[54] Overbeek B36379/49.
[55] Greenberg B32756/49.
[56] Benson B23887/48, Benson and Meek B39025/49.
[57] Heymans and Casier B23147/48.
[58] Libbrecht B37987/47.

remains problematic since phosphatases participate in so many physiologic functions.[58c]

Severe **x-irradiation** causes a rise in the alkaline phosphatase-activity of the plasma in dogs,[58a] but the mechanism and significance of this change is not known. In mice exposed to intense x-irradiation, the alkaline phosphatase content of the spleen rises, while that of the kidney and the intestinal villi tends to fall.[58d]

In rats given diabetogenic doses of **alloxan,** the alkaline phosphatase content of the adrenal cortex, ileum and the male accessory sex organ falls, while that of the spleen, thymus, lymph-nodes and lung rises. "This differential behavior of the various organs suggests that alloxan does not affect the phosphatase system through a direct action".[58e] It remains to be shown whether the above changes are due to an A-R elicited by non-specific stress, but this possibility should be considered.

Hypophysectomy and purified **ACTH** decrease, while purified **somatotrophin** increases the plasma-alkaline-phosphatase in rats. The hypophyseal regulation of this enzyme-activity may be concerned with growth and protein-synthesis.[58b]

Adrenalectomy diminishes the alkaline phosphatase content of the duodenum and jejunum in the rat. Corticoids restore it to normal, but apparently this effect lacks specificity as it is shared by several other steroids.[58f]

Cortical extracts reduce the frequently elevated serum-phosphatase-level in patients suffering from rheumatoid arthritis. At the same time there is symptomatic relief.[59]

As we shall see later (G-A-S → Kidney) in the rat, alkaline phosphatase disappears almost completely from the **"endocrine kidney"** after the operation, while the acid phosphatase decreases only in total amount, not in concentration.[60] Here again the interpretation of the finding is impossible as yet.

According to presently available data, renotropic **testoids** increase the phosphatase-content of the rat-kidney, but appear to exert a diametrically opposite effect in the mouse.[61]

Other enzymes

Rather extensive investigations have been performed concerning the effect of hemorrhagic shock upon various enzymatic activities, particularly upon **cocarboxylase,**[62] **amino-acid-oxidase,**[63] **lactic-dehydrogenase,**[63a] **cozymase**[64] and other enzyme activities in liver tissue and in plasma. It is not within the scope of the present survey to discuss all these observations in detail, but it may be said that during severe shock many of the hepatic enzymes are inactivated and this may contribute to the general systemic damage.

The possible rôle of **histaminase**-activity in the production of the A-R, has also been considered.[65] Interestingly the lymph — which plays an important

[58a] Prosser B26618/47.
[58b] Li and Evans **B29320/48.**
[58c] Herlant and Timiras B41763/50.
[58d] Arvy et al. B44851/49.
[58e] Arvy and Gabe B44852/49.
[58f] Verne and Hébert B46577/49.
[59] Watson A34185/40.
[60] Kochakian and Dontigny B3631/47.
[61] Beland **B18144/46.**
[62] Govier and Greig B26192/43, Greig and Govier B26190/43, B26193/43.
[63] Greig B26195/44, De Turk and Greig B26196/45.
[63a] Greig B26195/44.
[64] Greig B26198/44.
[65] Ungar B4934/47.

part in "serous inflammation" — possesses considerable histaminolytic power.[65a]

The nearly complete disappearance of renal arginase following the "endocrine kidney" operation [66] may be related to the cessation of urine secretion.

Various toxic substances increase β-glucuronidase-activity in the liver and other organs. Since this is true even after treatment with substances unlikely to form glucuronides, the response has been considered to be related with non-specific tissue-injury or repair.[67] It may thus be a manifestation of the G-A-S.

Hypertensin appears to compete with oxytocin as a substrate for **oxytocinase**; hence the latter, like **hypertensinase** (cf. above) may well participate in the regulation of vasopressor reactions.[67a]

A particularly interesting pertinent series of observations is concerned with the so-called **"adaptive enzymes"**. Enzymes of this type are perhaps formed by self-duplicating cytoplasmic units. It has been possible to prepare an adaptation-stimulating principle from galactose-adapted yeast-cells. Incubation with protein denaturants (such as urea) inactivates this principle in vitro; these same denaturants also inhibit normal adaptation of yeast.[68] It appears that enzymatic adaptation involves a modification in the protein components of the cell.[69] It is very tempting to assume that the production of specific enzymes, which help certain defense-reactions, represents an important part of adaptation to particular agents. Such selective adaptation must be clearly distinguished from the non-specific adjustments to systemic stress as such, which characterize the G-A-S. Yet, adaptation, in most of its phases, is largely an enzymologic problem.[69a]

The above data call to mind the so-called **"protective enzymes"** or "Abwehrfermente" of Abderhalden. Allegedly, after parenteral administration of extracts made from certain organs, the blood acquires the property to attack specifically proteins of these same organs. Similar "protective enzymes" may appear in the blood and urine of patients who suffer from circumscribed lesions in certain organs (e.g., endocrine glands, brain). These enzymes can be demonstrated in vitro by their ability to attack more or less selectively the organ-substrate in question.[70] Perhaps such "protective enzymes" also play a rôle during the G-A-S, but unfortunately, the protective-enzyme-theory has not received unanimous confirmation.

[65a] Carlsten et al. B46629/49.
[66] Kochakian and Dontigny B3631/47.
[67] Levy et al. B37530/48.
[67a] Croxatto et al. B46580/48.
[68] Reiner and Spiegelman B17737/48.
[69] Spiegelman and Reiner B17759/48, Spiegelman et al. B18092/47.
[69a] Cedrangolo B46622/49.
[70] Abderhalden and Buadze 21984/30, Buschhaus B19549/41, Harrer B37503/48, Merten and Starke B38534/47.

VITAMINS

Vitamin-A

The vitamin-A-content of the blood appears to describe a **characteristic** curve in the course of various conditions conducive to systemic stress. Following a transitory decrease to very low levels there is a rise. The former presumably corresponds to the A-R, the latter, which coincides with clinical signs of recovery, to the stage of resistance. Such curves have been observed after **traumatic** operations,[1] in **pneumonia**[2] and in a variety of **other febrile diseases.**[3]

The hepatic stores of vitamin-A are not necessarily reduced during the acute stage, hence it was assumed that the initial hypovitaminemia is due to a shift of vitamin-A into the liver; allegedly, from here it cannot be mobilized during acute stress, but is discharged into the blood at the time of recovery.[4] The probable relationship of this change to the G-A-S is suggested by the conclusion that: "the hypervitaminemia A is not specific for any one disease and it could just be an unspecific reaction of the body to a previous hypovitaminotic phase, without any relation to the nature of the disease...".[5]

Thiamine

Characteristic changes in the thiamine-content of the tissues [6] and plasma [7] have been noted after **hemorrhage,** but pertinent data are not yet sufficient to venture any specific statements concerning their relationship to the G-A-S.

Muscular exercise diminishes the urinary excretion of thiamine and increases thiamine-tolerance in man.[8] This may be a G-A-S change, but studies with several other stressors will be necessary before such a generalization were acceptable.

Riboflavin

Riboflavin excretion was not affected during the catabolic-phase in men who sustained traumatic injuries in convalescence, but when the N-balance became positive there was marked riboflavin retention.[9]

Nicotinic-acid

When nicotinic-acid is given by mouth, it is converted into nicotinamide in the liver. If nicotinic-acid is administered to patients in quantities exceeding the aminizing capacity of the liver, the excess reaches the circulation aud causes vaso-dilatation. This has been used as the basis of a "nicotinic-acid tolerance-

[1] Steigmann et al. B2024/45.
[2] Breese and McCoord B26924/40, Josephs B19998/43, Lindqvist B26925/38, Popper and Steigmann B26926/43.
[3] Popper and Steigmann B26926/43, Thiele B26928/40, Thiele and Scherff B26927/39.
[4] Josephs B19998/43, Steigmann et al. B2024/45.
[5] Steigmann et al. B2024/45.
[6] Alexander B26197/44.
[7] Govier B26194/43.
[8] Croxatto et al. B23943/48.
[9] Browne et al. B347/45, B46960/50.

test" to determine the aminizing power of hepatic tissue. During the catabolic phase elicited by a variety of diseases, the aminizing power of the liver is diminished as judged by such tolerance-tests.[10] During the post-traumatic catabolic phase the excretion of N-1-methyl-nicotinamide showed no characteristic change in man.[11]

Ascorbic-acid

Special attention has been devoted to changes in ascorbic-acid-metabolism during the G-A-S, because of the previously mentioned beneficial results obtained by ascorbic-acid-treatment during certain stress-situations (cf. Resistance ← Ascorbic acid, p. 79). The importance of this vitamin in resistance is further emphasized by the great variations in the ascorbic-acid-content of the adrenal-cortex which occur during the G-A-S. (Cf. G-A-S → Adrenals.) It should be kept in mind that according to one theory, the chief function of ascorbic-acid is the production and maintenance of intercellular substances [12] and that the tensile strength of healing wounds is allegedly increased by ascorbic-acid feeding.[13]

It is apparently **characteristic** of the G-A-S that stressors augment the ascorbic-acid requirements of the body. On the basis of an extensive review of the literature and personal investigations, it has been concluded that "if given in large doses, almost any drug causes a mobilization of vitamin-C from the cells during the first pharmacodynamic stage. This mobilization manifests itself by a transfer of this vitamin to the adrenals and the kidneys, sometimes the spleen, while the other organs such as the liver, lungs, heart, brain, generally react with a diminution in their ascorbic acid content ...adaptation itself to drugs may depend upon this factor".[14]

The ascorbic acid tolerance may be increased [14a] or decreased [14b] during stress.

In order to correlate such observations with the G-A-S-concept, it is essential, however, to take the time-factor into consideration. This was done in experiments on rats submitted to surgical trauma, barbiturate anesthesia, cold, fasting and foreign-protein-administration as representative alarming stimuli. "In all experiments the response of the plasma-ascorbic-acid assumed the typical triphasic pattern, characterized by an initial, marked decrease, followed by a rapid increase to above-normal levels. The intensity and duration of these changes were apparently related to the severity of the stress. In the final stages a progressive decline ensued. This type of response is similar to that of other metabolites during the general-adaptation-syndrome." [15]

During **traumatic** shock there is a transitory fall in plasma-ascorbic-acid.[15a] At the same time the urinary elimination of ascorbic-acid is greatly diminished following its oral administration in man [16] or intraperitoneal injection in the guinea-pig.[17] This increased tolerance was considered to result from an increased need for vitamin-C. This change is of such magnitude that it can hardly be ascribed exclusively to increased local utilization of ascorbic-acid by the directly injured tissues.

[10] Erdei B18506/48.
[11] Browne et al. B347/45.
[12] Wolbach B26929/37.
[13] Bourne B26846/44.
[14] Frommel and Beck **B35577/47.**
[14a] Andreae and Browne B35216/46.
[14b] Booker et al. B47110/50.
[15] Fortier and Skelton B38910/49.
[15a] Abbott et al. B29501/46, Schovanec B45099/44.
[16] Andreae and Browne B35216/46, Beattie B18456/47, Browne et al. B347/45, B46960/50.
[17] Reid B19301/48.

In fatal **hemorrhagic** shock the ascorbic-acid of the liver fell to low levels, while that of the plasma rose up to six-fold the normal value in the rat.[18]

After **burns** extraordinarily high (700 mg./day) amounts of ascorbic-acid can be given to patients orally without causing any noteworthy elimination of the vitamin through the urine.[19]

Following exposure to **cold** the ascorbic-acid-content of the tissues (not only of the adrenals but even that of the kidneys, liver, etc.) decreases in not-adapted animals and in those which are unable to resist exposure. Conversely, during the stage of resistance to cold, both guinea-pigs and rats retained excessive amounts of this vitamin in their tissues. The guinea-pig, unlike the rat, is unable to synthetize this vitamin; hence in the former, ascorbic-acid must be administered exogenously to demonstrate increased storage during adaptation. In both species, however, there appears to be a direct proportion between the ascorbic-acid content of the tissues and the degree of resistance to low temperature.[20] Significantly, upon exposure to cold, the urinary elimination of ascorbic acid is increased in the rat and decreased in the guinea-pig.[21] These changes have been considered to be characteristic of the G-A-S.[21a]

Various **infections** and intoxications with microbial products, elicit typical G-A-S-changes in ascorbic-acid-metabolism. In rats infected with trypanosoma hippicum, the liver, spleen and adrenals showed significant decreases in reduced ascorbic-acid-content. The dehydro-ascorbic acid concentration of the muscle was increased slightly and both dehydro-ascorbic- and reduced ascorbic-acid-concentrations rose markedly in the plasma.[22]

In guinea-pigs, receiving a complete diet, injections of diphtheria-toxin diminished the ascorbic-acid-content of the plasma, adrenal, liver and kidney.[23] As regards the liver, this has been confirmed both with diphtheria- and with tetanus-toxin.[24]

In view of the previously mentioned **diurnal variations** in corticoid-production, it is interesting that, in rabbits, the ascorbic-acid-concentration of the blood shows typical 24 hr. variations, with a maximum at midnight and a minimum in the morning. However, since fasting prevents these diurnal variations, they are apparently related to the food-intake itself.[24a]

In **undernourished** rats the ascorbic-acid-content of the liver is diminished; [25] in man, undernourishment, and especially lack of **vitamin-A**, allegedly also augments ascorbic-acid requirements, particularly if much **muscular exercise** is performed.[26] Various **infectious diseases** diminish the plasma-ascorbic-acid content and elicit certain signs of scurvy, while the urinary elimination of this vitamin rises above normal.[26a]

Hypophysectomy causes a marked and progressive decrease in the plasma-level of ascorbic-acid in rats. At the same time, removal of the pituitary prevents the plasma-ascorbic-acid-changes which normally follow exposure

[18] Long 98425/47.
[19] Andreae and Browne B35216/46. Browne et al. B347/45, B46960/50.
[20] Dugal and Thérien B3158/47, B2210/47, B2569/47, Thérien and Dugal B4624/45, B3157/47.
[21] Thérien and Dugal B23338/48, B43503/49.
[21a] Morros Sarda B46148/49.
[22] Nyden B28281/48.
[23] Ghosh 76328/39.
[24] Scartozzi B38631/46.
[24a] Hökfelt B39099/49.
[25] Mulinos et al. A38469/42.
[26] von Wendt B3173/47.
[26a] Figueroa B44762/48.

to *stress* (e.g., cold) *Corticotrophin,* on the other hand, increases the plasma-ascorbic-acid-level in hypophysectomized animals. "This is considered as additional evidence that the plasma-ascorbic-acid in the rat is intimately connected with the activity of the pituitary-adrenal system .[27] Allegedly, corticotrophin exerts no noteworthy effect upon the concentration of this vitamin in other tissues (e.g., liver, kidney, muscle, lymphoid organs).[28]

Reports concerning the effect of **ACTH** and **adrenocortical extract** in intact animals are difficult to evaluate.[28a]

It had been claimed that **adrenalectomy** fails to influence the ascorbic-acid-concentration of the plasma and urine in cats.[29] However, recent systematic investigations show that, at least in the rat, a marked fall in plasma-ascorbic-acid follows ablation of the suprarenals. Furthermore, adrenalectomy prevents the characteristic plasma-ascorbic-acid-response, normally elicited by stress (cold). Conversely, treatment with an adrenal-cortical extract raises the plasma-level of this vitamin even after suprarenalectomy.[30] Adrenalectomy prevents the rise in plasma-ascorbic acid normally produced by *adrenaline* in the rat.[31] *Pantothenic acid,* which exerts a life-maintaining effect in adrenalectomized rats, diminishes their urinary loss of ascorbic acid.[32]

Thus available data suggest that the plasma-ascorbic-acid varies during the G-A-S, describing a curve similar to that of the blood-sugar. Apparently in both cases the gluco-corticoids are required for the rise characteristic of the counter-shock and resistance phases, while the fall seen during the shock phase is associated with a relative corticoid deficiency.

[27] Fortier and Skelton B38910/49.
[28] Long 98425/47.
[28a] Booker et al. B47110/50, B47111/50.
[29] Demole and Verzar B25817/47.
[30] Fortier and Skelton B38910/49.
[31] Morros Sarda B46148/49.
[32] Dumm and Ralli B39044/49.

HEMOGLOBIN AND ITS DERIVATIVES

Some pertinent data have already been mentioned in connection with hemoglobin-determinations as an index of blood-volume-changes (cf. Water balance, p. 206) and in our discussion of iron-metabolism (cf. Iron metabolism, p. 202); additional data will also be found in subsequent sections on the blood-count, bone-marrow and the reticulo-endothelial system (cf. G-A-S → Hemopoietic system).

An increased rate of erythrocyte-destruction, and secondarily of hemoglobin-decomposition, is rather **characteristic** of various types of systemic stress; it is especially pronounced after **burns.** Here it is customary to distinguish two types of red-cell-damage: that caused by heat itself and that secondary to the resulting systemic stress.[1] Decomposition of erythrocytes, with the formation of pigment-granules, has been observed in burned dogs as early as 1868;[2] it was ascribed to the direct effect of heat. Subsequently, numerous observations on experimental animals and man confirmed that within the first 36 hours after burns, there is granular disintegration of erythrocytes, with subsequent hemoglobinemia and urinary elimination of hemoglobin and its derivatives.[3] While this process is under way, precipitation of blood-pigment or myoglobin-derivatives within the renal tubules may lead to severe complications (cf. G-A-S → Kidney).

Exposure to **cold** causes marked hemoglobinuria in sensitive individuals. This is generally referred to as "paroxystic hemoglobinuria a frigore".[4] In rats, sensitized by unilateral nephrectomy, NaCl and a high-protein-diet, hemoglobinuria is likewise common,[5] but the relationship of the latter phenomenon to that seen in man, has not yet been examined.

Total-body-**x-irradiation,** which depresses erythropoiesis, causes a transitory rise followed by a complete cessation of hemin-synthesis. This was demonstrated in rats given labelled (C^{14}) glycine, an amino-acid which is incorporated in hemin.[6] In various species there is a significant increase in bile-pigment-elimination, indicating that radiation-anemia is in part hemolytic in nature.[7]

Various types of **malnutrition and undernutrition** likewise cause erythrocyte-disintegration with consequent hemosiderosis of the reticulo-endothelium, for instance, in the spleen.[8] From such observations it was concluded that "the pigment-deposits stored here show indubitably that excessive catabolism of iron-containing chromoproteins occurs under such conditions"[9] (cf. Crush

[1] Hilgenfeldt 38008/36.
[2] Wertheim B26971/867, B26972/868, B26973/868.
[3] Billroth B26957/878, B26956/865, Dohrn B26958/01, Feltz B26959/870, Hilgenfeldt 38008/36, Hock B26960/893, Hoppe-Seyler B26961/881, Lesser B26962/880, Ponfick B26964/876-77, B26963/880, B26965/883, Sonnenburg and Tschmarke B26969/15, Strümpell B26966/886, Tschmarke B26967/897, B26968/27, Wilms B26970/01.
[4] Widal et al. A32637/13.
[5] Selye 35935/ND.
[6] Salomon et al. B32890/49.
[7] Schwartz B33435/49.
[8] Florentin and Hacquard B26974/43.
[9] Lamy et al. B26867/48.

syndrome). Yet, fairly severe undernutrition in man is not necessarily accompanied by a significant decrease in blood-hemoglobin.[10] Studies with labelled (C^{14}) glycine indicate that, in the rat, starvation inhibits hemin-synthesis, after a transitory rise. Thus its effect resembles that of x-irradiation.[11]

Various chemicals, especially the sulfa-drugs tend to cause porphyrinuria in man. This effect is also shared by aniline, lead-salts and many other compounds.[12] It is largely dependent upon erythrocyte destruction, but systemic stress may also play a rôle in derangements of porphyrin metabolism.

Various **diseases,** conducive to medical shock, raise the "icterus index".[13] This may well be related to their stressor action.

In **senile** individuals, a brown "wear-and-tear pigment" (the so-called "Abnützungspigment" of the German investigators) is often plentiful in heart- and liver-cells. Small amounts of it are normally present in these organs. The pigment is generally considered to be a lipochrome, an iron-free lipid-containing derivative of hemoglobin. As its name suggests, it is probably a by-product of metabolic processes incident to continued wear and tear; it may be related to changes characteristic of the stage of exhaustion.[14]

The **adrenals** do not seem to influence the normal hemoglobin level in rats, "though under conditions of stress, such as turpentine injection, they may play some rôle in preventing a drop in the level of hemoglobin that might otherwise occur".[15]

In rats, receiving large doses of *cortisone,* the macrophages of the spleen and liver, as well as many convoluted tubules (lumina and cell bodies) in the kidney, are often loaded with brownish pigment granules. These are presumably derived from hemoglobin.[16]

[10] Nizet 95585/45.
[11] Salomon et al. B32890/49.
[12] Figge et al. B35567/46.
[13] Davidson et al. 87543/46.
[14] Hueck 35545/12.
[15] Majumder and Wintrobe B42808/48.
[16] Selye 35935/ND.

VARIOUS OTHER SUBSTANCES

A decrease in the **oxygen-content** of venous blood is a characteristic manifestation of shock, but the arterial oxygen-saturation tends to remain normal until shortly before death.[1] The decrease in oxygen-saturation usually becomes obvious first in the veins of the extremities, then in the portal, hepatic and renal veins; the blood coming from the brain preserves its oxygen-content longest.[2] Presumably, the body's compensatory mechanisms are most adequate as regards the maintenance of oxygen-supply to the nervous system which is particularly sensitive to anoxia. (For CO_2, cf. chapter on pH changes.)

In patients in whom artificial fever was produced by pyrogens, there was a marked increase in the urinary elimination of **histidine;** then followed by a secondary fall as the fever began to abate.[3] (Cf. Histamine, p. 241-243.)

Allegedly a fall in the reduced **glutathione** of the blood occurs regularly in man following surgical interventions especially if they are severe and poorly tolerated.[4] These data require confirmation. It is especially noteworthy, however, that dietary depletion of the blood-glutathione sensitizes the rabbit to the diabetogenic action of alloxan and uric-acid.[5] (Cf. Diabetes, below.)

The possibility that endogenous **guanidine**-intoxication may play a rôle in the pathogenesis of "azotemic syndromes" has been considered.[6] There is no proof of its participation in the G-A-S, but it is suggestive that guanidine possesses a definite, hypertensive action and that an increased blood-guanidine concentration has repeatedly been reported in clinical and experimental hypertension.[7]

Pyrexin is the name suggested for a pyrogenic factor associated with the euglobulin-fraction of inflammatory exudates. It is allegedly not present in normal serum, but appears in the blood during inflammation and hemolysis.[8]

Incompletely characterized **toxic substances** have been claimed to occur in the thoracic-duct-lymph following experimental crush-injury and other types of trauma.[9] This observation is frequently quoted in support of the "toxic theory" of shock (cf. p. 87). During the A-R (muscular exercise. cold) various substances (adrenaline, histamine), which could not pass through the normal intestinal epithelium, can be absorbed from the exulcerated gastrointestinal tract. From this we concluded that the increased absorption into the blood of toxic substances, such as are usually present in the alimentary tract, probably plays an important part in the genesis of the shock-phase.[10]

[1] Aub and Cunningham 40959/20, Brofman and Green B25578/43, Frank and Fine B26173/43, Gutman et al. 81881/41, Price et al. B26011/41.
[2] Engel et al. B26172/44, Wood et al. A34379/40.
[3] Bonetti B19637/45.
[4] Larget et al. A57032/41.
[5] Griffiths B23068/48.
[6] Loeper et al. B19724/44.
[7] Dexter **91416/46.**
[8] Menkin B1166/45.
[9] Blalock B19952/43, Katzenstein et al. A59009/43.
[10] Selye A8052/38.

In this connection the "**reaction of inhibition of Donaggio**" [11] should also be mentioned. If thionine and ammonium-molybdate are mixed, the dye is precipitated; this reaction is not inhibited by normal urine or spinal fluid. However, in a variety of diseases, both urine and spinal fluid acquire the ability to prevent this precipitation. At first, Donaggio thought the reaction could help the diagnosis of individual diseases, however, it was soon recognized that the "phenomenon of inhibition" is not specific of any particular malady, but occurs in numerous *infections*, after *operations* and other *injuries*. Subsequent investigations suggested that the inhibition depends upon the polypeptide [12] or albumin [13] content of the fluids examined, but the underlying chemical mechanism remains unknown.

In some manner the phenomenon appears to be associated with the G-A-S. It has been considered to be an objective indicator of fatigue ("Ermüdungsreaktion") and was found to become highly positive after *muscular exertion*,[14] in *psychotic patients* who respond poorly to metrazol-shock therapy [15] and after surgical *trauma*.[16]

The relationship to the G-A-S of all the above-mentioned metabolic changes is not clearly established, but their occurrence under the influence of systemic stress suggests that they may participate in this syndrome.

[11] 55586/33, B26239/34, B26240/34.
[12] Greco B26241/36.
[13] Delmas-Marsalet B26881/46.
[14] Jezler B26242/37, B26243/38.
[15] Gerundo and Webman 79197/40.
[16] Perazzo A33129/39.

METABOLIC DISEASES OF ADAPTATION

This chapter will deal with those diseases of metabolism in which a derangement of adaptation to systemic stress has been suspected to play a major rôle. In reading these pages, it should be kept in mind that they are written at a time when the concept of the diseases of adaptation is just beginning to take shape. It is already quite evident that hormones whose production is influenced by systemic stress (e.g., anterior-pituitary hormones, corticoids) exert important actions upon metabolism and that derangements in their production may cause metabolic diseases. On the other hand, it is still very difficult, at present, to delimit those metabolic derangements in which maladaptation to stress is the major factor, from those in which the G-A-S is merely superimposed upon a specific metabolic disease which elicits the G-A-S as an incidental by-product of its systemic stressor action.

In view of these uncertainties, we shall make at least brief mention of all those metabolic diseases which have specifically been discussed as possible diseases of adaptation.

Diabetes mellitus. — A few years ago, we envisaged the possibility that diabetes mellitus may be a disease of adaptation.[1] Since that time, a good deal of evidence has accumulated in support of this view.

Many pertinent **experimental data** have been surveyed in the preceding section. Let us merely mention here that during the stage of resistance, animals tend to exhibit a "diabetic type" of glucose-tolerance curve and become rather insulin-resistant.[2] Furthermore adrenalectomy, or compensatory atrophy of the adrenal-cortex produced by a mineralo-corticoid (such as DCA), interfere with the normal hyperglycemic response to stressors and tend to cause hypoglycemic responses during the G-A-S.[3] On the other hand, adrenalectomized animals given maintenance doses of cortical extract, respond to stressors (e.g., trauma, typhoid vaccine) with the normal hyperglycemia.[4] From this it was concluded that perhaps "anterior-pituitary hormone which inhibits the hexokinase reaction is secreted in increased quantities during infections and stress, and that the hypersecretion of this hormone causes decreased glucose utilization and hence an exacerbation of diabetes".[5] Observations of this kind convinced us that the hyperglycemia of the resistant phase is not merely a direct consequence of increased gluco-corticoid secretion, but depends upon a peripheral synergism between these steroids and some other factor produced during systemic stress. (Cf. pp. 125, 126.)

After subtotal pancreatectomy, nephrosclerosis tends to develop in rats and histologically, these renal lesions are "very similar to those observed in the kidneys of diabetic patients".[6] This observation suggests that stress can not only produce a diabetic type of response, but that conversely, a primary pan-

[1] Selye B1204/46.
[2] Masson A34562/40, A36632/41, 98782/41.
[3] Selye and Dosne A37249/42.
[4] Selye and Dosne A37037/41, Tobian and Edwards B38783/49.
[5] Tobian and Edwards B38783/49.
[6] Foglia et al. B31714/48, B41177/48.

creatic diabetes can sensitize the organism to the production of renal lesions which resemble those induced by stress, LAP or DCA.

The production of an A-R (formalin injections) in slightly diabetic, partially pancreatectomized rats, actually diminished their glycosuria, despite the accompanying adreno-cortical enlargement.[7] However, as we explained above, stress augments glucose requirements; hence we cannot conclude from this observation that, under other conditioning circumstances, it could not aggravate diabetes as a result of a prolonged ACTH discharge. Here, presumably the availability of glucose or its precursors (glycogen, protein) determine the end result.

Among the pertinent **clinical data,** let us mention first, that hypercorticoidism (e.g., adreno-cortical tumors, Cushing's disease) tends to produce insulin resistance because the gluco-corticoids antagonize the action of the pancreatic hormone. Since stressors increase corticoid production, it is significant that patients with marked adiposity, essential hypertension,[8] malignant hypertension, collagen disease, psychosomatic disorders, advanced neoplastic diseases or active infections, often become relatively insulin resistant.[9] Furthermore, the lymphopenic effect of orally administered glucose is exaggerated in untreated diabetics. Since this is considered to be an index of ACTH secretion, the excessive lymphopenia so produced could be interpreted as due to an increased tendency to discharge corticotrophin.[10]

Typical systemic stressors. such as psychic or physical trauma [11] may elicit diabetes mellitus in man. Such instances of traumatic diabetes have been interpreted as diseases of adaptation due to a derailment of the G-A-S.[12] In one pertinent study on eleven diabetic individuals "increased glycosuria and ketosis were observed repeatedly during conflicts associated with fear, depression, frustrated anger and, as far as could be ascertained, in the absence of significant changes in diet, insulin or activity".[13] Furthermore, "significant emotional conflict has been shown to be associated with a rise in the blood-ketone level and a simultaneous 'washing out' of glucose through diuresis. The evidence indicates that such a mechanism is commonly involved in the decompensation of diabetes and the production of clinical ketosis".[14]

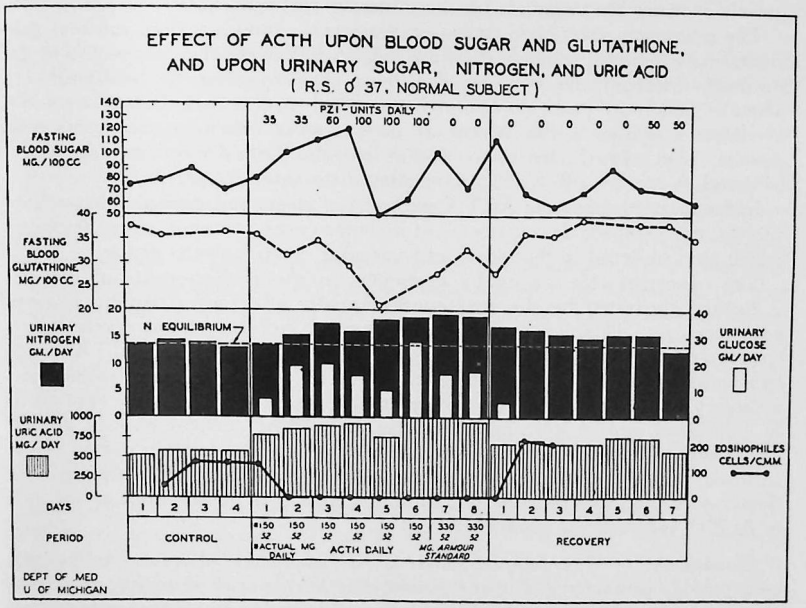
Allegedly, even changes in atmospheric conditions can aggravate diabetes mellitus in man.[15]

The well known fact that during war-time the incidence of diabetes tends to decrease [16] is not incompatible with the assumption that stress tends to elicit this disease. Here the beneficial effect is not due to non-specific stressors but to the accompanying malnutrition which has a specific antidiabetic effect.

Metabolic studies in man receiving large doses of ACTH furnished especially instructive pertinent data. It was found that corticotrophin not only produces a "diabetic state", but that this is accompanied by a decrease in blood glutathione.[17] It was assumed "that a purine metabolite having an alloxan-like effect is responsible for reducing the intracellular availability of free sulfhydryl groups

[7] Ingle B46486/50.
[8] Mirsky et al. B33429/49.
[9] Nuetzel and Olsen B32799/49.
[10] Marks et al. B19152/48.
[11] Liebig **B324/32**, Mirsky B43935/48, Smith and Cobb **A69389/43.**
[12] Harvier et al. B27379/48.
[13] Hinkle and Conger B32771/49.
[14] Hinkle et al. B33417/49.
[15] Thalhammer B43616/49.
[16] Vartiainen B39569/46.
[17] Conn B46959/50, Conn et al. B46372/48.

(necessary for normal function of many enzyme systems), causing functional abnormalities within the islet-beta-cells, as well as blocking normal glucose utilization peripherally." Furthermore, ACTH appears to decrease the renal-tubular reabsorption of glucose, presumably as a result of inhibition of an enzyme within the tubular epithelium. Interestingly, administration of large amounts of reduced glutathione abolishes an already established hyperglycemia in spite of continued ACTH treatment.[18] Presumably ACTH discharge could cause diabetes through: (1) increased production of alloxan-like purine metabolites, with a resultant decreased availability (binding ?) of the - SH groups (such as are furnished by glutathione), which are known to alleviate alloxan-diabetes. Since alloxan also causes a diminution of blood-glutathione, it is possible that the formation of alloxan-like purine metabolites participates in the genesis of this same change following ACTH administration; (2) renal diabetes, due to inhibition of tubular glucose reabsorption. Thus, a sudden discharge of ACTH during stress may play an important rôle in the initiation of diabetes among genetically predisposed individuals.[19]



Certain metabolic effects of ACTH in man. — Note transitory increase in blood-sugar, decrease in blood-glutathione, increase in urinary nitrogen and uric acid accompanied by glycosuria and typical eosinopenia, during ACTH administration.

(After Conn et al. B44962/49.)

During diabetic acidosis, increased adreno-cortical activity has been detected by a fall in circulating blood-eosinophils and a subsequent pronounced rise in the urinary excretion of corticoids.[20] Furthermore, the great potassium avidity

[18] Conn et al. B33407/49.
[19] Conn et al. B32328/49, B44962/49.
[20] McArthur et al. B35945/49.

of the tissues, in diabetics recovering from coma, has been compared to that caused by DCA overdosage.[21] It remains to be shown, however, whether hypercorticoidism at this time is the cause of diabetic acidosis or the result of the consequent systemic stress.

Studies concerned with the **pathologic anatomy** of diabetes have shown that arteriosclerosis and nephrosclerosis are very common, especially if the disease is of long standing. If diabetes is interpreted as a disease of adaptation, such lesions could be attributed to the same pathogenic stressor which causes the derangement in carbohydrate metabolism itself, since through corticotrophic stimulation, both diabetes and arteriosclerosis could be induced. It must be kept in mind, however, that although pure ACTH may cause diabetes, it does not usually elicit vascular hyalinosis and indeed tends to inhibit the latter through the production of gluco-corticoids. Hence, if we accepted this interpretation, we would have to assume that in diabetes, both gluco-corticoid and mineralo-corticoid production are augmented with a considerable predominance of the latter, or at least, that the metabolic derangements during this disease greatly sensitize the organism for the mineralo-corticoid effect.

The previously mentioned animal experiments, showing that subtotal pancreatectomy in itself suffices to cause nephrosclerosis, also suggest that the resulting metabolic derangement sensitizes the organism to hyalinosis (cf. above). Statistical studies indicate that optimal insulin and dietary treatment of diabetes postpones the advent of degenerative cardiovascular and renal disease. This led to the conception that at least the latter are due to a derailment of the G-A-S caused by continued exposure to metabolic stress.[22]

In summary, through the ACTH mechanism, stress can cause diabetes; conversely, the metabolic derangements of diabetes cause systemic stress responses which tend to derail so that renal and vascular complications ensue.

The important rôle played by corticoids in the pathogenesis of diabetes is further illustrated by the striking **therapeutic** effect of complete bilateral adrenalectomy. This was performed in a patient suffering from severe hypertension and diabetes. The blood-pressure fell and remained normal. Although this patient received only maintenance doses of cortical extract, insulin was necessary to prevent glycosuria. However, the insulin requirements were greatly diminished and roughly paralleled the amount of cortical extract given.[23] This clearly indicates that the persistence of diabetes is not solely due to hypercorticoidism, but this finding is not in contradiction with the previously discussed theory according to which the initiation of diabetes depends upon an increase in ACTH and corticoid production.

Glucopenia. — The fatigue which is so frequently observed in patients with various neuropsychiatric complaints, has been ascribed to hypoglycemia. During emotional stress, the latter is allegedly produced by prolonged vagal stimulation and the resulting hyperinsulinism, as judged by the fact that atropine tends to restore the blood-sugar to normal.[24]

Many additional observations discussed in other sections of this volume indicate that systemic stress can cause derangements due to increased vagal stimulation. A disproportionately intense hyperactivity of the parasympathetic

[21] Danowski et al. B30928/49.
[22] Millard and Root B29734/48.
[23] Green et al. B32755/49.
[24] Portis and Zitman B33339/43, Portis B47391/50.

nervous pathways during the G-A-S could thus produce hyperinsulinism as a disease of adaptation. The resulting hypoglycemia would tend to be particularly severe if the normal pituitary-adrenocortical response to stress were simultaneously diminished. Such derangements of the G-A-S deserve more attention than they have hitherto received, especially since it has now been shown that in children with "familial hypoglycemosis" ACTH, given during a few days, produces long-lasting remissions.[25]

Leanness. — We pointed out, in the section on lipid metabolism, that stress tends to deplete the fat reserves of the body as part of its catabolic actions. The fact that the adipose-tissue reserves are lost, both during acute stress situations and in the course of prolonged illness, is too familiar to deserve discussion. It should be pointed out, however, that the intimate humoral mechanism, through which the combustion of fat is effected during stress, remains to be elucidated. The hypophysis-adrenocortical system is certainly not indispensable for this response, since the fat depots are lost during stress, even in hypophysectomized or adrenalectomized animals.

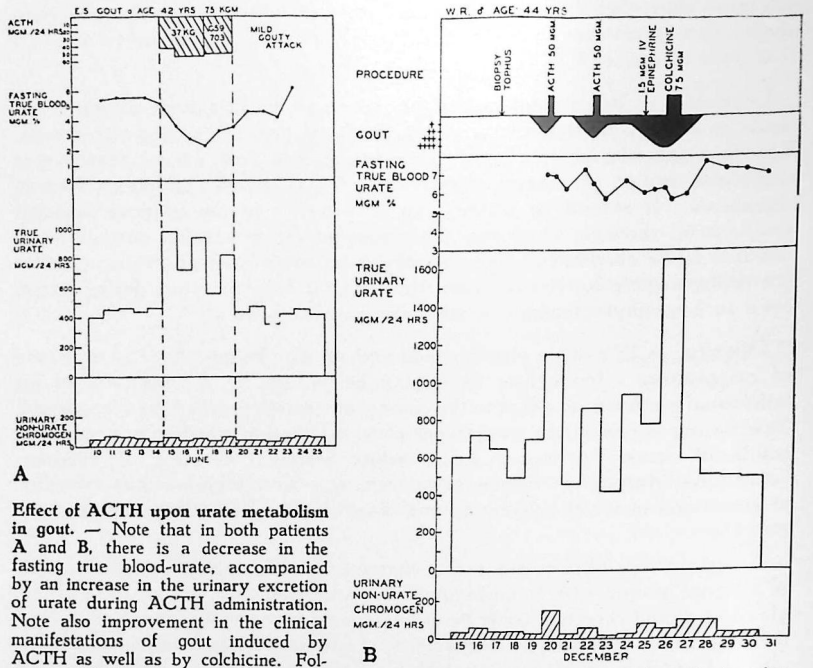
Obesity. — In a sense obesity could perhaps also be envisaged as a disease of adaptation. "Inadequate as it may be, obesity is the resultant of an individual's attempt to adapt to the emotional stresses to which he is exposed." Overeating is one of the many types of maladaptation which may occur as a result of stress.[26] Various social habits, maternal favoring of children, "emotional starvation", emotional conflicts, etc., have been listed as examples of situations in which overeating and obesity may act as protective mechanisms.[27]

A certain type of obesity is rather characteristic of Cushing's syndrome and, in adipose people with a "cushingoid" constitutional type, excess ACTH and gluco-corticoid secretion could be of pathogenic importance. However, forced feeding causes excessive fat storage even in adrenalectomized and hypophysectomized animals, hence in most instances, obesity is not the direct result of an excessive corticoid production.[28] We do not know whether the "lipophil dystrophy", which often follows starvation, is due to adaptive hypercorticoidism. It is suggestive however, that this condition is often associated with "cushingoid" manifestations.

Gout. — It has long been known that an attack of gouty arthritis can be precipitated in predisposed subjects by a variety of stressors [29] such as physical trauma,[30] infection, chilling, foreign protein therapy, x-irradiation, etc. Since all these agents are very effective in producing an A-R with the corresponding ACTH discharge, it has been suspected that the gouty attack may be related to this systemic response to stress.[31] In order to test this hypothesis, ACTH was given during an attack of gouty arthritis, with the result that the joint manifestations promptly disappeared. However, if the ACTH was injected during the interval period in patients predisposed to gout, an attack of arthritis

[25] McQuarrie et al. B46970/50.
[26] Mirsky B43935/48.
[27] Gastineau and Rynearson B45809/47.
[28] Selye **94572/49.**
[29] Paillard and Fauvert **98454/45.**
[30] Ficarra and Adams 89581/45.
[31] Hellman B32329/49.

was usually precipitated three to four days after the injection, apparently as a "withdrawal phenomenon".[32] Several subsequent investigators confirmed that ACTH causes a remission, when given to patients during an attack of gout.[33]



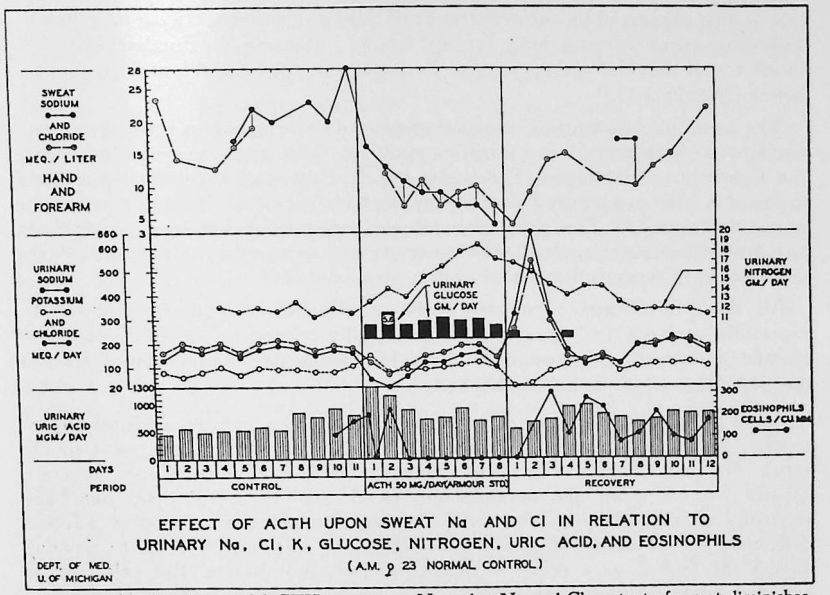
Effect of ACTH upon urate metabolism in gout. — Note that in both patients **A** and **B**, there is a decrease in the fasting true blood-urate, accompanied by an increase in the urinary excretion of urate during ACTH administration. Note also improvement in the clinical manifestations of gout induced by ACTH as well as by colchicine. Following withdrawal of such treatment a gout attack may be precipitated even in patients who were previously free of attacks for several months.

(Courtesy of Dr. J. W. Conn; partly after Robinson et al. B41851/48.)

There has been much speculation concerning the relationship between the colchicum and ACTH therapy of gout. The possibility has been suggested that, through the G-A-S mechanism, colchicine may elicit an endogenous discharge of ACTH, with a consequent uric-acid elimination, similar to that produced by exogenous ACTH.[34] Be this as it may, administration of colchicine, immediately after discontinuation of ACTH, impedes the "rebound" of acute gouty arthritic manifestations which otherwise might follow upon withdrawal of the hormone.[35] Studies with N^{15} uric acid suggest that in gout, colchicine and ACTH act through distinct mechanisms.[36] This may explain the particularly favorable results obtained with combined ACTH-colchicine therapy.[37]

[32] Hellman B32329/49, Robinson et al. B41851/48, B41844/48, B41843/49.
[33] Spies and Stone B44446/49, Margolis and Caplan B44575/50.
[34] Pincher B43467/49.
[35] Margolis and Caplan B44575/50.
[36] Bishop et al. B47207/50, Benedict et al. B47205/50.
[37] Wolfson and Cohn B46971/50.

Other investigators pointed out that the normal development of a G-A-S could not explain the whole syndrome of gout.[38] Carriers of hereditary hyperuricemia (before the development of gout) have normal urate levels until puberty, if male and until the menopause, if female. Furthermore, in gout, 17-KS excretion is markedly diminished without any clinical manifestations of hypogonadism and the ability to convert administered testosterone to 17-KS is impaired. These observations suggested that an abnormal testoid compound is produced in gout and that this hypothetical substance also controls hereditary hyperuricemia.[39]



Certain metabolic effects of ACTH in man. — Note that Na and Cl content of sweat diminishes, urinary nitrogen and uric acid rises and there is slight glycosuria during ACTH treatment. The urinary Na and Cl showed a transitory decrease during the first few days with a return towards normal levels as treatment proceeded. After interruption of ACTH administration there was a marked loss of both Na and Cl associated with some K retention. The eosinopenia was also well marked during the treatment period. (After Conn and Louis B45972/50.)

Should this theory prove to be correct, we would have to assume that the adrenal cortex of gouty patients responds to ACTH by the production of such an abnormal testoid, but this has not yet been proven by its direct identification.

Amyloidosis. — In man amyloidosis is seen in a number of chronic diseases (e.g., chronic suppuration due to osteomyelitis, tuberculosis, ulcerating tumors, syphilitic disease). It has been reproduced in experimental animals by repeated injections of staphylococci and other organisms, the injection of sodium-caseinate and the administration of various inadequate diets.[40]

[38] Wolfson et al. B37249/49.
[39] Wolfson et al. B35934/49, B41832/49, B41842/49, B37249/49, B38348/49.
[40] Boyd 99692/35, Heilmann B37872/48, Pirani et al. B37756/49.

In mice, amyloidosis is normally produced by parenteral administration of yeast-nucleic-acid salts, but urethane injections can prevent this.[41] It will be recalled that urethane also proved effective in certain diseases of the hemopoietic system, in which ACTH or cortisone can cause remissions (cf. below). Since the R.E.S. is assumed to play an important rôle in the formation of amyloid and since both urethane and ACTH exert similar actions upon the R.E.S., this finding appears to be of interest in connection with our problem.

The probable relationship between amyloidosis and the diseases of adaptation is also suggested by the occurrence of Addison's disease with amyloidosis, following burns causing long lasting wound infection.[42] Furthermore, "the incidence of amyloidosis appears to be higher in rheumatoid arthritis than is generally believed".[43]

The term "paramyloidosis" is sometimes used to designate a type of systemic amyloidosis with prominent cutaneous manifestations and a marked increase in the γ-globulins of the blood. Sometimes the deposition of amyloid-like material in the skin is so pronounced that certain authors speak of "pseudomyxoedema paramyloidosum".[44] The close morphologic connections between amyloidosis, paramyloidosis, plasmacytosis, allergic tissue reactions and the diffuse collagen diseases, have recently been analyzed in some detail.[45]

All these observations suggest some relationship to non-specific stress, especially since amyloid appears to be chemically related to "hyalin"; however, specific investigations to establish the relationship between amyloidosis and the G-A-S have not yet been published.

Acute porphyria. — Cases of acute porphyria often exhibit adrenal hypertrophy, renal damage and liver necrosis, conjointly with a decrease in the serum Na and Cl. Since in such instances DCA and pantothenic acid are usually without avail, the derangement in electrolyte metabolism has been regarded as secondary to the renal damage, rather than to some adrenal deficiency.[46] Yet derangements in blood-pigment metabolism tend to develop during the G-A-S as a result of R.E.S. stimulation; hence, the relationship between acute porphyria and the G-A-S would deserve further study.

Diseases of salt and water metabolism. — It has previously been mentioned that several hormones which affect water and salt metabolism (e.g., corticotrophin, corticoids, vasopressin, adrenaline) participate in the G-A-S. A derangement of their production during stress may thus cause disturbances in water and salt metabolism.

Famine-edema (cf. p. 212) may, in a sense, be interpreted as a disease of adaptation to malnutrition. The adrenals are usually enlarged in patients who die from famine-edema,[47] but this does not indicate that increased corticoid production is of major pathogenic significance here, since a similar suprarenal enlargement occurs upon exposure to other stressors, without eliciting any water retention. In famine-edema, the hypoproteinemia with the resultant

[41] Schettler B46524/48.
[42] Levenson et al. B24308/47.
[43] Unger et al. B42349/48.
[44] Miescher B36161/45.
[45] Teilum B38106/48.
[46] Davies B44673/49.
[47] Sinclair B45481/48.

decrease in the protein-osmotic pressure of the blood, and an increase in capillary permeability, are the most common causes of fluid retention; occasionally, renal damage may aggravate the condition. The participation of the G-A-S mechanism in the pathogenesis of famine-edema has not yet been clearly elucidated.

The effect of non-specific damage upon the renal elimination of water and electrolytes must also be kept in mind. It has been emphasized that "almost any serious illness or injury may be looked upon as a cause for **extra-renal uremia** and yet there is no common factor accountable for it. Some of the chief clinical characteristics uniformly present are dehydration, stupor, azotemia, low blood-pressure and a shock-like appearance". It has been postulated that in such patients shunting of the renal circulation towards the medulla of the kidney may be the principal cause of these derangements.[48]

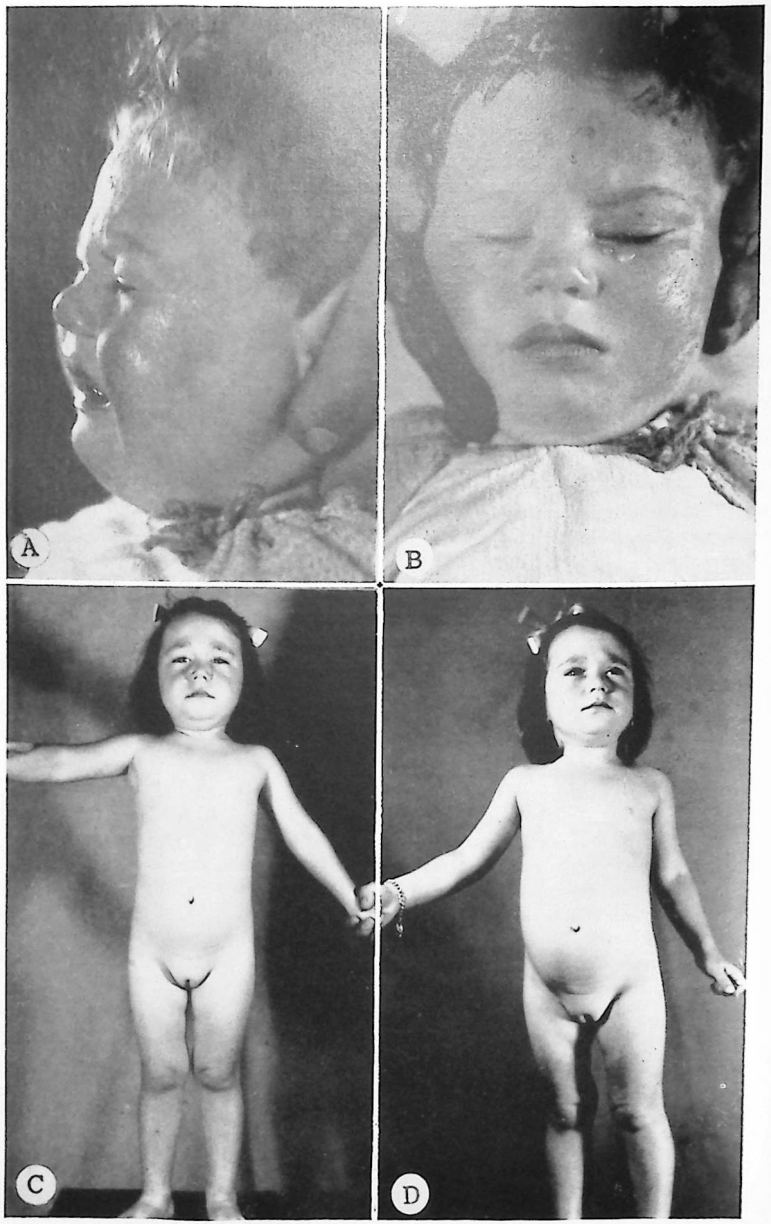
The so-called **"low-salt syndrome"** is a closely related phenomenon. It tends to develop especially when the NaCl intake is restricted while the water intake is not, or when salt is lost without corresponding amounts of water. Death occurs from uremia. In such instances the intravenous injection of hypertonic saline (5-6%), in an amount sufficient to replace the calculated deficit in extracellular fluid, proved to be very efficacious. This derangement occurs with particular frequency when there is slight impairment of renal function due to aging, hypertension or congestive circulatory failure. "It is probable that many so-called 'post-operative', 'reflex' and 'essential' anurias are the result of overhydration".[49]

Sodium withdrawal,[50] or administration of cation-exchange-resins, which interfere with the absorption of sodium,[51] tend to cause metabolic derangements similar to those of the low-salt syndrome, but the salt-deprivation thus effected exerts a favorable influence upon abnormal salt and water retention during certain derangements of the G-A-S.

Pink disease (infantile acrodynia, erythredema, "trophodermatoneurosis" or "raw beef hands and feet") has been defined as a condition "characterized by swollen bluish-red hands and feet, disordered digestion, followed by considerable muscular paresis, occurring in children between the ages of six and sixteen months." However, older children may also be affected. More recently, the view has been expressed that "pink disease should be included as one of those diseases which manifest the 'susceptible state'. These children show redness, coldness, swelling, sweating, itching and hyperesthesia, at some stage or other. Their hands are tender to touch, and they cry out in anticipation when one approaches, afraid of being handled". They also suffer from muscular weakness and photophobia. Significantly, their plasma-sodium values are unusually low.[52] NaCl supplements or DCA exert a truly dramatic curative effect, simultaneously with the restoration of the blood-Na level. Allegedly, in this disease "we are dealing with the adaptation syndrome of infants during their vegetative adjustment to post-fetal life".[53]

The appearance of such patients, and the effect of therapy based upon this concept, are illustrated by the following photographs (p. 272) and their description (p. 273).

[48] Murphy et al. B38929/48.
[49] Schroeder B33434/49.
[50] Thomas et al. B33445/49.
[51] Berger et al. B33404/49.
[52] Cheek B44563/50.
[53] Cheek and Hicks B44564/50.



Legend →

Theoretic Interpretation of Data Concerning Metabolism

In reading the following pages, it will be kept in mind that our interpretation of individual observations has already been given; here we shall merely attempt to integrate them.

The metabolic changes characteristic of the two catabolic periods of the G-A-S, namely of the A-R and the stage of exhaustion, are essentially similar. In the intermediate stage of resistance, on the other hand, such deviations from the norm usually disappear or are actually reversed.

Generally speaking, during the A-R there is an increase in the **breakdown of carbohydrates, lipids and proteins,** with a particularly marked diminution of the storage form of these body constituents (e.g., glycogen, neutral fats, "dispensable" proteins) accompanied by increased production of the corresponding breakdown products (lactic-acid, pyruvic-acid, amino-acids and other N.P.N. substances). During this great catabolic impulse, intermediate metabolites — formed in the course of the degradation of storage substances — may temporarily accumulate in one or the other compartment of the body. For instance, in the course of glycogen breakdown to CO_2, more glucose may be formed from glycogen than can be utilized by the tissues, so that hyperglycemia ensues. Similarly, very large amounts of fat mobilized from adipose tissue may temporarily be retained by hepatic cells in preparation for further degradation.

The accumulation of such intermediate products, during the G-A-S, depends upon many variables, for instance: (1) the availability of stored materials from which these intermediates can be made, (2) the intensity of their consumption by the target organs which require them during stress, (3) the intake of such substances or their precursors through the alimentary tract, (4) the rate at which they are excreted.

The part played by these variables in determining metabolic responses to stress, is subject to great individual variations, depending upon specific actions of the stressors themselves, as well as upon genetic, dietary and previous stress influences, all of which modify the responsiveness of the organism. Although essentially the basic pattern of response to systemic stress is always the same, these "conditioning factors" tend to distort the stereotypical picture. Thus a stressor with potent, specific, hypoglycemic actions, such as insulin, will mask the typical initial hyperglycemia normally observed during the adrenergic first phase of the A-R. Similarly, the transitory deposition of fat in the liver, so

←

Pink disease. — **A** and **B.** Non-pitting edema of the face in a "nervous child", who also suffered from photophobia. The plasma-Na was only 260 mg.% and the child suddenly died in circulatory collapse with cyanosis, vomiting, diarrhea and a temperature of 106°F. At post-mortem, the thymico-lymphatic apparatus was enlarged. The muscle-Na was 6.7 mg.%, as compared with 11.2 mg.% in a comparable child who died of broncho-pneumonia.

— **C.** 32-months-old girl with pink disease (before treatment). A typical "nervous child" with bad temper, poor appetite, sleeplessness, constipation, inertia, fatigue, a definite craving for salty foods; the plasma-Na was 260 mg.%. The disease was apparently precipitated by the stress of an incidentally contracted measles infection.

— **D.** Same girl after five weeks of treatment with NaCl and DCA. The facial expression of the child is now normal. She eats and sleeps well, does not tend to become tired and her temperament has greatly improved. At this time the plasma sodium was 350 mg.%.

(Courtesy of Dr. D. B. Cheek.)

commonly noted during the A-R, is not manifest if the individual has very little depot fat due to fasting, previous exposure to stress or a genetically determined lean constitution. The distortion of the characteristic picture by such conditioning factors was probably the greatest handicap in recognizing individual manifestations of the G-A-S as due to stress as such.

We mentioned that catabolism is largely dependent upon available "storage products". It is rather difficult, however, to draw any sharp line of demarcation between storage materials and those which form an essential part of living matter. The transition is quite imperceptible between labile, "dispensable" protein and that which constitutes the very essence of the living cell. Similarly, certain fats and carbohydrates which can be stored in excessive and dispensable amounts, also enter into the indispensable structure of living matter. Nevertheless, a gradient of dispensability should be recognized, both in each cell and in the organism as a whole. Within each cell, the most dispensable reserve materials are often stored in the form of granules (e.g., glycogen, lipids, proteins) which are quite clearly demarcated from the remaining cytoplasm. Considering the organism as a whole, the adipose, lymphatic and collagenous tissues appear to be most labile and dispensable. It is worthy of emphasis that during the catabolic periods of the A-R and exhaustion phases, these labile and dispensable structures are first to be attacked, while the most vital tissues (e.g., nervous tissue, heart, kidney), and here again the most indispensable parts of their cellular protoplasm, are protected with special care against the widespread tissue catabolism.

During both catabolic phases, the breakdown of materials is effected through the two great integrating systems of the body, the **endocrine and the nervous systems.** Available data do not yet permit any far reaching generalizations concerning the behavior of these coördinators during the G-A-S. However, it is already evident that in the course of the A-R, the production of catabolism-promoting hormones — particularly ACTH, glucocorticoids, adrenaline — are augmented and at the same time, the release of adrenergic substances is increased at the sympathetic nerve endings.

The hormones do not cause tissue catabolism directly, but presumably, through the intermediary of **enzyme systems.** Accordingly, during the A-R, the tissue concentration of certain proteases, lipases, phosphatases, amylases, etc. is increased; indeed some workers believe that even the acquisition of adaptation itself is dependent upon the formation of special "adaptive enzymes".

Vitamins are undoubtedly also involved in the regulation of metabolic changes during the G-A-S and it is presumably for this reason that the tissue concentration, especially of ascorbic-acid and certain members of the vitamin-B complex, undergoes characteristic variations during the three stages. The manner in which hormones influence the metabolism of energy yielding substances through the intermediary of enzymes and vitamins, is still very inadequately known, but there can be little doubt that these are fundamental mechanisms in the regulation of G-A-S phenomena.

We repeatedly had occasion to point out that certain metabolic actions of corticoids are dependent upon peripheral **conditioning factors.** Thus, the hyperglycemic effect of gluco-corticoids is considerably increased during the A-R, even in adrenalectomized animals. Presumably, some extra-adrenal

metabolic factor, present in the body at this time, potentiates the hyperglycemic effect of gluco-corticoids. The nature of this potentiating agent is not known, but it may well be a vitamin, enzyme, or some enzyme substrate. In our opinion, a more detailed study of these phenomena is very likely to furnish fundamental data concerning the mechanism of adaptive reactions.

Most of this discussion is based upon observations concerned with the A-R. The other **phases of the G-A-S** (resistance and exhaustion) have so far received but superficial attention. It appears that during the stage of resistance, the A-R manifestations disappear or are actually reversed owing to changes in the endocrine and nervous integrating systems. The extreme hyperactivity of the cortex, the maximal discharge of adrenaline from the medulla, the great stimulation, especially of the adrenergic vegetative nerves — all of which are so characteristic of the A-R — tend to vanish as resistance is acquired; at the same time, the great catabolic impulse gives way to anabolism and recovery. It should be clearly pointed out, however, that the basic factors which condition this change, as well as those responsible for the final reappearance of catabolism during the exhaustion stage, are still unknown.

It may be worth considering the following **working hypothesis.**

To help repair during stress, the gluco-corticoids (e.g., cortisone, cpd. F.) form amino-acids and carbohydrates at the expense of dispensable protein, especially that of the thymico-lymphatic organs, connective tissue, bone matrix and skeletal muscles.

These building blocks are then attracted to those cells whose "growth-potential" is most markedly raised by the need for defense and regeneration. Thus an internal transposition of protein is effected, which proves useful especially for resistance to acute stress, at times when food ingestion is impossible.

Later, however, when inflammation and scar formation begin to play an important rôle in the pattern of defense, an increased secretion of mineralocorticoids (e.g., desoxycorticosterone, 11-desoxocortisone) stimulates the deposition of extracellular protein to form the molds in which the more permanent repair structures (e.g., collagen) develop. If this deposition is excessive and its organization into fibers lags behind, the amorphous protein deposits condense into structureless masses of hyalin (and amyloid ?). The latter are not accepted as permanent prostheses and tend to be attacked as "foreign bodies" by an inflammatory granuloma (e.g., rheumatoid arthritis, periarteritis nodosa).

Conversely, during rest, intracellular protein is formed, a process aided by such anabolic hormones as somatotrophin and the testoids.

It is very probable that during stress changes in membrane permeability (caused primarily by corticoids) play a prominent rôle in the development, not only of these rearrangements of organic metabolism, but also in the regulation of electrolyte changes. During the A-R, the permeability of cell membranes increases, this facilitates the entrance of Na, Cl and Ca as well as the egress of K and PO_4 from the cell. Thus, the chemical composition of cells and plasma tends to become equalized, presumably as a result of increased cell-membrane permeability. At the same time, capillary membranes also become more permeable so that the composition of plasma and intercellular fluid also tends to become alike, and the volume of the latter rises.

During stress, it may be useful to promote the excretion of toxic K, liberated from injured cells, and to replace it by less toxic Na. It may also be advantageous to increase the intercellular fluid volume at the expense of intracellular and plasma fluid. Toxic metabolites, exogenous poisons and microbes, with which the body may become suddenly overloaded during stress, are presumably least damaging if they are removed from cells and circulation into the relatively inert tissue spaces, until they can gradually be dealt with.

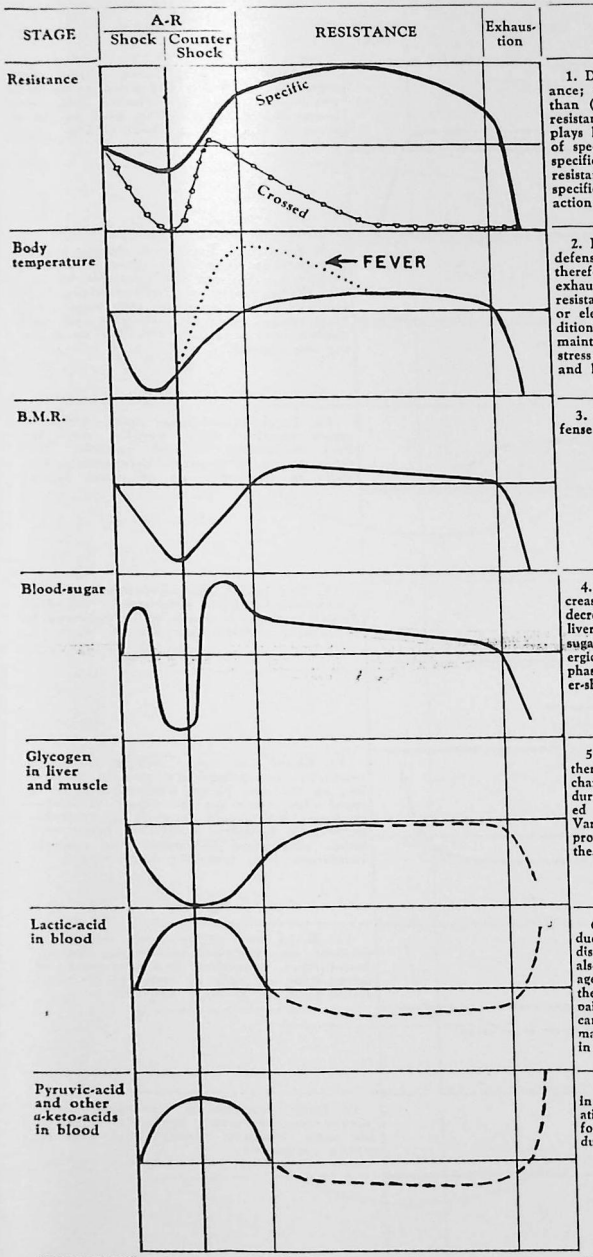
Summary of Observations Concerning Metabolism During the G-A-S.

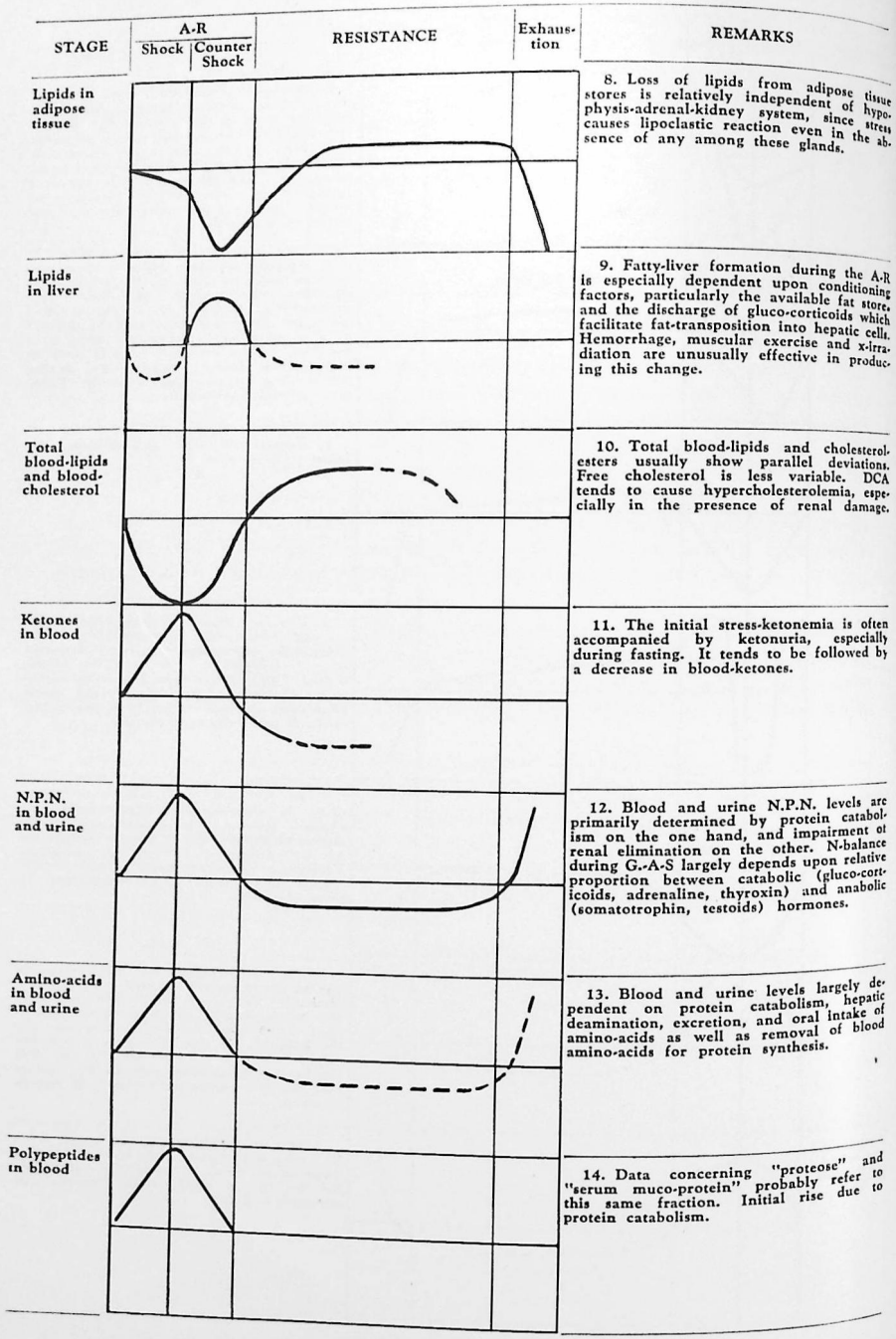
We have attempted to summarize the salient metabolic changes during the G-A-S in the form of the chart given below. In perusing this summary, it will be kept in mind that available data did not permit us to complete some of the curves. Most pertinent observations are unfortunately limited to the A-R stage; in other instances, relevant information is insufficient or contradictory. The curves should therefore merely be considered as tentative outlines of the metabolic changes which, in our opinion, are most readily compatible with the data we were able to compile from the literature or from personal observations. The most reliable data are indicated in solid lines, suggestive evidence is represented by interrupted lines and where pertinent observations are missing, the curve is interrupted.

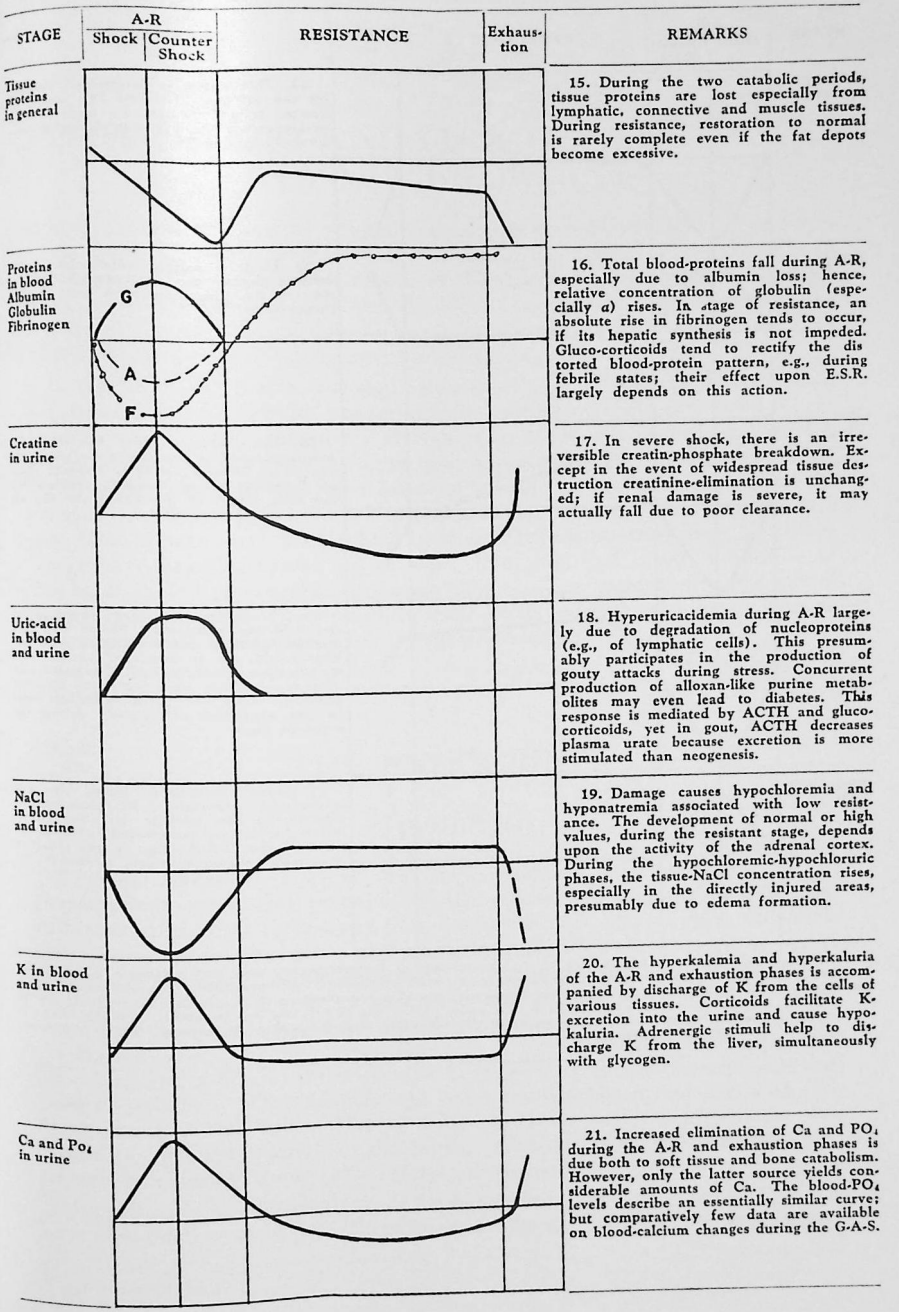
The length of the resistant phase varies greatly, depending upon the intensity of the stimulus and the adaptability of the organism. Except in the case of exposure to the most fulminant lethal stressors, it is proportionately much more prolonged than the space available on this page would have permitted us to indicate.

As we have repeatedly emphasized in the preceding pages, the metabolic responses during the G-A-S largely depend upon conditioning factors. Hence, important deviations from these "characteristic" patterns must be expected, especially with stressors known to possess a specific action upon metabolism. Nevertheless, it was felt that such somewhat idealized curves will help to visualize the deviations from the norm which appear to represent the standard pattern of response during the G-A-S.

The data concerning specific and crossed resistance are repeated here merely as a standard of reference. They will facilitate the correlation of the metabolic findings with the general course of the adaptation syndrome as described in the preceding section.




STAGE
A-R
Shock
Counter Shock
RESISTANCE
Exhaus-tion
REMARKS
Lipids in adipose tissue
8. Loss of lipids from adipose tissue stores is relatively independent of hypophysis-adrenal-kidney system, since stress causes lipoclastic reaction even in the absence of any among these glands.
Lipids in liver
9. Fatty-liver formation during the A-R is especially dependent upon conditioning factors, particularly the available fat store, and the discharge of gluco-corticoids which facilitate fat-transposition into hepatic cells. Hemorrhage, muscular exercise and x-irradiation are unusually effective in producing this change.
Total blood-lipids and blood-cholesterol
10. Total blood-lipids and cholesterol-esters usually show parallel deviations. Free cholesterol is less variable. DCA tends to cause hypercholesterolemia, especially in the presence of renal damage.
Ketones in blood
11. The initial stress-ketonemia is often accompanied by ketonuria, especially during fasting. It tends to be followed by a decrease in blood-ketones.
N.P.N. in blood and urine
12. Blood and urine N.P.N. levels are primarily determined by protein catabolism on the one hand, and impairment of renal elimination on the other. N-balance during G.-A-S largely depends upon relative proportion between catabolic (gluco-corticoids, adrenaline, thyroxin) and anabolic (somatotrophin, testoids) hormones.
Amino-acids in blood and urine
13. Blood and urine levels largely dependent on protein catabolism, hepatic deamination, excretion, and oral intake of amino-acids as well as removal of blood amino-acids for protein synthesis.
Polypeptides in blood
14. Data concerning "proteose" and "serum muco-protein" probably refer to this same fraction. Initial rise due to protein catabolism.


STAGE
A-R
Shock
Counter Shock
RESISTANCE
Exhaus-tion
REMARKS
Tissue proteins in general
15. During the two catabolic periods, tissue proteins are lost especially from lymphatic, connective and muscle tissues. During resistance, restoration to normal is rarely complete even if the fat depots become excessive.
Proteins in blood
Albumin
Globulin
Fibrinogen
G
A
F
16. Total blood-proteins fall during A-R, especially due to albumin loss; hence, relative concentration of globulin (especially α) rises. In stage of resistance, an absolute rise in fibrinogen tends to occur, if its hepatic synthesis is not impeded. Gluco-corticoids tend to rectify the distorted blood-protein pattern, e.g., during febrile states; their effect upon E.S.R. largely depends on this action.
Creatine in urine
17. In severe shock, there is an irreversible creatin-phosphate breakdown. Except in the event of widespread tissue destruction creatinine-elimination is unchanged; if renal damage is severe, it may actually fall due to poor clearance.
Uric-acid in blood and urine
18. Hyperuricacidemia during A-R largely due to degradation of nucleoproteins (e.g., of lymphatic cells). This presumably participates in the production of gouty attacks during stress. Concurrent production of alloxan-like purine metabolites may even lead to diabetes. This response is mediated by ACTH and glucocorticoids, yet in gout, ACTH decreases plasma urate because excretion is more stimulated than neogenesis.
NaCl in blood and urine
19. Damage causes hypochloremia and hyponatremia associated with low resistance. The development of normal or high values, during the resistant stage, depends upon the activity of the adrenal cortex. During the hypochloremic-hypochloruric phases, the tissue-NaCl concentration rises, especially in the directly injured areas, presumably due to edema formation.
K in blood and urine
20. The hyperkalemia and hyperkaluria of the A-R and exhaustion phases is accompanied by discharge of K from the cells of various tissues. Corticoids facilitate K-excretion into the urine and cause hypokaluria. Adrenergic stimuli help to discharge K from the liver, simultaneously with glycogen.
Ca and PO_4 in urine
21. Increased elimination of Ca and PO_4 during the A-R and exhaustion phases is due both to soft tissue and bone catabolism. However, only the latter source yields considerable amounts of Ca. The blood-PO_4 levels describe an essentially similar curve; but comparatively few data are available on blood-calcium changes during the G-A-S.

STAGE	A-R: Shock	A-R: Counter Shock	RESISTANCE	Exhaustion	REMARKS
Ca and PO_4 in tissues					22. This curve is determined primarily by the principal Ca and PO_4 stores, the bones. In soft tissues, Ca tends to accumulate when PO_4 is lost during the two catabolic periods.
Sulfates in urine					23. Urinary sulfate elimination is increased during the two catabolic periods, due to the liberation of S from organic compounds.
Alkali reserve in blood					24. The acidosis of the A-R is usually compensated, but sometimes the actual pH also falls. During the early resistant phase an "alkaline wave" tends to follow, but the later stages of the G-A-S did not yet receive much attention.
Diuresis					25. The decrease in urine output during the A-R and exhaustion phases is largely due to impaired renal filtration and perhaps partly, also to increased tubular water reabsorption (vasopressin). Decreased tubular reabsorption and increased filtration pressure (corticoids) play important rôles in the causation of diuresis during the resistant phase.
Intercellular water					26. Edema formation during the A-R is especially pronounced in tissues injured directly by the stressor (trauma, burns, inflammation) or by relayed catabolic actions of the G-A-S (e.g., in the thymico-lymphatic organs, stomach, pancreas).
Hormones Enzymes Vitamines					27. The complex changes in the metabolism of hormones, enzymes and vitamins, which occur during the three stages of the G-A-S do not lend themselves well to synoptic consideration. Let us merely state that the adrenergic hormones, the gluco-corticoids and the mineralo-corticoids appear to reach their respective peaks in this order during the G-A-S. — For pertinent data the reader is referred to the corresponding pages of the preceding section, and to the synoptic chart concerning the theory of resistance.

MORPHOLOGIC AND FUNCTIONAL CHANGES IN VARIOUS ORGANS

As a general reaction to systemic stress, the G-A-S influences every organ in the body, although some cells are of course much more selectively affected than others. The widespread nature of the reaction is readily understandable if we keep in mind that both the chemical constitution of the blood and the activity of the nervous system are markedly influenced by systemic stress and all cells depend in turn upon these two major integrators of activity.

In the following pages, we shall attempt to give a balanced description of our present-day knowledge concerning the morphologic and functional organ-changes which occur during the G-A-S. Our account is nevertheless patchy, undue attention being often given to one change, in proportion to another. We realize that this flaw was also manifest in our description of the metabolic changes. It is mainly due to the fact that we are dealing with a comparatively new field, some aspects of which received disproportionate attention, while others have been neglected up to now. We hope that in future editions of this book, it will be possible to correct this, while at present, the very lack of information on certain points will, in itself, be of heuristic value by showing us where further investigation is most urgently needed.

Let us begin with the endocrine system, because of its great importance in the evolution of the G-A-S.

THE ENDOCRINES

Hypophysis

Systemic stress. — It is not yet clear what can be considered to be the **characteristic** structural response of the pituitary during the G-A-S. Our earliest studies in the rat showed that, during the A-R, nuclear pyknoses appear in some circumscribed regions of the anterior-lobe, while other parts may remain normal. After more chronic treatment with various types of alarming stimuli, an increase in the number of basophiles was frequently observed. Many of these were found to assume a "signet-ring cell" appearance, not unlike that of "castration cells". In the intermediate-lobe, the epithelial cells tend to degenerate during the A-R and the borderline between middle- and posterior-lobe may become indistinct. Occasionally one gains the impression that debris of such degenerated middle-lobe cells, and perhaps even anterior-lobe basophiles, invade the posterior-lobe. In the latter, vacuolization of the pituicytes, with the development of "foam cells", is not uncommon.[1]

Hypertrophy and hyperplasia of the basophiles, following exposure to stress, have also been seen in rats by other investigators, e.g., after various surgical

[1] Selye 38798/37.

interventions and the injection of HCl or of hypertonic solutions into the cranial cavity. From these observations it was concluded that "probably in all these cases the pituitary changes are due to the same mechanism and represent a manifestation of the adaptation syndrome to severely damaging agents".[2]

Experimental **kidney lesions** in the rat[3] and rabbit[4] likewise stimulate basophile proliferation. Here again the accompanying organ changes lead to the conclusion that the pituitary response is part of the G-A-S.

Following **bile-duct ligature** in rabbits, the pituitary enlarges, the eosinophils lose their granules and there is an increase in the number of basophils and chromophobes. Since this is accompanied by adreno-cortical enlargement, thymus atrophy and other typical manifestations of systemic stress, the pituitary change was ascribed to the development of a G-A-S.[5] The histologic lesions agree with those described by other investigators, but it is doubtful whether the enlargement of the hypophysis should be ascribed to the G-A-S as such.

Upon exposure to **cold,** a diminution in the size of the anterior- and middle-lobes occurred in rats without any change in the dimensions of the posterior-lobe. This was accompanied by hypertrophy of the basophiles.[6]

Ionizing radiations appear to have an essentially similar effect upon the anterior-lobe. Thus, among the Japanese who died some time after exposure to the radiation effects of the atomic bombs, "large basophilic cells with much cytoplasmic vacuolation appeared in 25% of the males dying in the third to sixth weeks. Because cells of this type are found in mammals after castration, they are known as castration cells. In the second and third months, large basophiles were found only, a few being vacuolated".[7]

Exposure of urchins (Erinaceus europaeus) to excessive **noise** allegedly also causes hypertrophy of the anterior-lobe basophiles, with invasion of anterior-lobe debris into the posterior-lobe.[8]

The literature concerning hypophyseal changes in various spontaneous **diseases** is too voluminous to be analyzed here. Suffice it to mention that *hypertension and renal diseases* are allegedly often accompanied by the so-called "basophilic invasion" of the posterior-lobe; in the anterior-lobe the number of basophiles is likewise increased. Such changes are also common in otherwise normal, elderly individuals and hence they are difficult to evaluate. It is perhaps more significant that basophile adenomas in the anterior-lobe are often accompanied by hypertension and secondary contracted kidney (cf. Cushing's disease, p. 285). While it is true that here obvious lesions in the anterior-lobe are inconstant, the bulk of the published data suggests some relationship between basophilism and renal hypertension.[9]

Increased intracranial pressure caused by hydrocephalus, brain tumors, etc., in man, is usually associated with hyperplasia of the anterior-lobe. Only if the causative process destroys the stalk is there atrophy of the posterior-, and sometimes also of the anterior-lobe.[10]

[2] Herlant 86826/43.
[3] Herlant 86826/43.
[4] Rosselli del Turco and Matteini B37480/47.
[5] Rosselli del Turco and Matteini B37478/49, B37479/49.
[6] Brolin 91168/45.
[7] Anonymous B26330/48.
[8] Miline B29485/48.
[9] Selye **94572/49.**
[10] Selye **94572/49.**

In some cases of *Waterhouse-Friderichsen syndrome,* with bilateral adrenal hemorrhages, the basophiles of the anterior-lobe are completely degranulated. This has been interpreted as a sign of "functional exhaustion", incident to excessive corticotrophic stimulation.[11]

Diphtheria, in man and the guinea-pig, causes hyperemia of the pituitary with eosinophilia of the anterior-lobe and edema of the posterior-lobe. These changes are accompanied by manifold manifestations of the A-R,[11a] but their functional significance remains to be established.

Drugs capable of producing an A-R apparently also cause characteristic hypophyseal lesions. Thus, in a woman who died eight days after having taken 60 mg. of *colchicine,* there was an increase in the number of anterior-lobe basophiles with degenerative changes in the hypophysis. The lesions were considered to be typical of the A-R.[12]

Ascaris toxin appears to be especially effective in producing patchy anterior-lobe-cell necrosis in the rabbit.[13] This change is similar to that produced by toxic doses of *formaldehyde* (and many other drugs) in the rat.[14]

The hypophyseal changes caused by *alloxan,* in the rat, have also been attributed to the resulting G-A-S, rather than to any specific action of this drug.[14a]

Concentrated solutions of *NaCl,* given orally or intravenously in the rat, cause enlargement of the posterior-lobe with the appearance of many mitotic figures. This is often accompanied by degenerative changes in the anterior-lobe basophiles. Through confluence of colloid material, formed from the decomposed bodies of such basophiles, small cystic cavities may arise throughout the anterior-lobe. The pituitary cleft can likewise become filled with such colloid. It has been concluded that "the pituitary changes represent a reaction to derangements in the osmotic equilibrium of the body".[15] These lesions are not mere non-specific reactions to systemic stress; they are mentioned here for comparative purposes as they appear to be connected with specific hormonal adaptive responses to dehydration; yet dehydration is also an important factor during the A-R.

In guinea-pigs **starvation** allegedly causes "a progressive loss of acidophilia and an increase in the number of basophiles and chromophobes. The basophiles reveal cytologic manifestations of high secretory activity (cell hypertrophy, degranulation, abundant mitochondrial content and hypertrophy of the Golgi apparatuses)". In advanced starvation, the pituitary loses its specific staining reactions and degenerative changes in both nucleus and cytoplasm are marked. Since these manifestations were accompanied by adreno-cortical enlargement, they were "interpreted to mean that the cortical hypertrophy in the starving guinea-pig results from augmentation of adrenotrophin secretion by the basophiles of the anterior pituitary".[16] Degranulation of the basophiles has also been noted in another series of experiments on guinea-pigs and rats,[17] but it is debatable whether degranulation is a sign of increased or decreased hormone secretion.

[11] Cavallero B28485/46.
[11a] Prosperi B41943/49, B41940/47.
[12] Dustin 94160/41.
[13] Simonin B12416/22.
[14] Selye 38798/37.
[14a] Arvy and Gabe B44853/49.
[15] Selye A56582/43, Selye and Hall A57676/43.
[16] D'Angelo et al. B19839/48.
[17] Desclaux B31288/46-47.

In inmates of concentration camps, who died of exhaustion with severe signs of malnutrition, the anterior-lobe likewise showed very severe structural changes. Although the nature of these varied, depending upon circumstances, they have been regarded as non-specific manifestations of the G-A-S.[18]

Stimuli Influencing the Response of the Hypophysis During the G-A-S. — Little is known about stimuli which initiate or influence the hypophyseal response to systemic stress during the G-A-S. **Testoids** produce atrophy of the anterior-lobe in the rat and this effect remains manifest even if the dose administered is so high that definite G-A-S changes occur in the thymus and adrenals.[19]

Among the **corticoids,** DCA [19a] and cortisone [19b] proved to cause marked involution of the rat and mouse pituitary.

The anterior-lobe enlargement, elicited by **folliculoids** in the rat, is effectively inhibited by simultaneous treatment with testosterone [20] and many other testoids, while luteoids and corticoids are less effective.[21] The possible relationship between these responses and the G-A-S has not yet been examined.

Allegedly, the proliferation of basophiles normally produced by exposure to cold fails to occur in rats after **transection of the pituitary stalk,**[22] but in view of the technical difficulties involved in this operation, these results would require confirmation.

Diets rich in protein cause marked basophilia in the anterior-lobe of the rat.[23] It would be interesting to examine whether this response is related to the well known increase in the ability of the rat to secrete ACTH during the G-A-S if the animal is fed a high-protein ration.[24]

Hypophyseal Diseases of Adaptation

Simmond's disease. — Certain types of Simmond's disease have been interpreted as diseases of adaptation.[25] For instance, in women who develop hypopituitarism after complicated childbirth,[26] the anterior-lobe lesion may be ascribed to exhaustion resulting from a period of excessive stimulation during stress. The development of hypopituitarism, associated with the picture of multiple endocrine-gland sclerosis, after typhoid-paratyphoid vaccination [27] may also belong to this group. Should this interpretation prove to be correct, we would have to classify these cases among the secondary diseases of adaptation resulting from exposure.

Undoubtedly, Simmond's disease is much more commonly the cause of what we defined as primary diseases of the adaptive system. Any lesion (e.g., local tuberculosis, syphilis, gunshot wounds, tumors) which destroys the anterior-lobe, automatically interferes with the normal ACTH discharge following exposure to stress and hence leads to a deficiency of the pituitary-adrenocortical defense mechanism. The usual lymphocytopenia elicited by glucose administration is almost completely lacking in Simmond's disease.[28]

[18] Uehlinger B24304/47, **B27612/48.**
[19] Selye A35221/41.
[19a] Selye 94572/49.
[19b] Antopol B47052/50, Selye 35935/ND.
[20] Selye and Friedman A34228/41.
[21] Albert and Selye A37637/42.
[22] Brolin 91168/45.
[23] Tuchmann-Duplessis and Aschkenasy-Lelu B36787/48.
[24] Selye B1204/46.
[25] Selye B1204/46, 94572/49.
[26] Anonymous A34944/40.
[27] Rotter and Schroers B31990/48.
[28] Marks et al. B19152/48.

It may incidentally be mentioned that in one hypopituitary patient, cardiovascular and arthritic manifestations of "rheumatic fever" had developed during corticoid therapy,[29] but it is doubtful whether there is any relationship between the treatment and the evolution of the rheumatic lesions, because the hormone dosage was very low.

Cushing's syndrome. — The excessive production of corticoids, with the resulting changes in sugar and electrolyte metabolism, soon called attention to the relationship between Cushing's syndrome and the G-A-S.[30] The similarity with experimentally produced diseases of adaptation, especially the hyalinosis induced by DCA overdosage, is particularly striking in those cases of Cushing's syndrome in which the serum-K and -Cl levels fall below normal and the resulting hypochloremic alkalosis is associated with severe losses of K through the urine.[31] Following administration of NaCl solutions, patients with Cushing's syndrome excrete NaCl and water more rapidly than normals, presumably because of a diminished renal tubular reabsorption of these substances.[32] This derangement is again reminiscent of what we found in rats chronically overdosed with DCA.

Certain patients with Cushing's syndrome appear to be refractory to the salt retaining action of DCA.[33] It was suggested that this "may be due to the blocking action on the renal tubule of an excess of adrenal steroids of the 11,17-hydroxy type".[34] However, as we have previously stated, the salt-retaining action of small doses of DCA is actually reversed by previous chronic administration of large doses. Presumably the originally stimulating effect of the hormone upon renal Na reabsorption is subsequently followed by such tubular damage that reabsorption is impeded.

In Cushing's disease, as after excess ACTH administration, there is eosinopenia and an elevation of the urinary uric-acid:creatinine ratio,[35] the fall in blood-lymphocytes normally produced by oral glucose administration is greatly exaggerated,[36] fibroplasia in wounds is delayed, the bones become porotic, etc.[37]

It has also been emphasized "that the hematological manifestations of Cushing's syndrome are quite similar to those of the initial reaction of the body to non-specific damaging events — the adaptation syndrome of Selye. Since these hematological changes are due to changes in hormone production, the data herein presented strengthen the contention that the hormone alterations of Cushing's syndrome are similar to those of the early phases of the Adaptation Syndrome".[37a]

Electrophoretic analysis in patients with Cushing's syndrome showed low plasma albumin and γ-globulin levels; these were restored to normal by testosterone therapy.[37b] It will be recalled that ACTH depresses the plasma-γ-globulin level in a number of diseases in which it is elevated.

"It is significant, furthermore, that Cushing's syndrome is often conducive to nephrosclerosis and hypertension, that is, changes which are experimentally produced by anterior-lobe or corticoid hormones. These observations suggest

[29] Lerman and Means B9421/45.
[30] Albright 84530/42, B309/43, Reifenstein 96447/46.
[31] Cluxton et al. B13058/45, Willson et al. B343/40.
[32] Kries and Futcher B30921/49.
[33] Forsham et al. B33412/49, Soffer et al. A71716/44.
[34] Forsham et al. B33412/49.
[35] Forsham et al. B33412/49.
[36] Marks et al. B19152/48.
[37] **Selye 94572/49.**
[37a] de la Balze et al. B1245/46.
[37b] Lewis and McCullagh B2462/47.

that in Cushing's disease, we have a condition closely related to the diseases of adaptation, but differing from the latter in that the hormonal imbalance is the primary cause of disease, not the consequence of adaptation to exogenous damage". [38] In certain cases of Cushing's syndrome, malignant nephrosclerosis may be accompanied by a diffuse hyalinizing arteritis of the extremities.[39]

It is interesting, furthermore, that in one case of Cushing's disease, due to an adrenal-cortical tumor, both the VDM and VEM concentrations in the blood were high, just as in chronic essential hypertension.[40]

Adrenals

In view of the rather central position occupied by the adrenals in the regulation of defense the morphologic changes which occur in these glands during systemic stress have received considerable attention.[41]

In previous years, we emphasized — and perhaps over-emphasized — the fact that, in response to a great variety of non-specific systemic stressors, the adrenal cortex reacts in essentially the same manner. It has been more or less generally accepted, furthermore, that the activity and morphologic development of the adrenal cortex is regulated by a single, hypophyseal corticotrophin (ACTH) which can exert all the known corticotrophic actions.[42]

Similarly, the discharge of adrenaline from the adrenal medulla had been assumed to be exclusively (or almost exclusively) under the control of acetylcholine. The latter would reach the cells after being liberated at the endings of their secretory nerves, or, in rare instances, perhaps through the bloodstream.

It has been concluded, accordingly, that the wide variety of agents, which affect the adrenals act upon the cortex only by increasing or decreasing corticotrophin production, and upon the medulla by varying the degree of cholinergic (splanchnic) stimulation. Such an interpretation does not allow for any qualitative differences in adrenal response; it would necessarily lead to the conclusion that the gland can only be more or less intensely stimulated. We know, however, that the medulla secretes both adrenaline and noradrenaline, while the cortex produces a variety of hormones which are not necessarily secreted at the same time, in set proportions.

We do not yet have any definite evidence proving the existence of several hypophyseal corticotrophins. Our observations have led us to assume, however, that even if only a single ACTH is secreted by the pituitary, this substance may exert qualitatively different effects upon the adrenal cortex, depending upon "conditioning" factors.[43]

It has now been established beyond doubt that non-specific stressors cause an increase in ACTH production. It is equally certain, however, that various alarming stimuli may cause qualitatively different adreno-cortical changes. Probably the non-specific adrenal response to certain stimuli can be modified

[38] Selye B1204/46.
[39] Metzger et al. B19890/48.
[40] Shorr and Zweifach B36357/49.
[41] Greep and Deane **B37777/49.**
Hartman and Brownell **B36274/49.**
Selye B1204/46.
Straub and Schaberg **B39294/48.**
[42] Li B3610/47.
Sayers and Sayers B18350/48.
[43] Selye B28243/49.
Selye and Stone **B30224/49.**

by their specific actions. Increase in ACTH production is merely the simplest (most non-specific) response to systemic stress.

In preparation for the following complex discussion of adrenal responses to non-specific stress, it may be useful to define the principal **qualitatively different morphologic changes** which we [44] can distinguish in our experimental material:

(1) *Atrophy.* — This may affect all cells of the cortex equally, or it may be more or less limited to certain zones. It is sometimes, but not always, accompanied by marked loss of cytoplasmic granules (sudanophilic lipids, plasmalogens, cholesterol, ascorbic acid, etc.). It can be produced by hypophysectomy, overdosage with corticoids or testoids and — in the glomerulosa — by overdosage with Na salts.

(2) *Hypertrophy.* — This is characterized by the enlargement of individual cells. It may affect the whole cortex evenly, but is often limited to certain zones in a somewhat selective manner. Hypertrophy is sometimes associated with an increase, at other times, with a decrease in the storage of the various cytoplasmic granules. It can be produced by ACTH, folliculoids, various alarming stimuli, partial adrenalectomy and — in the glomerulosa — by Na-deficiency.

(3) *Hyperplasia.* — This is characterized by an increase in cell number due to mitotic proliferation. It does not tend to be entirely limited to any zone, although, usually the outer fasciculata is most, the reticularis, least, affected. It can be produced by the same agents which cause hypertrophy, but not necessarily to the same extent or at the same time.

(4) *Capsular adenomas.* — These are proliferations of hypertrophic cell groups which appear to arise from dormant glomerulosa islets within the adrenal capsule. They are often multiple and rich in lipids. Such adenomas are also produced by the agents listed under (2) and (3), but usually only after prolonged treatment, and only in genetically predisposed individuals.

(5) *Lipid-granule storage or discharge.* — Under this heading we discuss the multiple osmiophilic and sudanophilic granules present in the cytoplasm of cortical cells. We consider the process of multiple small granule formation as essentially different from the "fatty metaplasia" discussed in paragraph (9) below. Depending upon experimental conditions, storage of lipid granules may occur selectively in one or the other zone of the cortex. Discharge of lipid granules is especially obvious in the A-R, the stage of exhaustion and after folliculoid treatment; storage, during the stage of resistance and after continuous ACTH administration.

(6) *Cholesterol-granule storage or discharge.* — The adrenal-cortex is very rich in cholesterol. The concentration of this sterol in cortical cells runs roughly parallel with that of the sudanophilic lipids. Yet, discharge of cholesterol can be effected selectively. Acute corticotrophic stimulation tends to cause a more rapid discharge (followed by a speedier replenishment) of cholesterol than of other sudanophilic lipids.

(7) *Plasmalogen-granule storage or discharge.* — The adrenal cortex also contains a high concentration of "plasmalogens". Under various experimental conditions, plasmalogen storage and discharge tends to run parallel with that

[44] Selye and Stone **B30224/49.**

of sudanophilic lipids. However, here again, the parallelism is not absolute and the loss of these granules from different regions of the cortex does not necessarily coincide.

(8) *Ascorbic-acid-granule storage or discharge.* — The adrenal cortex is also extraordinarily rich in ascorbic acid. The storage of this vitamin likewise roughly parallels that of the sudanophilic lipids. Under the influence of acute corticotrophic stimulation, however, the ascorbic acid tends to be discharged (and later replenished) even more rapidly than cholesterol and hence, of course, much more quickly than the sudanophilic lipids.

(9) *Fatty metaplasia.* — Under this name we described a peculiar transformation of adreno-cortical into what appear to be common fat cells. These are characterized by the development of a single, large fat vacuole so that they assume the "signet ring" appearance of adipose cells. This change is rather specific inasmuch as it rarely occurs under the influence of any stimulus other than testoid-hormone treatment.

(10) *Colloid formation.* — In some experiments we noted that hyalin, homogeneous bodies are formed within the cytoplasm of adreno-cortical cells.[45] These globules stain intensely with eosin and fuchsin. In their tinctorial properties they resemble the colloid seen in the thyroid follicles or within the cytoplasm of the human corpus luteum of gestation. The functional significance of these corpuscles is not known, but they may well be storage products retained in the cell when more secretion is produced than discharged. They can be experimentally produced when secretion is stimulated (e.g., by ACTH), while granule discharge is inhibited (e.g., by DCA). Somewhat similar colloid bodies have occasionally been found in human adrenals.[46]

(11) *Fibrinoid degeneration.* — Under certain experimental conditions — usually those also conducive to colloid formation — we observed the appearance of a fibrin network within the cytoplasm of cortical cells. This is often seen in animals chronically treated with corticotrophic extracts or exposed to long lasting systemic stress, especially if they are simultaneously given certain steroids (e.g., corticoids or testoids), which tend to inhibit cortical secretion. It frequently occurs in combination with widespread cytolysis and may be a precursor of the latter.

(12) *Cytolysis.* — Sometimes entire cells (or parts of cytoplasm) disintegrate into more or less homogeneous or granular eosinophilic debris. This has been ascribed to exhaustive overstimulation, but it is not necessarily a purely degenerative phenomenon without functional value. Cytolysis may represent a type of holocrine secretion. Cell parts or entire cells could perhaps more rapidly discharge all their stored hormonal components, into the blood by actually disintegrating, than through the more timetaking process of selective secretion.

(13) *"Chromidiosis".* — This may merely be an artefact. Yet it is noteworthy that both in the cortex and in the medulla of the adrenal intensely basophilic granules and filaments can appear within the cytoplasm. Cells with such inclusions often exhibit condensation of basophilic, chromatin-like material at one point on the inner surface of the nuclear membrane; we termed this a "chromatin cushion". Sometimes fine fibrils emanate from it into the

[45] Selye and Stone B30224/49. Vélican B19887/48.
[46] Liebegott B46126/44,

cytoplasm towards the basophilic granules. The inclusions appear to be identical with what had previously been described in other cells under the name of "chromidia". It has been suggested that these chromidia are extruded from the nucleus, or that they are formed in the cytoplasm, but it is not impossible that in some instances they represent phagocytosed nuclear fragments. In glands showing intense chromidiosis, basophilic incrustations are often seen along the endothelial surfaces and sometimes, large globules of intensely basophilic material appear within the lumina of the sinusoids. The function of these chromidia is unknown, they appear to be closely related to the nuclear chromatin and may, like the latter, play a rôle in the elaboration of secretion products, enzymes and proteins. We found "chromidiosis" most frequentlv in the adrenals of rats exposed to chronic stress. Possibly related cytoplasmic granules have been noted in the adrenals of man [47] and guinea-pigs [48] during various infections. Yet, their development is very irregular and the possibility that they are merely artefacts, has not been ruled out with certainty.

(14) *Lymphoid and myeloid metaplasia.* — In the adrenal cortex, and less frequently, in the medulla, islets of lymphatic or myeloid tissue can be produced experimentally. These appear to be transitional stages between lymphatic or myeloid cells on the one hand and normal cortical cells on the other. It was assumed therefore that direct metaplasia of cortical into myeloid and lymphatic elements, can occur. Of course the reticulo-endothelial cells of the cortex probably also contribute to the formation of these islets, and some of their cells may invade the gland from the blood. These islets are especially common in the adrenals of animals in which widespread tissue necrosis has been produced, or which had been injected with extracts and implants of decomposing tissues. They appear to represent a rather specific response to the products of necrosis.

(15) *Formation of "lumina" within the cortical parenchyme.* — Sometimes comparatively large areas of the adrenal cortex are affected by the previously mentioned process of cytolysis, and then, the surrounding normal cells appear to form an "acinus" or "tubule". If the process of cytolysis involves the cortical sinusoids, these "lumina" come to communicate with circulating blood. In this event, there may be diffuse infarction of the cortex or discharge of the luminar contents into the blood. Such "lumen" formation is most common in the adrenals of animals exposed to very sudden intense stress, especially if the cortex was already hyperplastic, due to chronic exposure to a milder stress. This process is merely a modification of the cytolysis described above.

(16) *Holocrine secretion.* — The discharge of more or less intact or cytolyzed cells into the sinusoids of the adrenal has been interpreted as a process of holocrine-endocrine secretion. It is a common accompaniment of cytolysis and "lumen" formation. In a modified manner it also occurs in adrenals with lymphoid and myeloid metaplasia, since some of the newly formed blood cells are discharged into the blood.

(17) *Hyperemia.* — Under the influence of acute stress (e.g., an A-R) the adrenal becomes intensely hyperemic, due to dilatation of the cortical sinusoids and of the larger sinuses in the medulla. Especially pronounced hyper-

[47] Santee A58083/36. [48] Celestino de Costa B34056/46.

emia is observed after overdosage with folliculoids. In the latter event, certain regions of the fasciculata may assume an almost hemangiomatous aspect.

(18) *Hemorrhagic infarction.* — Extensive hemorrhagic infarction of the adrenal usually occurs as a result of intense cytolytic phenomena in a markedly hyperemic cortex. It may become so severe as to cause fulminating cortical insufficiency, especially in individuals who tend to bleed because of a decreased capillary resistance or a defect in blood clotting (cf. Waterhouse-Friderichsen Syndrome).

(19) *Anemic infarcts and focal necrosis.* — Circumscribed areas of anemic infarction and necrosis tend to develop in the adrenals of animals with periarteritis nodosa; for instance, that caused by prolonged systemic stress, DCA, LAP or the "endocrine kidney". It is presumably due to occlusion of vascular territories. When extensive, it may lead to acute cortical insufficiency.

(20) *"Toxic involution".* — Under this name we described a singular type of cortical involution, caused by certain drugs (e.g., germanin, DDD). It usually affects the reticularis and inner fasciculata rather selectively, while the glomerulosa and outer fasciculata undergo compensatory hypertrophy. This involution may be accompanied by intense hemosiderosis and myeloid infiltration of the reticularis. The pathogenesis of this reaction is not known, but since it is very different from the atrophy obtained by hypophysectomy or corticoid injections, it cannot be ascribed to a mere decrease in pituitary function.

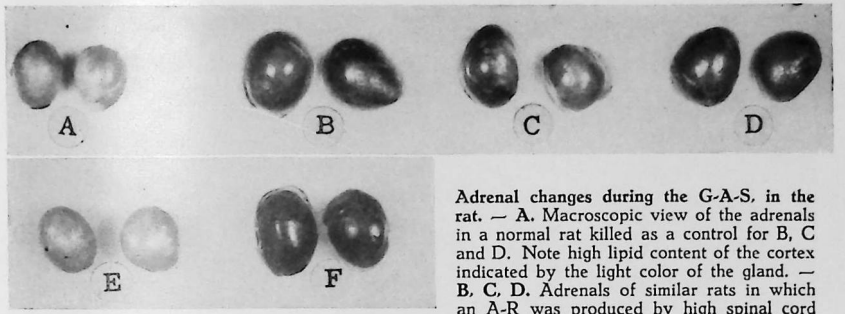
The above is by no means a complete list of all the changes that can be experimentally produced in the adrenal cortex. It merely comprises those lesions which we consider most important for the interpretation of adrenal responses during the G-A-S.

Although several of these changes may occur simultaneously in the same adrenal, we listed them separately in order to emphasize that they are relatively independent of each other. Thus, they represent qualitatively distinct reaction types of the adrenal. Similar changes also occur in man and we attempted elesewhere to correlate these with the above experimental observations.[49]

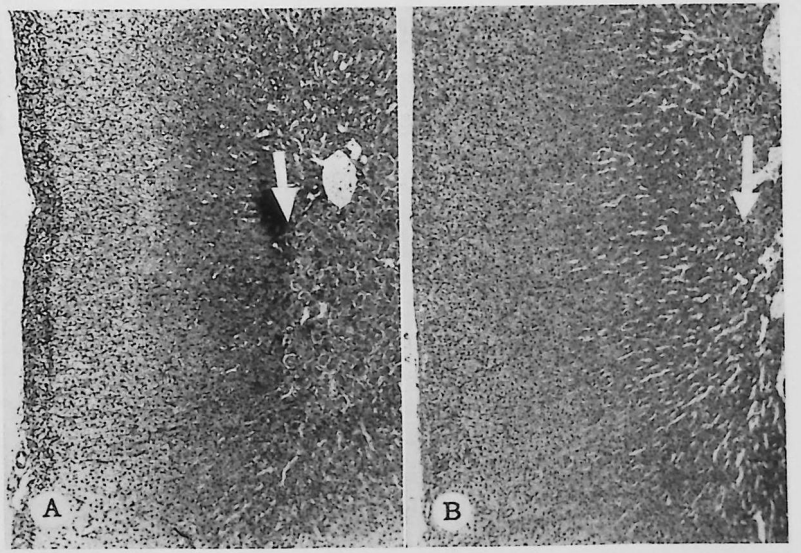
Systemic stress. — The adrenals — as most target organs — respond with a clear-cut triphasic reaction during the G-A-S. The changes are essentially different during the A-R, the stage of resistance and the stage of exhaustion. As previously stated, the non-specific adrenal response to certain alarming stimuli can be modified by the specific actions of the latter. Among the changes listed above, the following appear to be due simply to increased ACTH production: hyperemia, hyperplasia, hypertrophy and an increased cytoplasmic granule storage in spite of a simultaneously increased corticoid secretion. Other lesions occurring during the G-A-S are presumably due to "conditioning factors" which modify the effect of ACTH.

Here we shall first consider — irrespectively of the mechanism through which they were produced — the responses caused by any systemic stressor, that is, those which are characteristic of the G-A-S.

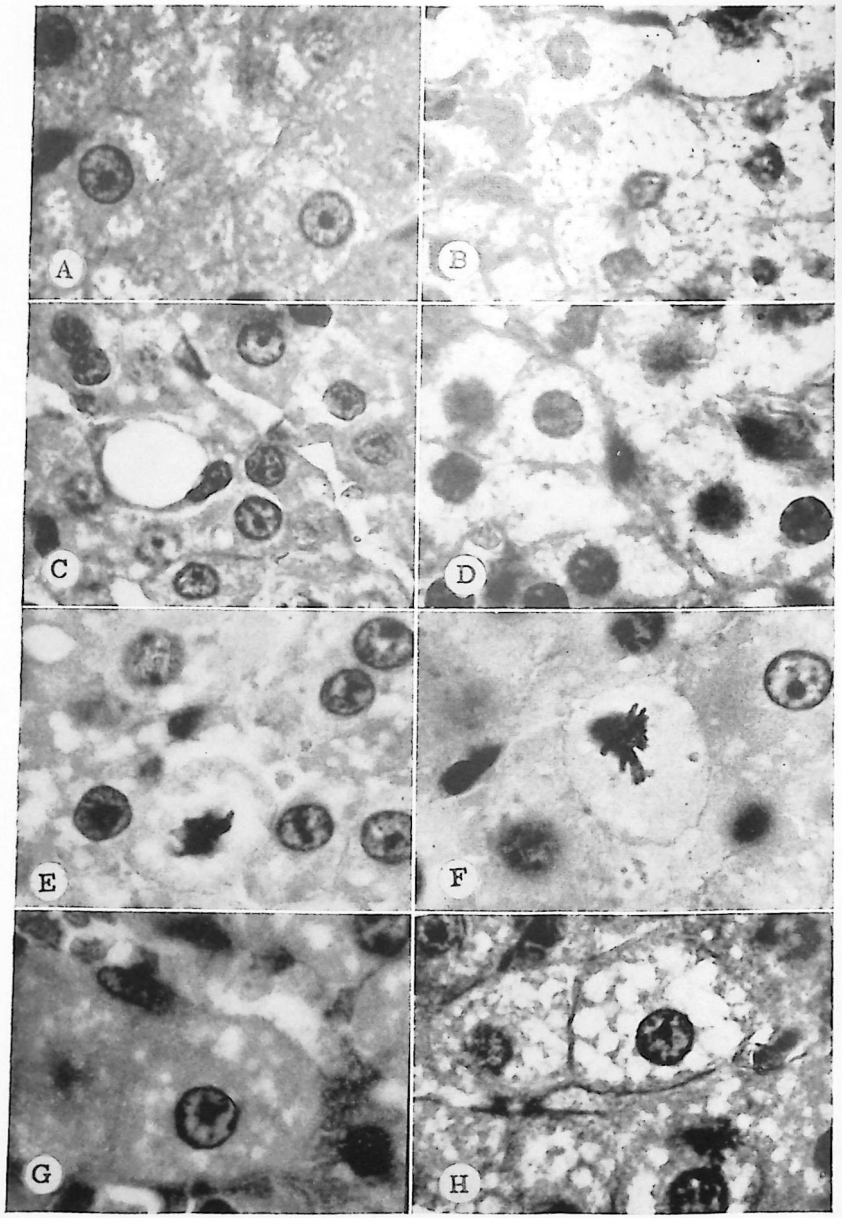
[49] Selye and Stone **B30224/49.**



Adrenal changes during the G-A-S. in the rat. — **A.** Macroscopic view of the adrenals in a normal rat killed as a control for B, C and D. Note high lipid content of the cortex indicated by the light color of the gland. — **B, C, D.** Adrenals of similar rats in which an A-R was produced by high spinal cord transection (B), exposure to a temperature of + 2 C° (C), and repeated, forced muscular exercise (D) respectively, during a period of 48 hours, while food was withheld. Note considerable enlargement of the adrenals whose color was now dark, reddish brown due to discharge of the lipid secretion granules from the cortex. — **E.** Adrenals of normal rat killed as a control for F. — **F.** Adrenals of rat exposed to cold during a period of 30 days. The animal died with obvious manifestations of the exhaustion phase, including gastric ulcers and thymico-lymphatic involution. Note that the adrenals are again enlarged and almost free of lipids just as they were during the A-R. In the intermediate resistant stage (not shown here) the adrenals are large, but otherwise macroscopically normal. (After Selye 35935/ND.)



Adrenals during the A-R. — **A.** Normal adrenal — section through the adrenal cortex of a normal rat. Note width of cortex (delimited by arrow) and clearcut differences between the zona glomerularis and fasciculata. — **B.** Adrenal in A-R — section through the adrenal cortex of a rat (similar to that shown in Fig. A.) which received toxic doses of formaldehyde, subcutaneously during 48 hours. Note greater width of the cortex, whole cells lost their light, lipid granules. The border between fasciculata and reticularis is no longer distinct.
(After Selye 94572/49.)



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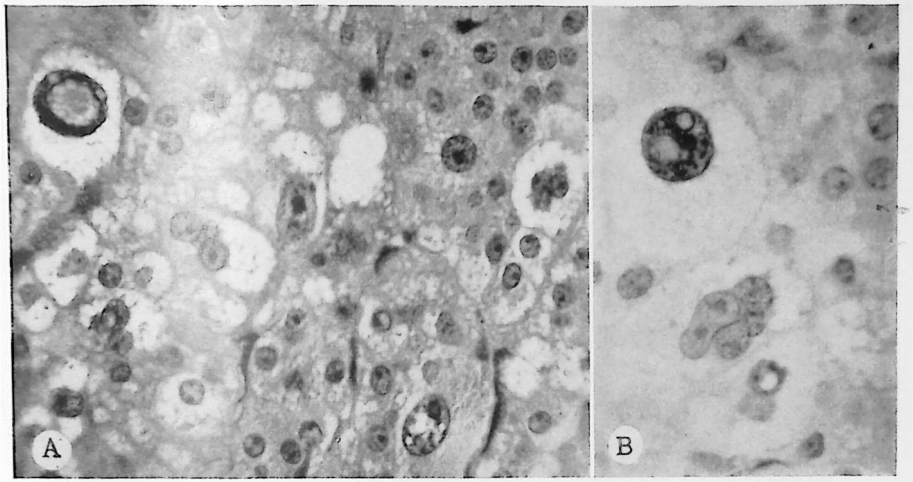

Adrenal hyperplasia with giant-cell formation, in man. — **A.** Circumscribed cortical hyperplasia with giant cells. Note many vacuoles in several of the giant nuclei. —**B.** Lipid storing giant cell with giant nucleus containing many vacuoles. Note also multinuclear lipid storing cortical cell in which one nucleus appears to undergo amitotic division.

(After Liebegott B46126/44.)

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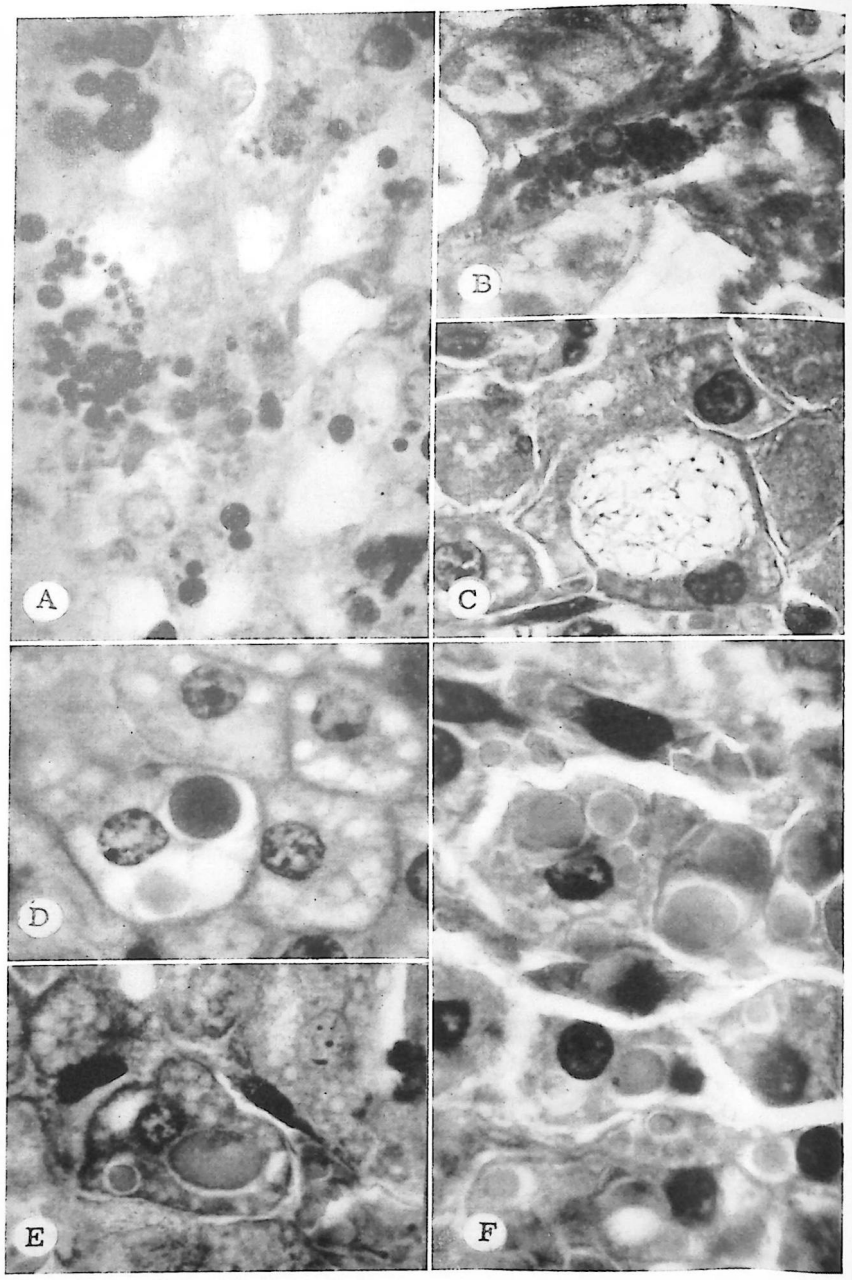
Adrenal atrophy, hypertrophy and hyperplasia under various experimental conditions, in the rat. All sections on this plate are shown at a magnification of x 1000 and show representative cells from the outer fasciculata of rats having approximately the same body weight. — **A.** Adrenal cortex of normal control rat. — **B.** Cortical atrophy caused by hypophysectomy. Note greatly reduced size and frequently excentric position of nucleus. The cytoplasm still contains many lipid vacuoles. Compare with other types of atrophy illustrated in Fig. C and D. — **C.** Cortical atrophy produced by testosterone. Note that here cytoplasm and nucleus are also poorly developed. There are few small lipid droplets, but "fatty metaplasia" has occurred in one of the cells. Note great distension of cytoplasm by a lipid vacuole, which compresses the nucleus and pushes it to the side so that the cell assumes the "signet ring" appearance of a common fat cell. — **D.** Cortical atrophy produced by DCA. Note especially prominent cell contours. Both cytoplasm and nucleus are subnormal in size, but small lipid vacuoles are clearly visible. — **E.** Cortical hypertrophy and hyperplasia produced by crude anterior-pituitary extract. Note large round cell in mitosis, with distinct spindle. The other cells are rich in cytoplasm, but the nucleus is not considerably enlarged. Binucleated cell in right upper corner of this field. — **F.** Cortical hyperplasia and hypertrophy produced by crude anterior-pituitary extract. Another typical mitosis is seen in the rounded, central cell of this field. The nucleus in the right upper corner is vesicular. Most cells have discharged their cytoplasmic lipid granules and scattered basophilic droplets are visible in the cytoplasm. Fig. E and F are rather typical of acute adrenal over-stimulation. — **G.** Hypertrophy with beginning lipid storage in the adrenal of a crude anterior-pituitary extract treated rat. Note great increase in cytoplasmic mass; nucleus is vesicular but not very much enlarged. The cytoplasm contains some medium-sized lipid vacuoles. — **H.** Hypertrophy and marked lipid-granule storage in the adrenal of a crude anterior-pituitary-extract and testosterone treated rat. Note the increase in cytoplasmic mass and the presence of numerous very coarse lipid granules. In the same adrenal many cells have undergone complete metaplasia into typical fat cells.

(After Selye and Stone B30224/50.)



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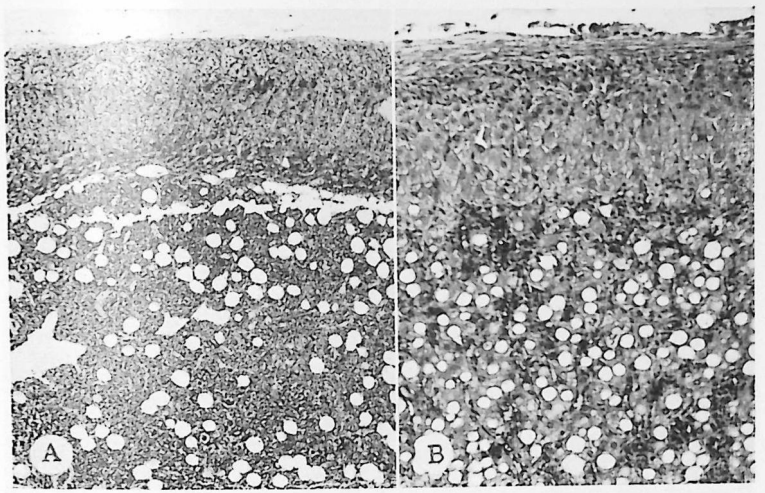

Myeloid transformation of the adrenal cortex. — **A.** Myeloid tissue spontaneously occurring in the human adrenal. Note great resemblance to experimentally produced myeloid metaplasia. — **B.** General aspect of adrenal cortex of a rat treated with LAP, testosterone and thyroxine. Note essentially intact glomerulosa and outermost fasciculata. The entire inner fasciculata and reticularis are no longer recognizable as adrenal, they assume the typical appearance of bone-marrow tissue. (After Selye and Stone B29705/50.)

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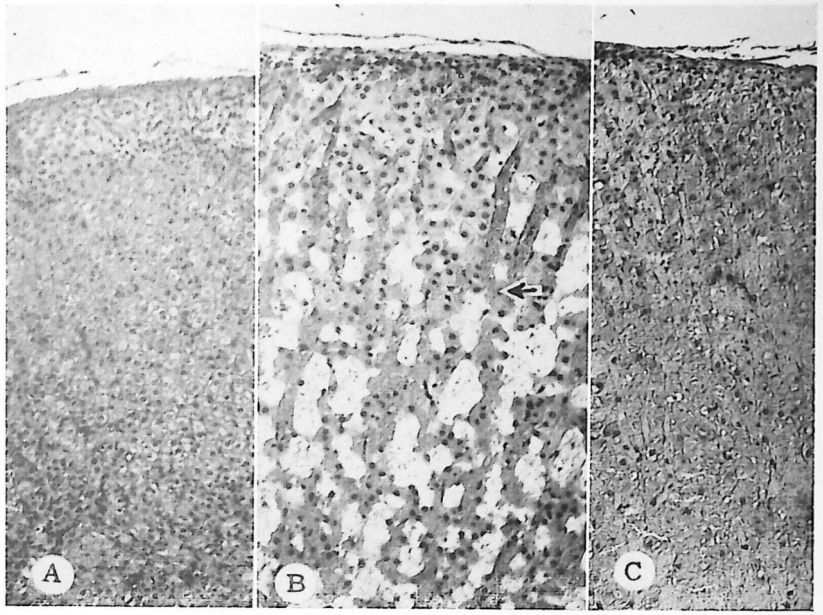
Colloid formation and fibrinoid degeneration in adrenal cortex. — **A.** Numerous hyalin droplets in the adrenocortical cells of a patient who died from sepsis after tonsillitis. — **B.** Very fine hyalin droplets in a cortical sinusoid (arranged around a centrally located erythrocyte). Note also similar droplets in one of the endothelial cells. Such figures have been interpreted as indicating the secretion of hyalin into the blood. — **C.** Fibrinoid degeneration of a cortical cell in the adrenal of a rat treated with anterior-pituitary extract and methyl-testosterone. Note that, within the large vacuole of this signet-ring cell, filaments have developed. At their intersections there are darkly staining nodules. The whole reticulum is clearly visible on this hematoxylin-eosin slide, but it becomes even more prominent on sections stained with Mallory's hematoxylin. — **D.** Colloid droplets in cortical cells of a rat treated with crude anterior-pituitary extract, methyl-testosterone and thyroxine. Note that central cell contains one dark, and one light colloid body, as well as a lipid vacuole. The other cells in this field contain only lipid vacuoles. — **E.** Colloid formation in the cortex of a rat treated with crude anterior-pituitary extract and methyl-testosterone. — **F.** Intense colloid storage in cortex of rat treated with methyl-testosterone and DCA. Note absence of the large fat vacuoles so characteristic of the adrenals of rats receiving testosterone alone. The colloid bodies formed under the influence of different treatments as illustrated in Figures D, E, and F are similar in appearance.

(A and B, after Liebegott B46126/44; C, D, E and F, after Selye and Stone B30224/50.)



"Lumen" formation, hyperemia and infarction in adrenals. — **A.** Adrenal cortex of normal control rat. — **B.** Numerous tubular structures in the cortex of a rat treated with crude anterior-pituitary extract and thyroxine. Note that the hypertrophic cortical cell columns surround tubule-like lumina, whose cavities are filled with disintegrating cast-off cortical cells and erythrocytes. The cortical sinusoids contain blood cells of normal appearance. At some points (one marked by arrow) these sinusoids appeared to empty their contents into the "lumina", but within the latter the blood corpuscles disintegrate. — **C.** Infarction of the entire adrenal cortex in a rat treated with crude anterior-pituitary extract. This picture is very reminiscent of that spontaneously occurring in the Waterhouse-Friderichsen syndrome. It appears to arise, at least partly, due to the sudden formation of lumina, with multiple massive hemorrhages into their cavities; this is probably caused by endothelial damage. Upon macroscopic inspection these adrenals exhibit a bright red color similar to that of blood.
(After Selye and Stone B30224/50.)

During the *alarm-reaction* there is an almost immediate discharge of chromaffine granules from the adrenal medulla.[50] This is merely a morphologic expression of the well-known adrenaline discharge caused by various emergency situations.[51] During very intense stress many medullary cells become necrotic.[52]

Perhaps somewhat more slowly, but still during the first hour of the A-R, the lipid granules of the adrenal cortex begin to be discharged, the gland becomes very hyperemic [53] and its whole vascular pattern is severely altered.[54] The result of these latter changes is readily distinguishable even upon naked-eye inspection, since the adrenals lose their characteristic yellowish-white color (which is due to lipid storage) and become reddish-brown, enlarged and

[50] Foglia and Selye A8424/38, Selye 73232/38, 38798/37, 36031/36.
[51] Selye **94572/49.**
[52] Selye 38798/37.
[53] Selye 36031/36, 36030/36, 73232/38.
[54] Gersh and Grollman 81744/41.

somewhat transparent. In the case of very acute exposure, the suprarenals may be even darker than the adjacent kidney or liver tissue.

The ascorbic acid and cholesterol content of the cortex likewise diminishes during the A-R, the former somewhat more rapidly than the latter.[55]

The plasmalogen content of the cortex is also depleted during the A-R.[56] This change runs approximately parallel with the loss of sudanophilic (and osmiophilic) lipids, but the depletion of these substances, from different regions of the cortex, does not necessarily coincide in the course of the A-R.[57]

Almost simultaneously with this sudden loss of various stored materials, there is hypertrophy of the cortical cells,[58] presumably in an effort to increase the mass of corticoid-producing tissue. Marked hyperplasia rarely occurs, however, before the resistant phase; indeed, during the early hours of the A-R, mitotic figures are hardly ever seen in the cortex.

In the event of very acute and intense stress, some cortical cells may undergo partial or complete cytolysis. If such cellular disintegration affects several adjacent cells, "lumina" appear within the cortical parenchyme. Occasionally, this process of lumen formation affects most of the adrenal cortex. As previously stated, involvement of the vascular endothelia in this cytolytic process can open communications between the cortical sinusoids and the "lumina". In this event, we may find diffuse infarction of the cortex, or "holocrine secretion" of disintegrating cortical cells into the sinusoids, presumably depending upon the relative pressures within the lumina and sinusoids respectively.[59] — Some cytolysis is quite common in the A-R, but extensive lumen formation and infarction tends to occur most frequently when a very intense, acute stress affects an already hyperplastic or exhausted adrenal (e.g., acute exposure to an additional new alarming stimulus in the stage of resistance or after chronic ACTH treatment).

The reticulo-endothelial cells of the cortical sinusoids are usually enlarged and their phagocytic power is increased during the A-R.[60]

During the *stage of resistance* the adrenal medulla regains its chromaffinity and the cortex its sudanophilic (osmiophilic) granule stores. The cortical cells remain hypertrophic and mitotic figures are more common than in the A-R. Cytolysis and the formation of "lumina" is unusual unless some incidental, acute alarming stimulus is superimposed upon the constant, chronic stress which led to the development of the resistant stage.[61] During this stage there is also a tendency to form capsular adenomas whose cells are likewise rich in lipids.[62]

The ascorbic acid [63] and plasmalogen,[64] content of the cortical cells likewise increases immediately after the A-R and may reach abnormally high

[55] Giroud A55272/40, Greep and Deane **B37777/49.**, Long B1736/47, 98425/47, Sayers and Sayers B18350/48, 98805/47.
[56] Deane et al. B23212/48, Greep and Deane **B37777/49.**
[57] Selye and Stone B30224/49.
[58] Selye 38798/37, Selye and Stone B30224/49.
[59] Selye and Stone B30224/49.
[60] Timiras and Selye B36271/49.
[61] Dosne and Dalton 81198/41, Foglia and Selye A8424/38, Selye 36031/36, 66551/36, A55493/42, 38798/37, 36030/36.
[62] Selye and Stone B30224/50.
[63] Greep and Deane **B37777/49.**, Long B1736/47, 98425/47, Sayers and Sayers B18350/48, 98805/47, Selye and Stone B30224/50.
[64] Deane et al. B23212/48, Greep and Deane **B37777/49.**, Oster B3393/47, Selye and Stone B30224/50, Tonutti 96841/41.

values during the stage of resistance. However, the data available concerning the characteristic behavior of these cortical constituents are not yet very plentiful.

It has been our experience that all laboratory animal species respond essentially in the same manner, although reviews of the pertinent literature [65] reveal some species differences. Thus, allegedly, in the fowl, exposure to alarming stimuli caused no obvious adrenal enlargement,[66] but here the possibility of a cortical change was not verified by histologic examination.

During the *stage of exhaustion* very few investigators have studied the structure of the adrenals. On the basis of the scanty data available at present, it appears that cytolysis and lumen formation prevail. Sometimes, infarction and adrenal necrosis may result from vascular involvement. Presumably extensive cytolytic phenomena are a manifestation of exhaustive stimulation reminiscent of that seen in the Langerhans islets following treatment with "diabetogenic" pituitary extracts or after extensive partial pancreatectomies. There also tends to be a second period of storage-granule discharge resembling that of the A-R.[67]

In *summary*, the characteristic changes seen in the adrenal during the three stages of the G-A-S are the following:

In the A-R:

Chromaffin granule discharge from medulla
Occasional cytolysis of medullary cells
Loss of (sudan, scarlet red or osmium-tingible) lipid granules from cortex
Loss of cholesterol from cortex
Loss of plasmalogens from cortex
Loss of ascorbic acid from cortex
Hypertrophy of cortical cells
Very few mitotic figures in cortex
Hypertrophy (and increased phagocytic power) of reticulo-endothelial cells in cortical sinusoids
Cytolysis and rarely, "lumen" formation in the cortex.

In the Stage of Resistance:

Medulla approximately normal
Increased total width of cortex
Increased number and sudanophilia of lipid granules
Increased cholesterol content
Increased plasmalogen content
Approximately normal or low ascorbic acid content
Hypertrophy of cortical cells
Occasional capsular adenomas
Plentiful mitotic figures in cortex
Extensive cytolysis (with "lumen" formation, necrosis or infarction) only if exposure to a violent, new stressor is superimposed upon the stage of resistance; hence these are probably phenomena of acute exhaustion.

[65] Ingle A55580/42, Tepperman and Engel 83735/42.
[66] Bates et al. A34931/40.
[67] Selye 38798/37, B1204/46.

In the Stage of Exhaustion:

Cytolytic phenomena, infarction and necrosis prevail; otherwise the changes resemble those seen in the A-R. A more detailed characterization is not yet possible since comparatively few data are available concerning adrenal changes in this stage.

There has been considerable confusion in the literature concerning the functional *interpretation of lipid storage and discharge* from the cortex during the G-A-S. The presence of sudanophilic and osmiophilic granules has been regarded by some as characteristic of increased,[68] by others as a sign of decreased [69] cortical hormone secretion.

In support of the latter view, it is emphasized that soon after hypophysectomy the cortex is rich in lipids, while during the A-R the lipid granules are discharged; obviously, in the former case, the cortex is inactive, in the latter, hyperactive. Those, however, who advocate the opposite theory have pointed out that several months after hypophysectomy, the cortex is poor in lipids and that after chronic treatment with ACTH, as well as in the resistant phase of the G-A-S, the cortex is large and its cells contain numerous lipid granules. Yet, in the former case, corticoid secretion is practically at a standstill, while during the latter conditions, it is greatly augmented.[70]

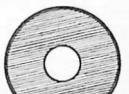
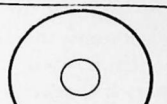
The study of our own experimental material [71] suggested that both these theories are partially correct and that they are not necessarily incompatible with each other. It appears that a few days after hypophysectomy the lipid content of the cortical cells is high, presumably because the gland is not affected by any corticotrophic stimulus, which could cause a discharge of granules. The total width of the cortex is subnormal, however, due to the atrophy occasioned by lack of ACTH. Several months after hypophysectomy, this cellular atrophy becomes so severe that the lipid granules disappear, together with most of the cytoplasmic constituents. In other words, immediately after removal of the anterior lobe, the cortical cell can still retain its stores, although it does not secrete. Later, the atrophy is so pronounced that the cell neither stores nor secretes any significant amount of corticoids — or of the lipids in which these hormones are presumably dissolved.

During acute exposure to non-specific stress (A-R) the demand for corticoids is excessive. The adrenal cortex undergoes hypertrophy to enlarge the "corticoid production plant". Thus the width of the cortex is increased, but it discharges its lipid (and presumably hormone) stores into the blood to meet the urgent demand. Hence, only few, if any, secretion granules remain stored in the cytoplasm. Similar intense degranulation with hypertrophy and hyperplasia is produced by folliculoids. However, these, unlike most stimuli, tend to retain their lipid-discharging effect even in the event of chronic treatment. Neither non-specific stress nor folliculoids cause a discharge of adrenocortical lipid in the absence of the pituitary, hence their effect is presumably dependent upon a simultaneously increased corticotrophin secretion.

[68] Flexner and Grollman 76813/39, Kutschera-Aichbergen B19177/48.
[69] Dosne and Dalton 81198/41, Photakis and Libérato A32939/40.
[70] Selye 94572/47.
[71] Selye B28243/49, Selye and Stone B30224/50.

Following chronic exposure to non-specific stress (stage of resistance) or treatment with ACTH, the cortex is enlarged and its cells store many, intensely sudanophilic, lipid granules. Under these conditions there is every functional indication of increased corticoid secretion, but apparently the gland has acquired the ability to store secretion droplets in spite of increased discharge into the blood.

In studying adrenal changes during the G-A-S, it is important to understand the correlation between the histologic structure of the cortex and its functional activity. Hence, it may be well to illustrate the above interpretation by a schematic diagram:

	A	B	C	D	E
APPEARANCE OF ADRENAL					
PRESUMPTIVE ACTIVITY	NO SECRETION DECREASED STORAGE	NO SECRETION NORMAL STORAGE	NORMAL SECRETION NORMAL STORAGE	HYPER-SECRETION NO STORAGE	HYPER-SECRETION INCREASED STORAGE
EXAMPLES OF CONDITIONS CAUSING CHANGE ILLUSTRATED	LONG AFTER HYPOPHYSECTOMY	SHORTLY AFTER HYPOPHYSECTOMY	NORMAL	ALARM REACTION, FOLLICULOIDS	STAGE OF RESISTANCE, ACTH

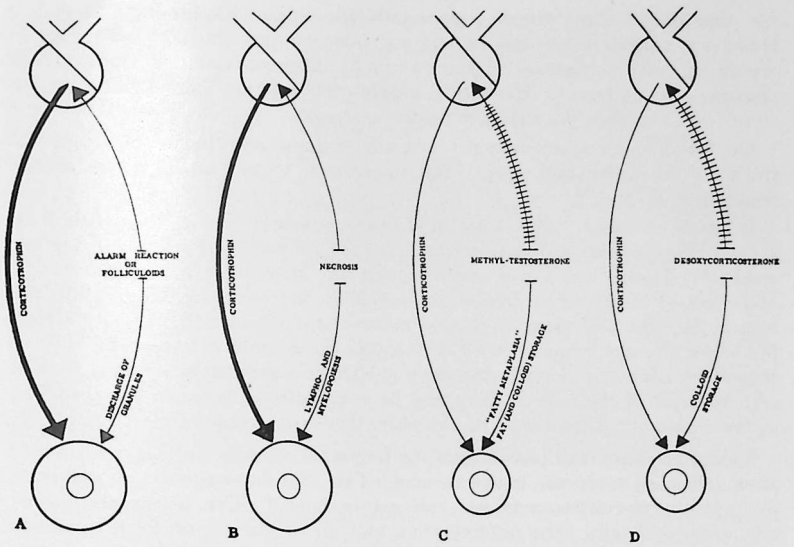
PROBABLE FUNCTIONAL SIGNIFICANCE OF THE SIZE AND LIPID CONTENT OF THE ADRENAL CORTEX UNDER VARIOUS CONDITIONS
(After Selye and Stone B30224/49)

It will be noted that under the experimental conditions which we studied, the adrenal medulla does not undergo any significant change in size (inner circle), while the cortex (space between two circles) is subnormal after hypophysectomy and enlarged during the A-R, the stage of resistance and treatment with folliculoid hormones or ACTH. — Depletion of lipid granules (shaded area) can occur both in inactive ("A") and hyperactive ("D") adrenal cortices; but when the cortex is simultaneously enlarged ("D") this is usually indicative of acute hyperactivity under conditions precluding adequate hormone storage, while in combination with atrophy ("A"), it suggests inability of both storage and secretion. Intense lipid storage is likewise compatible with both hypo- and hypersecretion but when it is accompanied by cortical enlargement ("E"), it suggests that the gland is capable of adequate storage in spite of increased secretion, while in conjunction with atrophy ("B"), it implies that the cortex is hypo-active, although it can still retain its stores. — It must be kept in mind, of course, that all these changes take some time to develop. The large and lipid-rich adrenal cortex of an animal during the stage of resistance retains its size and lipid granules immediately after hypophysectomy, although it is already inactive. Yet, we feel that this diagram helps to clarify the correlations between the structure and function of the cortex since it proved to be in accord with observations, if this time element was not neglected.

In this manner if both the width and the lipid content of the adrenal cortex are taken into consideration, morphologic criteria give us a fairly accurate indication of functional activity, under diverse conditions.

In discussing the various reaction forms of the adrenal cortex in the introduction above, it has been especially emphasized that certain stimuli may produce *qualitatively distinct, specific morphologic changes.* These are presumably caused by a dual effect: (1) an influence upon the ACTH production of the anterior-lobe, (2) a direct effect upon the adrenal cortex.

The following diagram may help to visualize the probable interrelations between the hypophysis and the stimuli capable of eliciting those structural changes which cannot be explained merely by a more or less intense ACTH production:



SCHEMATIC DRAWINGS ILLUSTRATING MECHANISM THROUGH WHICH VARIOUS AGENTS COULD CAUSE SPECIFIC CHANGES IN THE ADRENAL CORTEX
(After Selye and Stone B30224/49)

Not all the interrelations depicted in these graphs can be considered as definitely proven, but the mechanisms illustrated here appear to be compatible with all observations made to date. The drawings are merely intended to act as graphic expressions of a working hypothesis. This is, of necessity, based only on present knowledge, but by precisely formulating the problems involved, it may help to formulate the points requiring further experimental analysis.

Graph A. During the A-R or under the influence of folliculoids, the pituitary is stimulated to produce an excessive amount of ACTH. The latter tends to increase both storage and discharge of secretion granules. However, under these conditions, the cortex, though enlarged, discharges its lipids. Hence, we must assume that these agents do not act merely through ACTH production, but also exert a direct granule-discharging effect.

Graph B. Widespread tissue-necrosis acts as an alarming stimulus and as such, increases ACTH production. Yet, it also causes lympho- and myelopoiesis in the adrenal. This is not obtained with pure ACTH. It is assumed that this latter effect is direct, though dependent upon the adequate maintenance of the cortex by corticotrophin. It cannot be obtained after hypophysectomy and is particularly pronounced in animals simultaneously receiving both corticotrophic anterior-lobe extracts and necrotic tissue preparations.

Graph C. Methyl-testosterone (and other testoids) decrease corticotrophin production since they produce an involution of the adrenal cortex. This effect is presumably due to an inhibition of ACTH secretion, since testoids do not interfere with adrenal enlargement caused by exogenous ACTH. Nevertheless, the fatty metaplasia caused by testoids presumably results from a direct peripheral synergism between these steroids and ACTH; it is not seen after hypophysectomy and is particularly pronounced in animals simultaneously receiving both corticotrophic anterior-lobe extracts and methyl-testosterone.

Graph D. Corticoids (e.g., DCA) cause adrenal cortical atrophy, with colloid storage, presumably through a similar mechanism. They induce adrenal atrophy by inhibiting ACTH production, since they do not interfere with the corticotrophic effect of exogenous ACTH. Their ability to induce colloid storage in the adrenal cortex is probably due to a direct synergism between these steroids and ACTH; it cannot be elicited in hypophysectomized animals and is especially pronounced if DCA and corticotrophic anterior lobe extracts are simultaneously given.

The adrenal changes produced by various alarming stimuli are essentially in agreement with the characteristic picture outlined above.

Following **traumatic injuries,** an increase in the size of the adrenals, accompanied by a loss of *sudanophilic lipids,* has repeatedly been observed in the rat [72] and in man.[73] The particularly pronounced adrenal enlargement and degranulation noted in rabbits after bile duct ligature has been ascribed to the

[72] Foglia and Houssay 81580/41, Houssay B19962/47, Oka A18246/39, Popjak B26865/44, Selye 36030/36, 36031/36, 38798/37.
[73] Kalaja B37977/47.

fact that the resulting icterus is especially effective in producing a G-A-S.[74] However, various other specific surgical interventions, such as resection of the stomach [74a] or ligature of the pylorus,[74b] likewise produce typical A-R changes in the adrenals. Hence it is highly probable that, here again, we are merely dealing with the effects of systemic stress.

Similar changes occurred in the adrenals of dogs subjected to experimental trauma; here again they have been interpreted as a manifestation of the resulting A-R.[74c]

It has been found, furthermore, that in the course of an A-R produced by trauma, the *ascorbic acid* concentration of the adrenals decreases in various species.[75] During tourniquet shock in rats, an increase in adrenal size was accompanied by a rise in *protein, phospholipid* and *water* content, while the *neutral fat,* free and ester *cholesterol* content was diminished. In this series the above changes coincided with an increase in *"adrenal ketosteroids"* (?) as judged by Bennett's phenylhydrazine test. These observations confirm that in certain stages of the G-A-S, there may be a dissociation between the response of the various lipid fractions and the phenylhydrazine-positive material.

Special emphasis was placed upon the frequent occurrence of *"lumen"* formation following traumatic injury in man. This is a consequence of cytolysis for which post-mortem autolysis can not account.[76] The degranulation of adreno-cortical cells, their disintegration and the frequency of focal necroses in the suprarenal parenchyme of patients who died of secondary traumatic shock, were recognized as being similar to those which we produced during the A-R in animals.[77]

Adrenal *hemorrhage* is less common in man following surgical interventions; [78] while in the cat, adrenal congestion and hemorrhages are conspicuous after trauma.[79]

After an acute **hemorrhage,** the adrenal cortex of the rat is enlarged; its *ascorbic acid, cholesterol* and *sudanophilic lipids* are discharged in this order. The fall in ascorbic acid and cholesterol content is so rapid that it may reach its lowest point between two to seven hours after bleeding, returning to, or above normal within 24 hours. It is reasonable to assume that hemorrhage acts upon these adrenal constituents through the intermediary of the anterior-lobe, because essentially similar changes in adrenal ascorbic acid and cholesterol have been obtained with purified ACTH, while hypophysectomy prevents this effect of bleeding.[80]

Extensive **burns** also elicit all the changes characteristic of the G-A-S and, being an acute stimulus, mainly those of the A-R.[81] *Enlargement* of the cortex with discharge of *sudanophilic lipids* has been seen in various animal species.[82] Pronounced *hyperemia* sometimes accompanied by hemorrhages was noted in the cat.[83]

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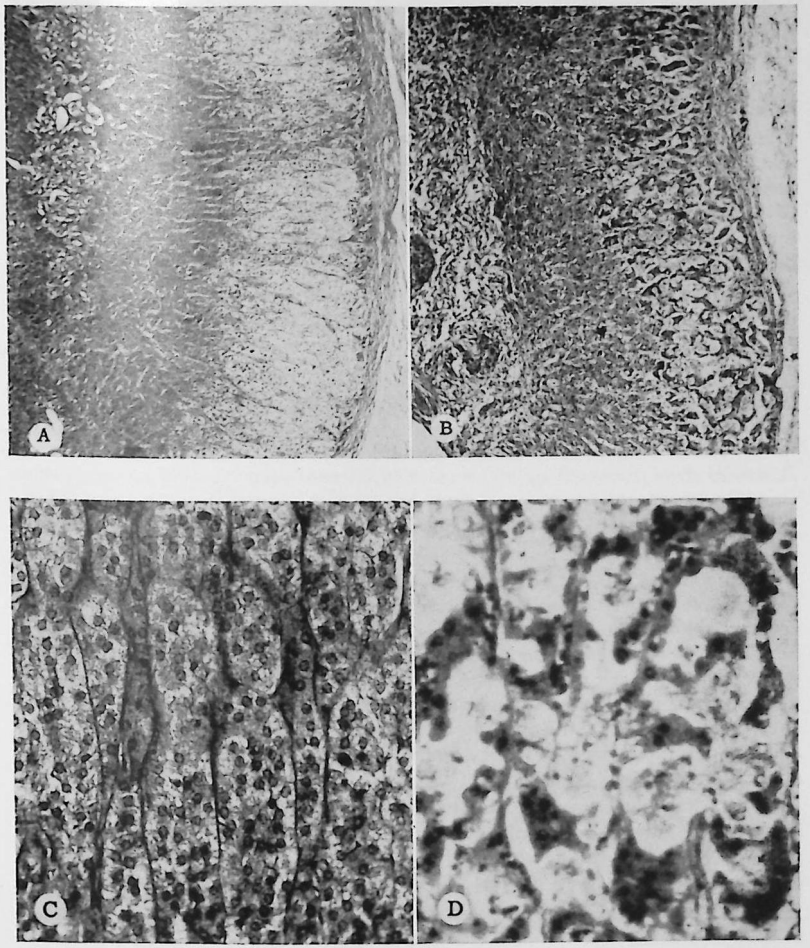
[74] Rosselli del Turco and Matteini B37478/49, B37479/49.
[74a] Gros B46501/49.
[74b] D'Aste B45079/42.
[74c] Berri B42340/48.
[75] Long 98425/47, Selye and Stone B30224/49, Stolfi A56827/36.
[76] Zamcheck B4289/47.
[77] Moon B19951/48.
[78] Kelly 90600/31, Lewis B8442/21.
[79] Kabat and Hedin A56063/42.
[80] Long 98425/47, Sayers and Sayers B18350/48, Wilhelmi and Long B19257/48.
[81] Hilgenfeldt **38008/36.**
[82] Zwemer B325/36.
[83] Kabat and Hedin A56063/42.



Adrenals during A-R in man. — **A.** Low magnification of normal adrenal cortex from a 24-year-old man who died from an accident. Note uniformity of fat-filled (light) cells in outer cortex. — **B.** Adrenal during A-R, due to very severe diphtheria which resulted in death on 7th day. Note characteristic pattern in outer cortex. The peripheral dark cells are lipid free and surround the fat-filled degenerating central cells. Similar changes have been noted following a variety of infections, intoxications and traumatic injuries in man. — **C.** Higher magnification of A. — **D.** Higher magnification of B. The degenerating fat-filled cells in the center of the "tubules" have often been interpreted as due to postmortal autolysis, but are now regarded as characteristic of the response to stress. (Courtesy of Dr. N. Zamchek; after Selye 94572/40.)

There is a particularly rapid loss of adrenal *cholesterol* after burns in the rat.[84] Both in guinea-pigs [85] and in rats [86] this is preceded by an equally severe, but more rapidly developing, drop in *ascorbic acid*. It has been concluded that these changes in "... adrenal cholesterol and ascorbic acid content appear to be manifestations of the adaptation syndrome following injury".[87]

In man, fatal burns cause essentially similar changes,[88] although *cytolytic* [89] and *hemorrhagic* [90] phenomena may predominate to such an extent that fatal, acute hypocorticoidism results. This condition, which is somewhat reminiscent of the Waterhouse-Friderichsen syndrome, often occurs in combination with other manifestations of the A-R, especially gastric ulcers, thymico-lymphatic involution and hemoconcentration.

Short exposure to extreme **cold** likewise causes typical A-R changes in the adrenals, especially in animals sensitized to stress by starvation.[91] In the rat [92] and in various other species [93] this is accompanied by a sudden discharge of *adrenaline* from the medulla.

During the A-R, the *cholesterol* content of the rat adrenal falls rapidly within the first few hours, but after 24 to 72 hours of exposure to cold, it returns to, or above, normal, presumably because the stage of resistance ensues.[94] A similar drop, followed by an increase in adrenal *ascorbic acid* concentration was noted in the guinea-pig and rat,[95] but both the initial drop and the subsequent rise in the ascorbic acid precede the corresponding variations in adrenal cholesterol.[96]

From relevant studies on guinea-pigs it was concluded futhermore "... that the relation between ascorbic acid content in the adrenals and the process of acclimatization to cold temperatures, as described here, postulates the probable beneficial effect of that vitamin for animals unable to synthesize it, in all cases where the response of those organisms to a stress of some sort (toxic effects, intense work, and all damaging agents causing the "alarm reaction") involves some activity of the cortex of the adrenal glands. Animals about to die (at cold temperatures) have much less ascorbic acid in their adrenals than control animals kept at room temperature".[97]

In rats, **frostbite,** produced by local freezing of the tail, causes an initial depletion of adrenal lipids followed by excessive lipid-storage.[98]

Acute exposure of rats to intense **heat** (induced by ultra-high-frequency radio emanations) caused marked *hyperemia* of the adrenals with little change

[84] Harkins 91182/44, Harkins and Long 87814/45, Long 98425/47, Ludewig and Chanutin B2706/47, Sayers B35911/49.
[85] Miyagi A19744/39.
[86] Des Marais and Dugal B23324/48, Dugal and Des Marais B39185/49, Long 98425/47, Ludewig and Chanutin B2706/47, Sayers B35911/49.
[87] Ludewig and Chanutin B2706/47.
[88] Hilgenfeldt 38008/36.
[89] Zamcheck B4289/47.
[90] Berkow 91241/31, Ficarra and Naclerio B808/44, Harris 90255/29, McLaughlin 92906/33.
[91] Itoh et al. B37081/49, Leblond and Dugal A72918/43, Selye 36030/36, 36031/36.
[92] Kayser and Aron A19096/39, Selye 36030/36, 36031/36.
[93] Kayser and Aron A19096/39.
[94] Levin B364/45, B32055/45, Long 98425/47, Sayers and Sayers B18350/48.
[95] Dugal and Thérien B23325/48, B3158/47, B2569/47, Long 98425/47, Thérien and Dugal B32840/49, Thérien et al. B39699/49.
[96] Long 98425/47, Sayers and Sayers B18350/48.
[97] Dugal and Thérien B2569/47.
[98] Zenow B28100/44.

in *lipid* distribution; upon chronic exposure, however, the cortical sudanophilic-lipid content was greatly increased. These findings were interpreted as essentially consonant with those noted in the G-A-S produced by other stressors.[99] In the rabbit, fever (induced by the diatherm or radiotherm) caused marked depletion of adrenal lipids with extensive cortical *necrosis*.[100]

In men dying of heat-stroke or "therapeutic pyrexia", focal necrosis and *"lumen"* formation may also occur. Engorgement of the sinusoids is the rule after short exposure, while later, relative ischemia is frequent. *Hemorrhages* are common but usually remain confined to the capsule and the cortico-medullary border zone.[101]

Exposure to **x-rays,** especially if large parts of the body are affected, causes typical G-A-S changes in the adrenal. *Enlargement* of the gland with loss of *lipid* granules was seen in the rabbit [102] and rat.[103]

The adrenal sudanophilic lipid and *cholesterol* concentration is markedly, and rapidly, diminished by x-irradiation in the mouse [104] and rat.[105] In the rat, a remarkable decrease in adrenal cholesterol has been observed as soon as 3 to 6 hours following x-irradiation, while after 7 to 8 days the adrenal-cholesterol levels were very significantly above normal. The results of this latter series were examined in the light of the G-A-S hypothesis. The acute cholesterol depletion was considered to resemble that of the A-R, but the characteristics of the resistant phase were apparently not taken into account, since the delayed increase in adrenal cholesterol was interpreted as follows: "This may be a result of prolonged stimulation of the adrenal cortex, indicating either a maintained, increased cortical activity or actually a decrease in activity due perhaps to a type of exhaustion. In this connection it is interesting to note that injection of pituitary adrenotrophic hormone over a period of three days also results in an elevated adrenal cholesterol".[106] It may be well to re-emphasize therefore that an increase in adrenal cholesterol is characteristic of the resistant stage; it is presumably due to the fact that ACTH secretion is high at this time, irrespective of the agent which elicits the G-A-S.

In rats the *ascorbic acid* content of the adrenals shows the same variations after x-irradiation as after other stressors.[107]

In connection with deaths due to the radiation effects of **atomic explosion,** it is interesting that allegedly, here the adrenals showed no progressive changes characteristic of the G-A-S, but predominantly signs of damage. They were usually depleted of lipids but, in patients who survived for more than a month, the cortex became extremely thin. "Microscopically, most cells were granular rather than foamy and the atrophy was most marked in the outer zona glomerulosa, contrary to what was expected. When foam cells were present, they were usually in the inner layer. The medulla was normal".[108]

Electric injury, incident to electro-convulsive therapy, was claimed to increase cortical activity in the same manner as other types of systemic stress. However, this conclusion was apparently based only on purely functional

[99] Bernstein 78168/40, A36327/41.
[100] v. Haam and Frost A30282/39.
[101] Gore and Isaacson B41903/49, Kopp and Solomon B30247/37, Malamud et al. B18019/46.
[102] Hoshi 23951/28, Podljaschuk 20989/27.
[103] Leblond and Segal 82724/42.
[104] Dougherty and White 95612/46.
[105] North and Nims B32798/49.
[106] Patt et al. B3611/47.
[107] North and Nims B32798/49.
[108] Anonymous B26330/48.

criteria (blood-count, uric acid and creatinine excretion, etc.), although the brief communication dealing with this subject does not definitely say so.[109]

Nervous stimuli are particularly effective in causing G-A-S changes in the adrenal. This has been emphasized ever since the first experiments on the A-R. In rats (especially if sensitized by fasting) transection of the spinal cord at the level of the first thoracic vertebra proved to be extraordinarily active in causing marked *hyperemia* and *enlargement* of the adrenal cortex, loss of sudanophilic *lipids*, discharge of *chromaffin granules* from the adrenal medulla, and sometimes actual *necrosis* of medullary cells.[110] Similar changes have also been noted after mere immobilization of a rat by tying it down to a board.[111] It has been claimed that the adrenal enlargement caused by spinal cord transection in the rat cannot be prevented by maintaining the body temperature.[112] Nor can intense muscular activity, incident to various types of nervous stimulation, be regarded as the eliciting factor, since, after spinal cord transection, muscle contractions are actually prevented in a large part of the body.

An initial fall, followed by a rise, in adrenal *ascorbic acid* and *cholesterol* content has been produced in rats by intense sound or light [113] and (even under general anesthesia) by stimulation of the sciatic and brachial nerves.[114] These responses began to be manifest within 30 minutes and resembled those obtained by exposure to other alarming stimuli or treatment with ACTH.

In the dog, bilateral denervation of the carotid sinus caused pronounced hyperplasia and marked lipid deposition in the glomerulosa. This was interpreted as a sign of increased adreno-cortical secretion, especially since, in one patient, unilateral denervation of the carotid sinus caused a pronounced increase in corticoid elimination as judged by urinary bioassays.[115] The evaluation of these findings must await the results of further observations.

Adrenal changes characteristic of the G-A-S have also been described in women imprisoned in concentration camps during World War II.[116] However here, malnutrition, overwork, etc., presumably complicated the effects of emotional stimuli.

Intense **muscular exercise** has been one of the agents routinely employed in the earliest experiments concerned with the production of G-A-S changes in the adrenal. Especially in rats sensitized by fasting, it elicits loss of *chromaffin granules* and, occasionally, extensive necroses of medullary tissue as well as cortical enlargement with lipid discharge.[117]

The fact that intense muscular activity causes adrenal *enlargement* in various species had been described much earlier, but it was then regarded as a rather specific effect having no relationship to a general defense reaction.[118] Most investigators studied the functional value of this adrenal enlargement specifically in connection with the physiology of muscular exercise.[119]

[109] Cleghorn et al. B19125/48.
[110] Selye 36030/36, 36031/36.
[111] Fortier B24848/48, Selye 36032/36, B1204/46.
[112] Frank A34171/40.
[113] Fortier B38914/49.
[114] Long 98425/47.
[115] Léger A35901/40, Léger and Mollard A57148/41.
[116] Stieve A57136/42.
[117] Selye 36030/36, 36031/36.
[118] Andersen 32606/35, Bardier and Bonne 89531/04, Ciovini B14793/12, Hatai A10936/15.
[119] Benetato and Fosto 90919/38, v. Beznak and Korényi A57235/41, v. Beznak et al. A15465/38, Hajdu and Korényi A72497/42, Hajdu et al. A72232/42, A72012/42, Hasch and Hajdu A31457/39, Ingle 75145/38, Korényi A35132/39, Skutta A38880/39.

One group of workers [120] expressed the opinion that the experiments which led us to consider this adrenal enlargement as due to an A-R are not convincing, but they did not mention what led them to this conclusion. Following forced exercise, the changes in the structure and chemical composition of the adrenal are essentially the same as after exposure to any other alarming stimulus, hence, in the absence of any evidence to the contrary, we would hesitate to regard this adrenal enlargement as specific.

Our investigations revealed that, in the rat, the adrenal becomes extremely *hyperemic* during the first hours of muscular exercise, that is, at a time corresponding to the A-R.[121] Experiments on guinea-pigs showed that as a result of long continued training, both the number of the cortical sinusoids and their blood content increases, especially in the fasciculata region.[122] These vascular changes are also similar to those observed upon exposure to other alarming stimuli.

Numerous experimental observations, in various animals, show that sudden, intense muscular fatigue causes depletion in cortical sudanophilic *lipids*, while during subsequent rest, or after adaptation to prolonged muscular activity, an inverse reaction takes place.[123] Complete disappearance of birefringent material from the cortex was also seen in a man who suffered from Huntington's chorea for five years.[124] A similar depletion of cortical lipids was often reported in patients with prolonged motor agitation due to various diseases.[125] One wonders whether this is due to exhaustion or to some conditioning factor which interferes with the usual lipid storage characteristic of the resistant stage.

It has been claimed, on the basis of experiments in rabbits, that the total *phosphorus* content of the adrenal may rise as much as 500% during muscular fatigue.[126] In view of the paucity of pertinent data it would be premature to attempt an interpretation of this finding in relation to the G-A-S.

The *ascorbic acid* [127] and *cholesterol* [128] determinations in the adrenals of exercised animals revealed an initial decrease followed by an increase, that is, a response characteristic of the G-A-S. It has been especially emphasized that the initial fall in cholesterol is principally due to a depletion of the esterified fraction and is not necessarily accompanied by a corresponding reduction in the amount of total lipid.[129]

Much has been written about the effect of **anoxia** and **asphyxia** upon the adrenal cortex.[130] An *enlargement* of the adrenals in the rabbit,[131] and rat [132] has quite consistently been noted upon exposure to decreased barometric pressure, and several authors pointed out that this is merely part of the result-

[120] Korényi and Hajdu A56945/42.
[121] Selye 36030/36, B1204/46.
[122] Bengsson et al. A19743/39.
[123] Andersen 32606/35, Bardier and Bone 38167/03, Bernard and Bigart 38312/03, Elliot and Tuckett 5946/06, de Jongh and Rosenthal 15108/33, Knouff et al. 79713/41, Mulon A611/13.
[124] Mulon and Porak 35601/12.
[125] Brüning 94739/21, Laignel-Lavastine 32470/18, Lingjaerde A57058/41, Popea and Eustatziu A37511/25.
[126] Goldberg et al. B30427/32, Kutschera-Aichbergen B19177/48.
[127] Ratsimamanga 94047/39, Sayers and Sayers B18350/48.
[128] de Jongh and Rosenthal 15108/33, Knouff et al. 79713/41, Sayers and Sayers B18350/48.
[129] Knouff et al. 79713/41.
[130] Giragossintz and Sundstroem A6932/37, Sundstroem and Michaels 83691/42.
[131] Armstrong and Heim A18224/38, Itoh et al. B37081/49.
[132] Darrow and Sarason A71713/44, Hailman A69737/44, A69734/44, Lawless and van Liere B26143/47, Tornetta et al. 83894/43.

ing A-R.[133] Only one investigator reported an absolute loss of adrenal weight in rats exposed to brief anoxia. He concluded that "this is probably due to a loss of tissue, since the water content is actually increased and histological examination reveals areas of necrosis, exhaustion, atrophy and edema".[134] Since cytolytic phenomena are quite characteristic of very intense alarm-reactions, these observations are not in contradiction with the generally accepted view that the response of the adrenal to anoxia is essentially the same as to any other stressor.

It has been suggested that, in the case of reduced barometric pressure, acapnia, not anoxia is the most important factor. Rats subjected to decreased barometric pressure in the presence of 15% CO_2 allegedly did not develop any adrenal hypertrophy.[135] Here, it was felt, that the CO_2 prevented a disturbance in the acid-base balance and "that the adrenal cortex is stimulated by either a relative or absolute increase in basic cations or acidic anions".[136] However, subsequent investigations, in animals in which an A-R was produced by spinal cord transection, failed to reveal any consistent inhibition of the adrenal response to decreased atmospheric pressure by excess CO_2. Indeed, a great excess in atmospheric CO_2 in itself proved to be capable of causing adrenal enlargement. It was concluded that these results "...disproved the possibility that an alkaline shift of the acid-base balance is the necessary prerequisite for the development of the alarm-reaction, as the response of the organs (adrenals, spleen, thymus and lymph nodes) was of the same order in animals submitted to high and normal carbon-dioxide tensions. The adrenal cortical hyperplasia as well as the lymphatic tissue involution of the animals exposed, without other change in their environment, to a high carbon-dioxide atmospheric tension, imply that this factor is, in itself, an alarming stimulus, perhaps through its action on the acid-base balance of the blood".[137]

Extensive investigations concerning changes in adrenal *lipids* (sudanophilic and osmiophilic) of animals exposed to anoxia and asphyxia, also led to results consistent with the view that these are merely manifestations of the G-A-S.[138] In the rat, histologic evidence of adrenal-lipid depletion was found within two hours, and reached its maximum after about 48 hours of exposure to reduced atmospheric pressure (equivalent to 20-25,000 ft.). Recovery of cortical lipids was apparently complete within 7 days, even though exposure to the same degree of anoxia was continued throughout the experiment.[139] In similar but more chronic experiments, the initial lipid depletion of the cortex was followed by an increase above normal after six weeks of repeated discontinuous exposure. It was concluded that "these changes in the adrenal glands, along with changes in other organs, suggest that adaptation to conditions of lowered oxygen tension may result from discontinuous exposure.[140]

After acute exposure to anoxia, some lipid material may remain in the glomerulosa, when all sudanophilic granules are lost from the fasciculata and reticularis. Marked recovery of lipids was noted as soon as five hours after such an exposure.[141] Since numerous other alarming stimuli cause essentially similar adrenal changes, all these observations agree with the theory that anoxia acts merely as a stressor.

[133] Dohan A37744/42, Langley and Clarke 83179/42.
[134] Edelmann B279/45.
[135] Langley et al. B30426/43.
[136] Hailman A69734/44.
[137] Fortier B24848/48, B26249/48.
[138] Itoh et al. B37081/49.
[139] Darrow and Sarason A71713/44.
[140] Dalton et al. 84981/44.
[141] Nichols B26390/48.

Very long-lasting, discontinuous exposure to reduced atmospheric pressure confirmed that there is first a period of enlargement, increased lipid storage and hyperemia of all cortical layers characteristic of the resistant stage. After about 200 days, however, exhaustion sets in and there is depletion of lipids in the zona glomerulosa, "especially in rats which had lost their adaptation".[142]

The changes in adrenal *cholesterol*[143] and *ascorbic acid*[144] are essentially the same following anoxia as after other alarming stimuli; an initial decrease is followed by a secondary increase to or above normal levels.

The *chromaffin cells* of the medulla likewise exhibit typical A-R changes in rats exposed to acute reduction of atmospheric pressure.[145]

A great variety of **diseases** have been shown to cause adrenal changes more characteristic of the G-A-S than of any specific pathogenic agent. Several investigators pointed out, for instance, that the effect upon the suprarenals of various acute infections is similar to that of traumatic injury, poisoning, burns and other stressors.[146]

Because of the great importance of the adrenal in the defense against disease we shall review the pertinent literature in some detail. In keeping with our approach to this problem, relevant data will be classified according to the most prominent adrenal change and not the causative pathogenic agent. This manner of presentation will help to examine how far the facts agree with our tenet that the adrenal changes seen in spontaneous diseases — as those caused by various other stressors — depend partly upon the specific actions of pathogenic agents ("conditioning" of response to ACTH), but largely upon the duration and intensity of the stress they cause.

The most prominent adrenal change following acute infections is the *enlargement* of the cortex with hyperemia, loss of lipid granules and often necrosis or hemorrhages. More chronic infections, which permit some degree of adaptation, also tend to cause enlargement of the cortex, but this is usually accompanied by marked lipid storage unless the patient dies during an acute exacerbation of the disease, which superimposes an A-R upon the resistant phase. In support of this interpretation one might quote the adrenal changes observed in typhoid fever,[147] yellow fever,[148] spotted fever,[149] generalized purulent peritonitis,[150] scarlet fever,[151] measles,[152] protozoan infections[153] and a variety of other spontaneous infections of man or experimental infections in animals.[154] Similar lesions occur in acute porphyria.[155] Indeed most of the figures given for the weight of the normal adrenal are probably much too high, because they are largely based on glands taken from patients who died from diseases hitherto

[142] Altland B24784/48, Sundstroem and Michaels **83691/42.**
[143] Levin B364/45, B32055/45, Nichols B26390/48, Rabbeno 89982/26, Sayers and Sayers B18350/48, Tepperman et al. B4674/47.
[144] Sayers and Sayers B18350/48, Tepperman et al. B4674/47.
[145] Thorn et al. B335/45.
[146] Golden A17869/48, Selye 94572/49, B1204/46, Zamcheck B4289/47.
[147] Martinez and Gamboa B42869/48, Wahl A31954/39.
[148] Magarinos Torres and Penna de Azevedo 90104/28.
[149] Wajnapel B31243/47.
[150] Katsuragi A58142/36.
[151] Bazgan et al. 92161/32.
[152] Macciotta 90290/31.
[153] Elmassian 90393/28.
[154] Chilla 90647/33, da Costa B34056/46, Federici 5942/03, Fordyce 88547/06, Giampalmo B29742/47, B27673/47, Kozdoba A58144/35, A58145/36, Langlois and Charrin 89037/893, Liebegott **B46126/44.** Nicolau 87876/28, Nybauw 89072/897, Photakis 6981/21, Pinchot et al. B39038/49, Sarason A59040/43, Stenger A32003/39, Tscherniak 90332/29.
[155] Prunty B37297/49.

not considered to have any bearing upon adrenal structure. On the basis of a study including over 800 cases, it has been shown that the normal human adrenals rarely exceed the weight of 10-12 gm. in healthy young individuals whose death was due to a sudden accident. On the other hand, as a result of various diseases, especially systemic infections, the adrenal weight may rise to 15-30 gm.[156]

The often quite enormous adrenal enlargement in newborn infants with erythroblastosis fœtalis, though unexplained, deserves special mention.[157]

In rabbits in which rheumatic fever-like cardiac lesions were elicited by group-A streptococci the adreno-cortical enlargement was especially pronounced.[158] Rats bearing transplantable lymphosarcomas likewise have large adrenals, especially when the tumors regress.[159] It would be interesting to examine whether here the development of rheumatic changes and the regression of the tumors are causally related to the adrenal stimulation.

In chronic diseases, especially in hypertensive, cardiovascular and renal diseases, enlargement of the cortex and adenomatosis is usually associated with increased lipid and cholesterol storage (see p. 314).

Adrenal *hyperemia* has been singled out as one of the prominent systemic manifestations of diphtheria[160] ever since the earliest pertinent animal experiments of Roux and Yersin.[161] It has also been shown to occur in almost every other infection and especially in those causing acute systemic stress, e.g., cholera.[162]

This hyperemia is usually accompanied by hemorrhages, necroses, granule-discharge and other typical A-R changes.

More or less extensive *hemorrhages* are commonly found in the adrenals of patients dying from a great variety of infectious diseases,[163] particularly those which cause marked derangements in blood-coagulation or capillary resistance.

Especially pronounced and usually bilateral adrenal hemorrhages — a veritable "apoplexy of the adrenals" — is characteristic of the so-called Waterhouse-Friderichsen syndrome. This condition is almost always caused by a fulminating meningococcus septicemia. It is usually associated with other purpuric manifestations (for instance, in the skin), and is often fatal unless adequate, early therapy with sulpha drugs or penicillin is instituted. The manifestations of this syndrome are so reminiscent of acute adrenal insufficiency that most investigators regarded the adrenal hemorrhages as the cause of a particularly acute hypocorticoidism. The apparently great value of corticoid therapy (see page 68) in this condition is in keeping with such an interpretation. Morphologically, the adrenal changes resemble those which we have experimentally produced by very intense and acute stressors. Particularly, they recall the adrenal hemorrhages and necroses seen in animals exposed to acute stress at a time when their suprarenals were already enlarged and hyperemic, due to

[156] Materna A39175/41.
[157] Ranström B18502/45-46, Sarason A59040/43.
[158] Murphy and Swift B37498/49.
[159] Murphy and Sturm B39451/48.
[160] Chalier et al. 90008/27, Liebegott B46126/44, Prosperi B41940/47, B41943/49, Ravina 91132/27.
[161] 7004/889.
[162] Chatterjee 79158/39.
[163] Aschoff 5092/23, Betz B23971/46, Liebegott B46126/44, Thomas 7046/23.

pretreatment with LAP or chronic stress. As in the rat, the adrenal hemorrhages in man can extend throughout the entire gland, destroying both the cortex and the medulla almost completely.[164] For these reasons the Waterhouse-Friderichsen syndrome has been interpreted as an unusual type of the A-R.[165]

[164] Abramson and Mayner B29503/46, Aegerter B30430/36, d'Agati and Marangoni B28020/45, Albahary 93962/46, Aluja B40802/47, Andrewes B30423/898, B30429/06, Anger B1941/46, Arneil B30322/46, Auger B28005/45, Banks and McCartney B30443/42, 96605/43, Battin B30422/898, Bergstrand 93971/45, Bernhard and Jordan B649/44, Barsoum A58122/36, Bickel A39967/40, Blaker and Bailey B30424/01, Boger 96103/44, Bottura and Neves B40818/47, de Bruin 95114/37, Bush and Bailey B23447/44, Cabot B30441/40, Careddu 94416/39, Carey A33942/40, Castoldi B30334/47, Cavallero B28485/46, Ceballos et al. B29014/45, Chaudhuri B30337/46, Chetingil and Aksoy B41815/47, Copans and Segal B29021/45, Cosgriff 96108/44, Craster and Simon B30432/38, Cuningham 95974/42, Cutler et al. B30438/38, Day 96109/44, Desbioles B34010/46, Desclin and Verniory B30353/46, Drummond and Tooke 96755/41, Etcheverry and Pages B23482/43, Farber and Salkin B6380/44, Ferguson and Chapman B28252/48, Filberbaum 96113/44, Fontanel 87692/24, Foucar A58137/36, Friderichsen 36812/18, Froehner 96610/42, Garrod and Drysdale 87243/897-8, Ginsburg and Bell B40860/47, Ginsberg and Braunstein B28033/45, Grace et al. A34945/40, Graser 96615/42, Gray and Talisman B40863/47, Grubschmidt et al. B3985/47, Haas B23574/44, Harris and Leviton B29035/45, Hayes and Whalen B837/45, Herbut and Manges 96620/43, Hester B23585/44, Hoff and Shaby 96623/43, Hoffman and Mamelok 93348/46, Holley B30442/42, Holmes and Cowan B2418/45, 96300/45, Hopper and Schofield B40868/47, Hughes A34643/40, Humphrey and Toomey B23588/44, Ikeda and Rosenthal B28044/45, Isaacson B46001/47, Jacobi et al. B2026/45, Johnson 96157/45, Jonsson B34021/46, Julianelle and Reimann B30437/27, Kasich and Disick B23596/43, Kaufman 96126/44, Keele and Keele A56698/42, Kinsman et al. B34024/46, Kirketerp B28049/44, Klemola and Tammilehto B34025/46, Kramer B40875/47, Kunstadter 94447/39, Kwedar A38429/42, Landis A56138/42, A39082/42, Leichliter and Fish 96637/43, Leone B30433/41, Levinson A31736/39, Lindsay et al. B30435/41, Little B30425/01, Luckács and Révész B46052/49, MacLangan and Cooke B30428/16, Macleod A34947/40, Magni A58078/36, Magnusson A58079/36, Mair B30436/28, Marangoni and d'Agati A71846/44, Martins Barbosa B40888/47, Martland 96806/44, Massias B40889/47, Massias and Tranvan-Bang B45693/48, Mayner 96807/43, McNamara 95988/43, Meisel 96133/44, Meneghello et al. 96191/45, Michael and Jacobus A38426/42, Monfort and Mahrling 93831/41, Moss and Schenken 95895/40, Murano B34030/46, Murphy A34946/40, Newcomb 96200/46, Newman 97256/46, Nunes 95901/40, Pasqualini and Bonetti B30396/46, Peabody 96810/43, Pelaez Redondo B40897/47, Perez B29074/45, Piacentini 94603/38, Potter and Bronstein B658/44, Pratt-Thomas et al. B28073/45, Rodriguez-Izquierdo B28081/44, Rotondo et al. B31761/46, Rucks and Hobson 95995/43, 93470/44. Sacenti B42342/48, Sacks B30434/37, Sacks B30434/37, Schroder and Wells 96144/44, Schwarz 93714/46, 93372/46, Scott et al. B31762/46, Sharkey 93847/41, Simmel 96829/44, Simpson B30431/37, Stein B40913/47, Stigliani B30414/46, Strick B676/44, Talbot 36581/900, Taylor and Landry B3987/47, Thomas 96830/44, 96865/43, Traina B40917/47, Turner and Dent B44802/49, Vézina B29096/45, Voelcker B30421/894-5, Wasserman B1926/47, Waterhouse B30439/11, Wilkinson and Bard A55918/40, Williams 96032/42, Wright and Reppert 96398/46.

[165] Pasqualini and Bonetti B34035/46.

Washed meningococci (living or dead) are highly effective in producing the "generalized Shwartzman phenomenon". It is interesting to note therefore that lesions similar to those seen in the Waterhouse-Friderichsen syndrome have been reproduced in rabbits by injecting bacterial filtrates and (living or dead) washed meningococci, in two injections 24 hours apart.[166]

Significantly, not all cases of the so-called Waterhouse-Friderichsen syndrome are due to the meningococcus. More or less diffuse hemorrhagic infarction of the adrenals, with essentially similar clinical manifestations can occur in: malignant diphtheria,[167] streptococcus infection,[168] scarlet fever[169] anthrax,[170] typhoid fever,[171] Friedländer bacillus,[172] dysentery,[173] pneumococcus,[174] influenza,[175] suppurative mastoiditis,[176] puerperal complications [177] and a variety of other acute fulminating infections.[178] Somewhat similar adrenal hemorrhages with purpura occur following exposure of the whole body to ionizing radiations (see above), injury of the newborn during delivery,[179] chronic nephritis,[180] intestinal occlusion,[181] malignant hypertension,[182] severe jaundice,[183] intoxication with insulin [184] or various other drugs causing intense systemic damage.[185]

In one series of 119 cases [186] less than 23% were ascribed to meningococcus infection, yet in general, this is by far the most common etiologic agent. Presumably the syndrome develops whenever an intense A-R (non-specific component) occurs in combination with purpura (specific conditioning factor).

More or less extensive adrenal *necrosis* follows quite regularly after the above-mentioned hemorrhagic infarction, if the patient survives long enough. Quite frequently, however, acute focal necrosis of certain adrenal areas also occurs without any marked hemorrhage; for instance in medical shock [187] varicella,[188] typhoid,[189] dysentery [190] and many other infectious diseases.[191]

In one published case, meningococcus encephalitis appears to have terminated in a syndrome of "multiple endocrine gland sclerosis", with particularly marked adrenal and pituitary atrophy.[192] It is possible that here we are dealing with an "exhaustion atrophy" due to excessive stimulation.

Periarteritis nodosa, experimentally produced by LAP or DCA, is likewise conducive to adrenal necrosis (see p. 338). It is interesting therefore that in

[166] Apitz B30444/34, Black-Schaffer et al. 99936/47.
[167] Cavalcabo B37917/48, Claveaux and Salveraglio 96106/40-2, Clevers and Goormaghtigh 87612/22, McLean 95052/37, Poinso and Poursines 92927/33.
[168] Betz B23971/46.
[169] Beauchesne et al. B40810/47, Cavalcabo B37917/48.
[170] Roger 92575/17.
[171] Cassaute and Raynaud 94970/28.
[172] Sicard 89336/04.
[173] Kellner 90643/33.
[174] Betz B23971/46.
[175] Daddi and Pana 95120/37, Ginandes and Howard B40857/47, Kovács 90627/29, Winter 92597/18.
[176] Cabot B29002/45.
[177] Dodds B29024/45.
[178] Blaker and Bailey B30424/01, Little B30425/04, MacLagan and Cooke B30428/16, Thomas and Leiphart 96148/44.
[179] Baldi B29006/45.
[180] Photakis 89820/26.
[181] Provenzale B38037/45.
[182] MacMillan B30166/47.
[183] Godfrey B30366/47.
[184] LaBarge and Ogilvie A37692/41.
[185] Betz B23971/46.
[186] Taylor and Kean A57957/43.
[187] Meessen B23957/47.
[188] Schleussing 87888/27.
[189] Macchia and Cicala B30382/45.
[190] Blazso A39829/40.
[191] Mitchell and Angrist A57688/43, Photakis 6981/21.
[192] Rotter and Schroers B31990/48.

man, periarteritis of adrenal vessels also tends to produce focal necroses and subsequent scar formation.[193]

Extensive *cytolysis with the formation of "lumina"* is quite common in the human adrenal cortex, especially in patients who died of acute systemic infections.[194] These lesions can also occur in pregnancy and the so-called diseases of old age (arteriosclerosis, atherosclerosis, etc.), hence their appearance was ascribed to excessive demands upon the adreno-cortical function.[195] Since such lumina appear in patients after exposure to a variety of fatal systemic stress (e.g., infections, wounds, burns) they have been recognized as a rather typical manifestation of the A-R in man.[195a] (Cf. 296, 303.)

Much has been written concerning the development of a functional hypocorticoidism in patients and experimental animals infected with malaria. This is often accompanied by more or less extensive cytolytic and degenerative changes in the adrenals, lesions which are reminiscent of the suprarenal damage characteristic of the stage of exhaustion. More extensive anatomic studies would be required to establish the exact relationship of these adrenal changes with the G-A-S; however, the pertinent literature suggests that malaria has a special tendency to cause adrenal exhaustion.[196]

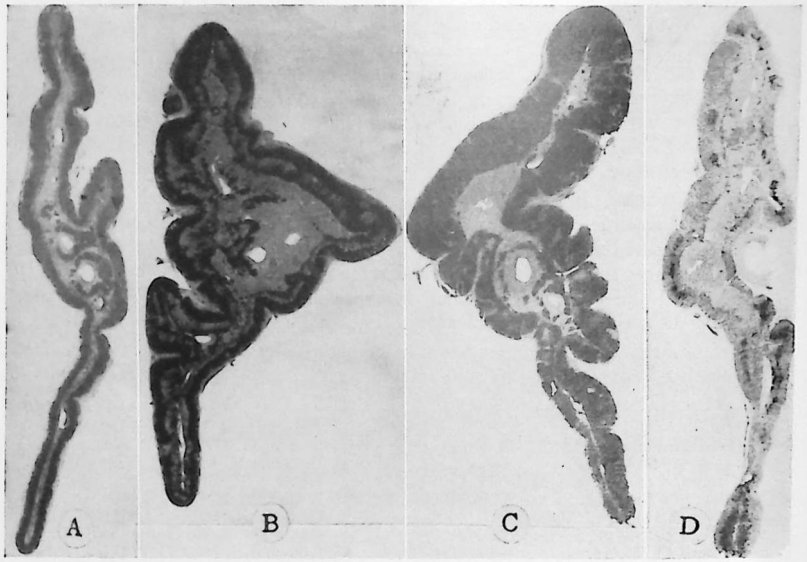
Hypertrophy, hyperplasia and adenomatosis of the adrenal cortex, with increased storage of *lipid* and particularly *cholesterol* granules, have frequently been described as characteristic of hypertension, arteriosclerosis, and chronic renal diseases in man.[197] Indeed an increase in the lipid (especially cholesterol) content of the adrenal is common in hypertension and chronic renal disease, even if the cortex is not significantly enlarged.[198]

Of course not all patients with "essential" hypertension show manifest adrenal changes and conversely, adrenal-cortical enlargement is not necessarily

[193] Balo and Nachtnebel A64492/29, 90115/29, Bau 90768/34, Bennett and Levine 90117/29, Brenner 94534/38, Carr 90466/30, Diaz-Rivera and Miller B2032/46, Giese 89858/27, Klinger 91883/31, Lamb 94268/14, Logue and Mullins B2028/46, Mertens 87587/22, Steen 94214/42, Vance and Graham 91591/31, Washburn and Otto 94226/45, Weir 94552/39, Wilmer 94227/45.
[194] Demole 5833/16, Dietrich 6776/18, Dietrich and Siegmund 5822/26, Golden B28034/45, Gossman 5865/27, Liebegott B46126/44, Paunz 5866/23, Rich A71835/44, Thomas 5906/11.
[195] Lucadou A15713/38.
[195a] Zamcheck B4289/47.
[196] Ciavaldini and Lartigue 93998/45, Detre 92605/24, Flosi B2020/44, B32317/48, Fraga 92587/17, Golden B17869/48, Golden and Overman B17868/48, Paisseau and Lemire 88694/16, Poleck 95002/28, 95003/28, Zhgenti 90369/27.
[197] Albrecht and Weltmann 6686/11, Aubertin and Ambard 89514/04, Bergstrand B37884/47, Bruger et al. B550/44, Delanoe B43625/48, Della-Lena 88186/05, Dietrich and Siegmund 5822/26, Dublin 96609/43, Dufour 89515/04, Duthoit 90650/33, 7157/33, Ferrara 94429/39, Fisher and Hewer B24202/47, Friedman and Eisenberg 95128/37, Giampalono B29742/47, Gossman 5865/27, Guichard and Boulliat B38074/48, Josué 89456/04, 89458/04, Liebegott B46126/44, Mosinger B30627/48, Neuhaus A58336/36, Rimbaud and Delmas A33671/39, Rinehart et al. A36716/41, Russi et al. 96237/45, Sarason A59040/43, Wertheimer and Guichard B33837/49, Widal and Boidin 88226/05.
[198] Borberg 33410/15, Chauffard et al. 6751/12, 36345/14, Fex 11748/20, Ida 29724/31, Knack 33504/15, Kohno 22766/28, 23989/29, Weltmann 7072/13.

conducive to hypertension.[199] This does not alter the fact that anatomic changes in the cortex (hyperplasia, adenomas and lipid storage), similar to those characteristic of the "stage of resistance", are unusually common in hypertensive, cardiovascular and renal diseases. Significantly, most of the pertinent observations have been published much before the concept of the "diseases of adaptation" could have influenced their evaluation.

In patients with chronically increased intracranial pressure, basophilia of the anterior-lobe and hyperplasia of the adrenal cortex are allegedly also common.[200] This may play a part in the arterial hypertension which is frequently associated with lesions causing a rise in intracranial pressure.



Adrenal changes in clinical hypertension. — **A.** Normal human adrenal under low magnification. Note moderate lipid content of cortex indicated here by the degree of darkness of the outer rim. — **B.** Compensated hypertension with enlargement of both medulla and cortex. Note also increased lipid content in the latter. — **C.** Compensated hypertension with marked cortical enlargement and increased lipid storage; the medulla is essentially normal in this case. — **D.** Decompensated aortic insufficiency with almost complete exhaustion of the cortical lipids. (After Liebegott B46126/44.)

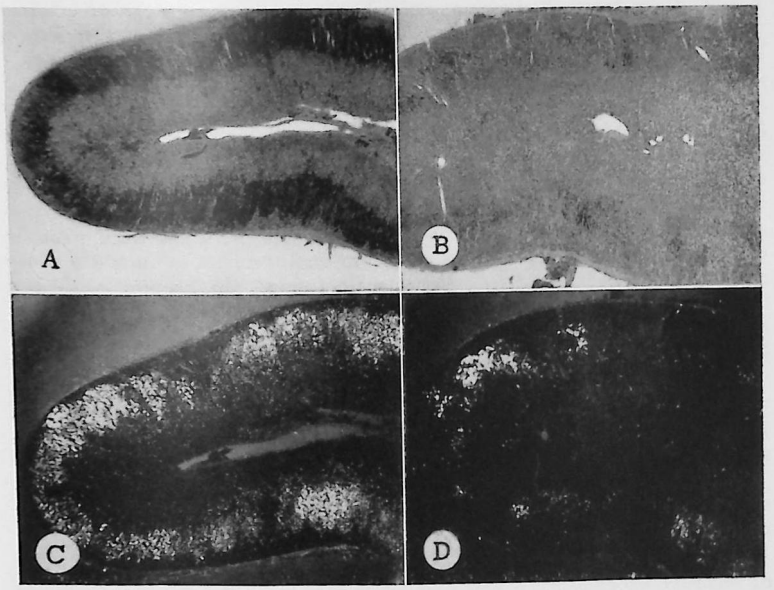
In Buerger's disease, lipoidosis, hyperplasia and adenomatosis of the adrenals is allegedly so common that partial adrenalectomy has been recommended as a therapeutic measure, in the belief that hypercorticoidism may be involved in the pathogenesis of the vascular derangement.[201]

On the other hand discharge of cortical lipids (corresponding to the A-R) occurs in animals during acute diseases, e.g., massive infections or intoxication

[199] Commons and Callaway B36571/48. Dempsey A57768/42.
[200] Bertolotti 94700/37, Kraus A30768/38.
[201] Maillet et al. B37575/47, Plauchu et al. B37574/47.

with diphtheria toxin,[202] B. Tularense and B. Coli.[203] In man, various acute infections likewise tend to deplete the adrenal cortex of its lipid granules. Several investigators pointed out that under the influence of infections, the loss of lipids does not necessarily occur simultaneously from all layers of the cortex. Indeed the lipid distribution pattern may become very irregular and spotty under such conditions, until finally — in extreme stress situations — almost all lipid granules are discharged.[204]

A recent review of the literature led to the conclusion that "... the cholesterol content and the sudanophilic material of human adrenal glands vary greatly under different circumstances, in general being low in patients with severe infections, moderately decreased in those with chronic debilitating diseases and cancer, and high in people who die of cardio-renal disorders".[205]



Adrenal changes in clinical diphtheria. — **A.** Early death in diphtheria. Note that the cortex still contains much fat. — **B.** Late death from diphtheria with marked hemorrhagic diathesis. Note almost complete disappearance of cortical lipids. — **C.** Adrenals of Fig. A as seen under polarized light. — **D.** Adrenals of Fig. B as seen under polarized light. Note that birefringent lipids closely parallel total lipid content. (After Liebegott B46126/44.)

In the severe infections the sudanophilic lipid and ascorbic acid content of the human adrenal is usually — though not always — proportionately reduced.[206] Comparative investigations, in which the cortices of normal and lipid-depleted human adrenals were studied with various histologic techniques

[202] Albrecht and Weltmann 6686/11, Weltman 7072/13.
[203] Pinchot et al. B39038/49.
[204] Menten and Smith A58080/36, Napp 6949/05. Sarason A59040/43.
[205] Rogers and Williams **B4237/47.**
[206] Menten and Smith A58080/36.

revealed that sudanophilia, phenylhydrazine reaction, birefringence, autofluorescence and the chemically determined cholesterol content also roughly parallel one another. It has been concluded that the degree and direction of the changes observed in human material are generally in agreement with the corresponding changes seen during the A-R in animals.[207]

Lymphatic leukemia (spontaneous or transmitted) in mice is allegedly associated with an especially marked decrease in adrenal-cholesterol,[208] but the significance of this observation cannot yet be evaluated.

The *plasmalogen* content of the adrenal was found to rise under the influence of diphtheria toxin treatment just as after corticotrophin injection.[209] This observation likewise agrees with the view that the adrenal changes caused by bacterial toxins are essentially similar to those produced by other stressors.

In guinea pigs inoculated with diphtheria toxin [210] and in rats infected with B Coli, B. Tularense [211] or trypanosoma hippicum, the *ascorbic acid* concentration of the adrenals was found to be diminished.[212] Here as in man, suffering from a variety of infectious diseases, the loss of adrenal ascorbic acid roughly paralleled that of lipids [213] (cf. bacterial toxins, p. 322).

The formation of "round cell infiltration islets", corresponding to *foci of lymphatic and myeloid elements*, has recently been reviewed,[214] hence we need not discuss the pertinent literature in great detail here. Suffice it to say that, both in man and in experimental animals, such infiltrations occur with particular frequency and intensity if there is much tissue necrosis, in addition to non-specific systemic stress.[215] Apparently, the products absorbed from necrotic tissue condition the response of the adrenal to corticotrophin in such a manner that lymphatic and hemopoietic elements are formed. In keeping with this interpretation, neoplasms tend to cause lymphatic or myeloid infiltration islets in the adrenals only when they undergo extensive liquefaction necrosis.[216] Significantly some pathologists claim that such lymphoid infiltration is also common in hypertensive patients.[217]

A particularly pronounced stimulation of the reticulo-endothelial apparatus in the adrenals of animals bearing transplanted tumors has likewise been described.[218]

The so-called *"epinephritis"*, in man suffering from scarlet fever [219] and other types of acute infections,[220] may be related to these lymphocytic and myeloid infiltrations, since the latter also tend to contain polymorphonuclear leucocytes.

In addition to the above mentioned infiltrations (presumably specific effects of necrosis), experimental tumors also induce changes in the size, lipid content and histologic structure of the adrenals, which are merely due to systemic stress as such and resemble those elicited by other alarming stimuli.[221] The

[207] Rogers and Williams B4237/47.
[208] Levin B30261/48.
[209] Tonutti 97841/41.
[210] Scartozzi B38631/46.
[211] Pinchot et al. B39038/49.
[212] Nyden B28281/48.
[213] Menten and Smith A58080/36.
[214] Selye and Stone **B29705/50.**
[215] Guichard and Boulliat B38074/48, Paunz 5866/23, Selye B28243/49, Selye and Stone B29705/50.
[216] Selye and Stone **B29495/49, B29705/50.**
[217] Wertheimer and Guichard B33837/49.
[218] Sokoloff 91579/31.
[219] Bazgan et al. 92161/32.
[220] Chilla 90647/33, Mosinger B30627/48.
[221] Ball and Richards B20002/38, Dalton 85161/44, Daniel A31919/39, Greene and Saxton B10976/38, B10975/38, Maddaloni 98398/40. Murphy and Sturm B39451/48. Savard B23929/48, Sure et al. A30935/39. Vicari A61359/43, 87042/46, 87061/46. 83850/43. Vicari and Little B11472/45.

decrease in the ascorbic acid content of the adrenal of tumor bearing rats [222] probably belongs to this type of change.

The so-called *"brown degeneration"*, in the adrenals of tumor bearing rats and mice [223] and the formation of large *"lipid blocks"* in the zona reticularis of cancer-susceptible mice [224] may be specific changes, in any case, their possible relationship to the G-A-S has not yet been established.

Characteristic changes in the *adrenal medulla* have also been described in various spontaneous diseases of man. In fulminating infections (e.g., malignant scarlet fever), loss of chromaffinity is particularly striking.[225] This corresponds to the adrenaline discharge of the A-R.

In cases of hypertension, on the other hand, hyperplasia of the medulla is allegedly of common occurrence.[226] It is true that some pathologists [227] refuted the theory according to which adreno-medullary changes play an important rôle in clinical hypertension, but it is noteworthy that even in their material, eleven of thirty-five cases with hypertension exhibited hypertrophy of the medulla. It is an uncontested fact, of course, that chromaffinomas and diffuse hyperplasia of the adrenal medulla can lead to hyperadrenalinism with a paroxysmal or even persistant, rise in blood-pressure; [228] The question is only how often proliferative changes in the medulla participate in the etiology of the common types of clinical hypertension. In recent years hyperadrenalinism has been somewhat neglected as a possible etiologic factor in essential hypertension; yet many of the above publications suggest that proliferative changes in the adrenal medulla are quite common in patients who die of what appears to be essential or renal hypertension.

In this connection, it may be well to mention, furthermore, that even if there is no great enlargement or adenoma formation in the medulla, certain signs of hyperactivity (e.g., dilatation of the sinusoids with swelling of their endothelium, intense vacuolization of medullary cells, enlargement of the nuclei and formation of giant cells) are quite regularly seen, both in animals and in man, following treatment with bacterial toxins, infections and other stressors.[229]

The systemic stress occasioned by various **serologic reactions** (e.g., anaphylaxis, allergy, administration of toxic sera) tends to cause typical G-A-S changes in various organs including the adrenals.[230] In some instances these are difficult to differentiate from the allegedly specific cytolytic effects of so-called anti-adrenal "cytotoxic sera".

A large variety of **drugs** capable of producing systemic stress, have been shown to elicit typical G-A-S changes in the adrenals. Among these, subcut-

[222] Sure et al. A30935/39.
[223] Blaisdell et al. A37988/41, Cramer and Horning A33071/39, Iki 96859/41.
[224] Dobrovolskaia-Zavadskaia 99778/38, B21529/37, Dobrovolskaia-Zavadskaia and Pezzini A33194/39. Dobrovolskaia-Zavadskaia and Zaphiroff B7699/38.
[225] Thomas 5906/11.
[226] Drake et al. B7060/44, Duthoit 7157/33, 90650/33, Frei A49817/34, Goldscheider 38807/26, Goldschmidt 6812/09, Goldzieher A71161/32, 528/31, Goldzieher and Molnar B31261/08, Goldzieher and Sherman 38804/28, v. Lucadou 33073/35. 35118/36. Mosinger B30627/48, Opsahl 94599/38, Schur and Wiesel 7013/07. 50319/07, Tarozzi and Barbanti 90324/48, Westphal and Sievert B31259/38.
[227] Cohen and Aschoff B31262/08.
[228] Selye **94572/49.**
[229] Elaut B31258/28, Goormaghtigh 10999/31.
[230] Criep and Mayer B38223/49. Delaunay et al. B31255/48, B31256/47, B31257/47. Della Vida 88133/04, 89234/03, 89308/03, Porta A18969/38. Saphir and Binswanger 87962/30, Scalabrino 92144/32, Simonin B23373/48.

aneous injection with protein precipitants (e.g., formalin or alcohol), autonomic drugs [e.g., atropine, adrenaline and narcotics (e.g., morphine)] were found to be particularly effective.[231] Curiously, in newly-hatched chicks, the adrenal failed to respond to treatment with various toxic drugs, although exogenous ACTH caused marked suprarenal enlargement.[232] Perhaps at this early age, the hypophysis of the fowl does not yet respond to stress, although the adrenal is already quite sensitive to corticotrophin.

It would hardly be profitable to discuss the entire pertinent literature in detail, since the effect of all drugs is fundamentally similar as long as they are given in doses conducive to comparable degrees of systemic stress. We shall merely mention (in alphabetic order) the changes caused by compounds whose effect upon the adrenals appears to be of special interest; for data concerning chemicals which may be regarded as food constituents, the reader is referred to the next section (cf. Diet, p. 323).

It has been mentioned that certain manifestations of **alloxan** intoxication are reminiscent of an acute A-R. It is of interest, therefore, that in rabbits receiving high doses of this compound, necrosis of cortical cells as well as infiltration with polymorphonuclear neutrophilic and eosinophilic leucocytes often develop concurrently with diabetes and hyperlipemia.[233] In rats, adrenal enlargement with a sudden discharge of adrenaline, ascorbic acid and cholesterol was found to occur immediately after alloxan injection,[234] while in otherwise similar chronic experiments the lipid content of the cortex rose.[235] Similar lesions occur in dogs.[236] These and other [237] observations agree with the interpretation that alloxan — like so many other drugs — causes adrenal changes due to its stressor effect and that during the stage of resistance, some of these are actually the reverse of what is seen during the A-R.[238]

Most experimenters found the adrenal medulla unchanged in alloxan-intoxicated animals, although, occasionally, in the rabbit, cytoplasmic vacuolization and mild cytolytic phenomena may occur.[239]

It is especially noteworthy that **anesthetics** can also cause G-A-S changes in the adrenals. This suggests that such lesions are not necessarily due to exaggerated nervous activity, although nervous system stimulants can also elicit them.

During profound *chloroform* anesthesia, the chromaffinity of the medulla and the lipid content of the cortex diminish in the guinea pig.[240] *Barbiturates* can likewise cause adrenal enlargement with typical A-R changes.[241] In view of the fact that, in near physiologic doses, corticoids cause compensatory atrophy of the adrenal, it is especially interesting that DCA — in amounts sufficient to cause general anesthesia — elicits marked enlargement of the adrenal cortex, with loss of its lipids and ascorbic acid, that is, changes typical of the A-R.[242]

[231] Masson A17984/39, Selye 36030/36, 94572/47, B1204/46, 36031/36.
[232] Bates et al. A34931/40.
[233] Kendall et al. A95806/45, Ruben and Yardumian B2138/46, B15815/46.
[234] Arvy and Gabe B34748/48, De Majo B3446/47.
[235] Bennett and Koneff 99884/46.
[236] Marcozzi and Prosperi B31554/44.
[237] Applegarth B31758/49.
[238] Arvy and Gabe B34748/48, B44853/49, Covian B45944/49, Eränkö B47322/50.
[239] Hard and Carr A69284/44.
[240] Scaglione 7008/15.
[241] Chanutin and Ludewig A95935/46, Ludewig and Chanutin B2706/47.
[242] Moya and Selye B19381/48, Selye B1433/48.

It is noteworthy that *urethane*, in doses adequate to produce lymphopenia, does not alter the ascorbic acid content of the adrenals in the rat; indeed it allegedly prevents the depletion of adrenal-ascorbic acid normally elicited by adrenaline administration. The possible bearing of this finding upon the concept of the G-A-S has been discussed, but is not yet clear.[243]

Among the so-called **caryoclastic poisons**, *colchicine* has a very pronounced stressor action. In the case of acute intoxication it causes marked adrenal enlargement with discharge of cortical lipids both in the rat [244] and in man.[245] It will be recalled that several of the "caryoclastic drugs" (e.g., tripaflavin, sodium cacodylate) differ from most stressors in that they cause thymus involution even in the absence of the adrenals (as do ionizing radiations, steroids and certain vesicants); nevertheless, as far as is known at present, their action upon the adrenals is essentially the same as that of other alarming stimuli.

Cholesterol feeding leads to enlargement with a marked increase in the lipid (especially cholesterol) content of the adrenal cortex in the guinea pig.[246] Most investigators agree that this is chiefly due to cholesterol storage. It leads to the formation of "pseudoxanthoma" cells in the adrenal cortex. Similar elements appear in the rabbit adrenal after feeding with egg yolk, lanoline and olive oil.[247] It has been claimed [248] that in rabbits fed with cholesterol, 23% of the total increase in adrenal weight is due to deposition of the sterol. The storage is greater in males although normally, the adrenals of females are richer in cholesterol. Here the medulla showed no change, but occasionally, myelocyte-like cells appeared in the cortex under the influence of chronic cholestrol treatment.[249] In hamsters, cholesterol feeding likewise results in the storage of this lipid by the adreno-cortical cells.[249a]

Contrary to what happens in the guinea pig and rabbit, the changes are moderate in the rat; [250] in the mouse [251] the cholesterol content of the adrenal does not increase under the influence of cholesterol feeding.

All these findings suggest that cholesterol, as one of the "macromolecular substances" (mentioned below), produces a very specific type of thesaurosis. An enlargement due to such storage must not be confused with the G-A-S changes.

Sodium **cyanide**, administered in repeated sublethal doses to rats, causes adrenal hypertrophy with lipid depletion in the inner zones of the cortex.[252]

Intraperitoneal administration of hypertonic **glucose** to cats resulted in a sharp fall in adrenal-ascorbic acid.[253] Glucose appears to have a greater adrenal stimulating action than would correspond to its stressor effect (cf. stressors), but here it was given in definitely toxic doses, so that its influence upon the adrenal may well be attributed to the G-A-S.

[243] Dury B28241/48.
[244] Leblond and Segal A50424/38.
[245] Dustin 94160/41.
[246] Hueck 5958/12, Ignatowsky 6852/09, Krylow 5913/14, Landau and McNee 5957/03, Ligas A9457/37, Matsunami 8068/32, Milbradt 11532/30, Reineck 19145/28, Sternberg 7033/14, Wacker and Hueck 5910/13, Weltmann and Biach 7094/13, Zinserling 5959/23.
[247] Suzue 38509/36.
[248] Kay and Whitehead 53519/35.
[249] Krylow 36290/14.
[249a] Goldman B46712/50.
[250] Hajdu and Korényi A72497/42.
[251] Whitehead 29376/34.
[252] Nichols and Miller B41169/49.
[253] Dohan and Lukens B19202/48

Histamine also causes an ascorbic-acid depletion with other A-R changes in the rat,[253a] presumably again merely as a consequence of the resulting non-specific stress.

Intravenous injection of certain **"macromolecular substances"** such as *gum arabic* elicit what has been termed the "macromolecular hematologic syndrome" (reduction of erythrocytes and hemoglobin, accelerated erythrocyte sedimentation rate, transitory leucopenia, persistent leucocytosis or leucopenia and reduction of serum proteins). Gum arabic cannot be readily and completely depolymerized in the body; hence following intravenous injection, the substance is stored in the reticulo-endothelial system in the form of "foam cells" which are often very prominent both in the medulla and in the cortex of the adrenals.[254] Although this response may be accompanied by typical G-A-S manifestations in the suprarenal, the thesaurosis itself is a specific reaction.

Nicotine intoxication received a great deal of attention because this drug effects a marked adrenaline discharge from the medulla and can elicit arteriosclerotic lesions in various animal species, perhaps even in man. It has been claimed that in the rat, chronic nicotine intoxication leads to adenomatous proliferations in the adrenal medulla [255] as well as signs of increased adrenaline discharge.[256] Yet some rats can tolerate comparatively large doses of nicotine without any obvious adrenal change.[257] In the dog [258] and guinea-pig, proliferative changes in the medulla, with signs of increased adrenaline production, have also been noted.[259] One investigator reported that in guinea-pigs receiving chronic nicotine injections, the ascorbic acid content of the adrenals rises in proportion to the dose.[260]

Considerable attention has been given in recent years to adrenal changes caused by various organic **sulfur derivatives** and especially the thioureas. It was found, in the rat, that addition of 1% thiourea to drinking water produced adrenal atrophy, simultaneously with signs of hypothyroidism.[261] After three or four months of treatment with thiouracil, all three layers of the cortex showed considerable involution, with marked lipid deposition in the fasciculata; occasionally, there were hemorrhages and cysts in the reticularis. Simultaneously, there is a progressive increase in the size of the adrenal medulla (50% or more). This latter change is difficult to interpret, but it is significant that the medullary cells become very chromaffinic and rich in adrenaline. The cortical involution "may be regarded in large measure as an extreme attempt of compensation, probably due to depression of the adrenocorticotrophic factor, since the cortex of such animals promptly respond to infections with hypertrophy".[262] The production of adreno-cortical atrophy with thioureas has repeatedly been confirmed in the rat,[263] cat,[264] mouse [265] and guinea-pig.[266] It can be counteracted by simultaneous thyroxine administration [267] and since

[253a] Sayers and Sayers 98805/47, Covian B45944/49, Gray and Munson B47258/50.
[254] Hueper 91720/42.
[255] Staemmler B31271/35.
[256] Handley and Warner 79027/39, Hueper 91722/43.
[257] Wilson et al. A18094/38.
[258] Trevisini B38174/47.
[259] Mosinger and Bonifaci A30552/39, Mosinger et al. A34149/39.
[260] Kin A17452/38.
[261] Leblond and Hoff A97859/44.
[262] Baumann and Marine B337/45, 85878/45, Marine and Baumann B29060/45.
[263] Deane and Greep B3167/47, Glock B23056/45, Leathem B11477/45.
[264] McGlosky et al. B3086/47.
[265] Dalton et al. B15796/46.
[266] Florentin et al. B35135/47, McQuillan and Trikojus 93748/46.
[267] Florentin et al. B35135/47.

this atrophy is essentially similar to that produced by thyroidectomy, it is probably due to the resulting hypothyroidism. In the rat, occasionally the cortical involution is sufficiently severe to produce a functional hypocorticoidism in which NaCl or cortical extract treatment appears to be beneficial.[268]

In patients with fatal *sulfathiazole* intoxication the adrenals often show necrotic foci within the inner fasciculata and reticularis; the medulla is apparently not involved.[269]

Experimental observations suggest that certain sulfur-containing compounds such as *sulfonal* [270] or *sulphocyanate* [271] are concentrated in the adrenal cortex following oral administration, especially when free elimination is prevented. The relationship between the cortical atrophy produced by these organic sulfur compounds and the so-called "toxic involution" (produced by DDD and germanin, see below) would well deserve further study.

Various **vesicants** (e.g., the nitrogen mustards or "yperite", "arsine") and *asphyxiating combat gases* ("phosgene", "chloropicrine") produce hyperemia, marked hemorrhages, discharge of lipid granules, cytolytic phenomena and loss of medullary chromaffinity in the guinea-pig.[272] In rats, treatment with *mustard* and various *nitrogen and sulphur mustards* causes an increase in the total weight, water, protein and phospholipid content of the adrenal, while the ascorbic acid, cholesterol and total-lipid content diminishes.[273]

Such changes were considered to represent manifestations of the G-A-S,[274] especially since the initial lipid and cholesterol depletion was subsequently followed by the typical secondary rise. These changes together with the secondary increase in ascorbic acid content "appear to be manifestations of the adaptation-syndrome following injury".[275] In rabbits, *phenyldichloroarsine* produced multiple adrenal infarcts and necroses.[276] Additional investigations in rabbits revealed that nitrogen mustards cause a decrease in cortical lipids and cholesterol accompanied by a rise in 17-ketosteroids. It was concluded that this toxic substance acts as a "stress eliciting an alarm-reaction".[277]

Various **toxic tissue and urine extracts** likewise cause adrenal enlargement with discharge of lipid granules and other G-A-S changes. The so-called "cancer reaction" of Aron [278] is presumably also due to this non-specific effect, since it was based upon the observation that injection with the urine of cancerous patients often causes such non-specific adrenal changes in the rabbit. Some investigations [279] suggest that polypeptides and other toxic urinary excretion products,[280] rather than any specific "cancer-metabolite", are responsible for this effect.

The adrenal changes produced in rats by treatment with *"menstrual toxin"* [281] have also been interpreted as due to the resulting A-R.[282]

It would be futile to assign much space here to G-A-S changes in the adrenals produced by various hormones and other pharmacologically active

[268] Glock B23056/45.
[269] Lederer and Rosenblatt 83667/42.
[270] Régnier B15319/36.
[271] Healy B6390/31.
[272] Manieri and Gronchi 18650/28.
[273] Chanutin and Ludewig A95935/46, Ludewig and Chanutin B19833/48, B2706/47, B1348/46.
[274] Graef et al. B39006/48.
[275] Ludewig and Chanutin B2706/47.
[276] Dekanski B37985/48.
[277] Heusghem et al. B31783/48.
[278] Aron B31272/38, Fontaine et al. B37792/48.
[279] Bulliard and Grundland 99802/38, Grundland and Bulliard B43313/38.
[280] Masson A17984/39.
[281] Smith and Smith A32972/40.
[282] Smith and Smith 92761/46, 81127/41.

tissue constituents (e.g., histamine, acetylcholine). We have considered these elsewhere in some detail, showing that they merely tend to parallel the degree of systemic stress produced.[283] In the literature considerable confusion was often created because these non-specific adrenal reactions had been misinterpreted as characteristic of a particular hormone effect. To give but one example, in the guinea-pig, the enlargement and change in lipid distribution caused in the adrenal by parathyroid-hormone intoxication, is apparently due to hypercalcemia; yet singularly similar suprarenal changes accompany the hypocalcemia of oxalate intoxication.[284] It is understandable that before the G-A-S was described, the interpretation of such observations caused considerable difficulty.

Several drugs cause **"toxic involution"** of the adrenal-cortex. Among these *"DDD"* [285] and "germanin" [286] have received special attention. This change differs significantly from that produced by other alarming agents and is certainly not merely due to systemic stress. We have already discussed it in other connections and mention it here merely for the sake of completeness.

Many **toxic products produced by microbes and higher animals** have likewise been shown to produce intense G-A-S phenomena in the adrenals. Among these, the effect of *diphtheria toxin* has been given especial attention, since it produces extraordinarily intense systemic stress effects, particularly in the guinea-pig. There is adrenal enlargement, discharge of ascorbic acid, lipid and chromaffin granules during the A-R, with an essentially inverse reaction during the stage of resistance. During the acute phase, severe cytolytic phenomena and adrenal hemorrhages are also frequently found.[287] Since scurvy causes purpuric manifestations in the guinea-pig, it is interesting that, at least in this species, administration of ascorbic acid allegedly inhibits the causation of adrenal hemorrhages by diphtheria toxin [288] (cf. also: G-A-S → Adrenals ← Diet, p. 346).

Several *other microbial toxins* exert similar actions. In the rabbit (in addition to diphtheria), meningococcus, staphylococcus and streptococcus toxins cause "toxic adrenal insufficiency" characterized by: adrenal hemorrhages, hyperemia and necrosis, skin hemorrhages, adynamy, cyanosis, hypothermia and hypotension, a rise in blood N.P.N., leucocytosis and death. All these effects were found to be qualitatively independent of the specific toxin used; they were considered to be the result of "toxic hypoadrenalism", duplicating the Waterhouse-Friderichsen syndrome.[289]

Yet, these reactions are not entirely non-specific since they also depend upon conditioning factors, e.g., the ability of the pathogen to produce purpura or hypothermia. Systematic investigations along these lines led to the conclusion that "the adreno-hemorrhagic and hypothermic factors are present only in certain groups of microorganism"..., in the rabbit ..."heavy reactions

[283] Selye 94572/49.
[284] Domini 4263/32.
[285] Nelson and Woodard B17877/48, Selye and Stone B30224/49.
[286] Humphreys and Donaldson A37828/41, Weis and Gaunt B1994/46.
[287] Abramow A6873/12, Agnoli 76875/36, Ashford A32719/39, Cardoso 31909/35, Clevers and Goormaghtigh 87612/22, Cramer B31268/28, Ghosh 76328/39, Giroud et al. 93596/41, Harde 54488/34, Haas 95084/37, Lithander 97243/45, Lyman and King 56191/36, Mourignand et al. 22269/28, 33882/35, Olitzki et al. 84474/42, Pettit 87186/896, Schudy A35103/39, Torrance A33918/40, B30445/37, A30233/39, Villela and Penna de Azevedo 84805/36
[288] Torrance A30233/39.
[289] Lithander 97243/45.

were produced by less than 1 mg. of certain eubacteriales, but could not be produced even by large amounts of organisms belonging to the mycobacteria. In general, the hypothermic, hemorrhagic and leucopenic reactions were associated".[290]

Essentially similar changes are produced by various animal poisons, for instance, the *toxins of tenias* [291] the perienteric fluid of *ascaris* [292] and *snake venoms*.[293]

Various types of unbalanced **diets**, which cause stress, have been shown to produce typical G-A-S changes in the adrenals of animals and man.

The total fat content of the cortex increases while the birefringent lipid granules tend to disappear from the cortex during prolonged *starvation* in birds (e.g., fowl, pigeon). This is accompanied by an increase in the size of the cortex.[294] Only in a few experimental series was there any indication of adreno-medullary enlargement in the fasting pigeon.[295]

In the fasting dog, the adrenal cholesterol falls below normal,[296] but comparatively few investigations have been performed on this species.

In the guinea-pig, the principal changes observed during starvation are: hypertrophy of the cortex, with an increase in total fat and a decrease in birefringent lipid and ascorbic acid content. This is sometimes accompanied by hemorrhagic infiltration, especially along the cortico-medullary border line. The chromaffinity of the medulla may be decreased, but this is inconstant.[297] Unlike in scurvy, there is no increase in the dehydroascorbic-acid:ascorbic-acid ratio.[298]

In the mouse, a number of investigators noted a decrease in the total lipid content of the cortex during starvation.[299] It has also been stated that in mice subjected to chronic undernutrition (due to discontinuous starvation), large syncytial elements develop at the cortico-medullary junction and this may be accompanied by infiltration of this zone with polymorphonuclear leucocytes.[300] Ascorbic acid determinations gave inconsistant results.[301]

In the rabbit, starvation likewise decreases the lipid content of the cortex.[302] This loss of lipid granules may selectively affect certain circumscribed areas.[303] The cholesterol content of the cortex [304] and the chromaffinity of the medulla [305] are not necessarily altered even when starvation causes an increase in the total weight of the gland.

In the rat, marked adrenal enlargement with loss of cortical lipids occurs especially in advanced stages of complete starvation; this is often accompanied by an increase in the water content.[306]

The protein content of the rat suprarenal, unlike that of most other organs, does not decrease even after seven days of complete starvation.[307] The pertinent

[290] Olitzki et al. 84474/42.
[291] Bedson A537/13, A571/13, Pomella A16234/12.
[292] Simonin B12416/22.
[293] Boquet B19963/48, Boquet and Delaunay B31263/42, B31264/42, Ri B31356/39.
[294] Elliott and Tuskett 5946/06, Findlay 5963/21, McCarrison 13219/22.
[295] Tiba **A16403/38.**
[296] Marino 16932/23.
[297] Blumenthal A34179/40, D'Angelo et al. B23894/48, Iwabuchi 13759/32, Kojima 24249/28, Lindsay and Medes 6904/26, Rondoni and Montagnani B23143/15.
[298] Martini and Bonsignore 31642/35.
[299] Hett 27970/26, Ponomarrow 5945/14, Whitehead 29376/34, Wolff 4152/27
[300] Hett 27970/26.
[301] Sure et al. A30451/39.
[302] Ewald 5940/02.
[303] Babes and Jonesco 47641/08.
[304] Okuneff 5949/23.
[305] Lucksch 5955/11.
[306] Cameron and Carmichael 93398/46, D'Angelo et al. B23894/48, Meites and Reed B27700/49.
[307] Addis et al. 39944/36.

literature contains many apparent contradictions, adrenal atrophy being observed by some, hypertrophy by others. It has been claimed that starvation causes cortical atrophy in very young [308] and hypertrophy in adult rats.[309] Chronic underfeeding allegedly results in a kind of "pseudohypophysectomy" with severe atrophy of the adrenal cortex.[310] Data concerning the ascorbic acid concentration of the adrenal in starving rats are likewise very contradictory.[311]

The interpretation of these findings is complicated by the fact that many investigators who studied partial undernutrition did not state distinctly what type of diet they used. Perusal of the literature suggests, however, that acute, complete starvation acts as an alarming stimulus and causes an increase in cortical size with loss of lipids, while chronic underfeeding can elicit a stage of resistance with an increase in the lipid content and size of the cortex, if the diet contains sufficient amounts of protein. On protein deficient diets chronic undernutrition may be accompanied by atrophy of the cortex, presumably due to inhibition of ACTH production.[312] Thus, if the composition of the diet is kept in mind, it appears that partial starvation acts like any other stressor in that it elicits an ACTH discharge, but the effects of this response can be modified by conditioning factors.

In man, observations concerning the effect of hunger on the adrenals have often been made on a large scale in times of famine. Most investigators agree that the lipid content of the cortical cells can remain high even after most of the fat disappeared from other tissue, for instance in cases of severe malnutrition with hunger edema.[313] Indeed the total lipid content is often above normal although the total cholesterol is greatly diminished.[314] Only in very grave, acute starvation is there considerable hydropic degeneration, hemorrhage and cytolysis in the adrenal cortex. It was noted, for instance, during a famine in Southern Russia [315] and in the inmates of German concentration camps during the second World War.[316]

All these data are consonant with the view that in man, as in animals, chronic undernutrition tends to cause resistant stage manifestations with lipid storage in the adrenals, while acute, complete starvation imitates the A-R with a predominance of cytolytic phenomena and lipid discharge. After very prolonged, fatal, partial starvation, A-R like changes may reappear synchronously with other manifestations of the exhaustion stage.[317]

Overfeeding likewise causes adrenal enlargement, for instance in the rat. Such an enlargement is produced not only by acute "food shock", but also by chronic overfeeding. It is accompanied by involution of the accessory sex organs, testes and thymus. The possibility has been considered that this again may merely be a manifestation of the G-A-S.[318] Presumably adaptation, both to lack and excess of food elicits G-A-S changes in the adrenal.

Various *qualitatively inadequate* diets likewise cause G-A-S responses in the suprarenals. This has been shown for instance in guinea pigs kept exclusively

[308] Jackson 32686/19, 7389/32.
[309] McLennan and Jackson 14969/33, Quimby B19203/48, Selye 36032/36.
[310] Meites and Reed B27700/49, Mulinos and Pomerantz A36788/41, A36729/41, Mulinos et al. A38469/42.
[311] Deane and Morse B25816/48, Mulinos et al. A38469/42.
[312] Selye B1204/46.
[313] Federici 5942/03, Herrmann 5948/05, Jaffe and Sternberg 6856/21, Lubarsch 6909/21, 6910/21, Paltauf 6973/17, Traina 5941/04.
[314] Overzier B36500/47, B45391/48.
[315] Stefko 5950/26.
[316] Uehlinger B24304/47, **B27612/48.**
[317] Uehlinger **B27612/48.**
[318] Ingle and Nezamis 98817/47.

on corn,[319] in rats fed excessive quantities of cabbage and water [320] and in rats given various diets deficient in several vitamins.[321] We have repeatedly emphasized in this book that *protein-rich* diets greatly facilitate the production of corticotrophin in animals under stress. On the other hand, in animals not exposed to alarming stimuli, the concentration of protein in the food exerts no significant action upon the adrenal cortex, unless the protein concentration is so high (70-90%) that the diet itself becomes a stressor.[322]

It would not be rewarding to describe in detail the extensive literature concerning the effect of various avitaminoses upon the adrenals, but a few key references may be useful. *Avitaminosis-A* causes cortical enlargement in the rabbit,[323] but allegedly no significant adrenal change [324] or even an inhibition of cortical development [325] in the rat. In man, xerophthalmia can perhaps also be accompanied by adrenal atrophy,[326] but the mechanism of this response is not understood, and it would be highly desirable to conduct further studies specifically planned to examine whether this type of avitaminosis differs from other types of malnutrition in its effect upon the adrenals.

Much work has been done concerning adrenal changes in *vitamin B_1 (thiamine)* deficiency.[327] Interest in this subject has been stimulated especially by the often made observation that pigeons suffering from beri-beri have unusually large adrenals due to an excessive increase in the size of the cortex.[328] It has been claimed that this is merely the non-specific result of inanition.[329] but subsequent observations revealed that the adrenal enlargement is much more pronounced in pigeons (and fowl) suffering from beri-beri than it is in fasting birds; hence inanition cannot be the only factor involved.[330] There is some disagreement regarding the changes in the chromaffinity and adrenaline content of the medulla,[331] but the cortical lipid content appears to be definitely increased in such avitaminotic birds.[332]

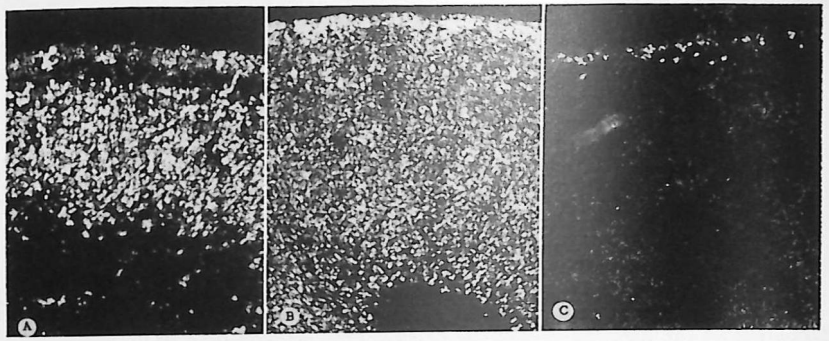
Perhaps the hypertrophy is not entirely limited to the cortex, but involves the medulla also,[333] but this has been contested.[334] An important part of the adrenal enlargement in avian beri-beri is merely due to local edema.[335] Since all these adrenal changes are very similar to those caused by cyanide poisoning they are certainly not entirely specific.[336].

Comparable adrenal changes also occur in various other species suffering from beri-beri, for instance in the fowl,[337] monkey,[338] mouse,[339] rabbit,[340] rat [341] as well as in man.[342]

[319] Rondoni 5965/22, Rondoni and Montagnani B23143/15.
[320] McCarrison and Madava 7475/32, 7476/33.
[321] Kolliner 5627/32.
[322] Ingle B360/45, Selye B1204/46, Tepperman et al. A58184/43, Tepperman and Engel 83735/42, Tuchmann-Duplessis et al. B24538/48.
[323] Giedosz 34107/35.
[324] Emmet and Allen 6789/20, Thatcher and Sure 8918/32.
[325] Lockwood and Hartman 15573/33, Mitzkewitsch 18217/34.
[326] Pillat 3307/32.
[327] Berg 5964/22, van Driel **10497/20.**
[328] Kellaway 6867/20, McCarrison 5961/19, 5962/20, 13338/21, 13219/22, 5960/23.
[329] Vincent and Hollenberg 7059/21.
[330] Beznak 6723/23, Findlay 5963/21.
[331] Verzár and Beznák **14098/23.**
[332] Findlay 5963/21.
[333] Korenchevsky 16663/23, Lasowsky and Sinmitsky 6898/26, Satwornitzkaja and Simnitsky 14611/30.
[334] Verzar and Péter 21373/24.
[335] Marrian 19393/28.
[336] Messerle 6932/26.
[337] Sakai 29004/34, Souba 13553/23.
[338] McCarrison 13338/21, 13219/22.
[339] Skutta A38880/39.
[340] Verzar and Péter 21373/24.
[341] Deane and Shaw 96879/47, B30043/47, Emmett and Allen 6789/20, Fukusi and Okubo A67178/31, Goodsell A36757/41, Janes and Brady 98541/47, Nishimura and Tanaka 23779/29, Parhon-Stefanescu and Coban 30252/34, Verzár and Péter 21373/24.
[342] Ohno 5967/17.

In connection with the G-A-S, it is of particular interest that muscular exercise causes especially marked adrenal enlargement in rats having insufficient stores of thiamine [343] and that exogenous administration of yeast extract prevents this hypertrophy.[344]

The adrenal lesions in thiamine deficient animals are generally accompanied by thymus involution and other G-A-S manifestations and have hence been interpreted as part of this syndrome.[345] This view received further support by pertinent histochemical studies concerning the sudanophilic, plasmal, birefringent and autofluorescent granules of the adrenal cortex in vitamine-B deficient rats.[346]



Birefringent material in adrenal cortex during the G-A-S. — **A.** Adrenal cortex of a normal control rat as seen under the polarizing microscope. Note large amounts of birefringent lipid both in the zona glomerulosa and in the outer fasciculata; none in the transitional zone between glomerulosa and fasciculata, nor in inner fasciculata. — **B.** Great increase in width of the cortex and its birefringent lipid content during the resistant stage of the G-A-S. — **C.** Almost complete disappearance of birefringent granules from the adrenals during the exhaustion phase of the G-A-S. Note that only the glomerulosa contains birefringent granules. Essentially similar lipid depletion is seen in the A-R phase. In this instance the G-A-S was produced by pantothenic-acid deficiency.

(Courtesy of Drs. H. W. Deane and G. M. McKibbin; after Selye 94572/49.)

Pantothenic acid deficiency causes essentially similar changes with depletion of the cortical sudanophilic, plasmal, birefringent and autofluorescent materials, often accompanied by necroses and hemorrhages into the adrenal parenchyme.[347] Administration of pantothenic acid prevents the adrenal hemorrhages in filtrate factor deficient rats.[348]

In view of the accompanying thymus atrophy and the qualitative changes in the histochemical structure of the adrenal cortex, several investigators con-

[343] Beznák and Perjés 31579/35.
[344] Perjés A31/36.
[345] Deane and Shaw B30043/47, Skelton B41300/50.
[346] Deane and Shaw B30043/47.
[347] Ashburn 96043/40, Daft and Sebrell B31441/39, Daft et al. 95890/40, Deane and McKibbin B1349/46, Deane and Shaw B30043/47, 96879/47, György B19250/48, McQueeney et al. B4907/47, Mills et al. B31442/40, Morgan and Simms B31443/40, Mushett and Unna A37733/41, Nelson B31445/39, Ralli and Graef 96825/44, Salmon and Engel A35289/40, Supplee et al. A37638/42.
[348] Daft et al. 95890/40.

cluded that the response is probably just one manifestation of the G-A-S.[349] Nevertheless, some degree of specificity in the reaction is suggested by the often pronounced adrenal hemorrhages and by the observation that the glomerulosa tends to retain its sudanophilic lipids even when the other layers became completely depleted of them.[350] Interestingly, marked adrenal hemorrhages (reminiscent of the Waterhouse-Friderichsen syndrome) tend to occur in pantothenic acid deficient rats only if they are suddenly exposed to an acute alarming stimulus.[351] Presumably the avitaminosis produces a purpuric diathesis which conditions this type of an adrenal response to stress.

Studies concerning *riboflavin and pyridoxine deficiencies* in the rat lead to the conclusion that at first "... mild stimulation of the adrenal cortex occurs, but this later disappears. Possibly, this transitory stimulation results from the moderate inanition, induced in these animals, to which they later became adjusted. The time of stimulation coincides with that of the most acute signs of deficiency". In spite of these findings the authors expressed the view that: "In contrast to deficiencies of pantothenic acid or thiamine, the dietary absence of riboflavin or pyridoxine, fails to produce the adaptation syndrome".[352] Significantly both these vitamin deficiencies cause severe thymus atrophy, but certain physiologic tests were interpreted as showing a failure of adrenal stimulation in riboflavin deficiency.[353] In any event, whatever adrenal stimulation is detectable in pyridoxine-deficient rats is no greater than in pair-fed, undernourished controls.[354]

The transitory initial adrenal changes suggest that some degree of an A-R is produced, although apparently, adaptation ensues quite rapidly in the rat.

In addition to the well-known hepato-renal changes, *choline deficiency* elicits adrenal hypertrophy with a broadening of the glomerulosa and rather typical adrenal-lipid changes in the rat.[355] Allegedly "These observations suggest that the renal disfunction in choline deficiency causes stimulation of the glomerulosa. This zone is believed to secrete hormones of the desoxycorticosterone type. The increased fasciculata activity and the thymus involution probably result from the 'alarming' stimulus of inanition".[356]

Ascorbic acid deficiency causes especially pronounced adrenal lesions in the guinea-pig, which is notoriously sensitive to scurvy. There is marked enlargement and hyperemia of the cortex; at the same time, hemorrhages are particularly common, especially along the cortico-medullary junction line.[357] This enlargement is more pronounced than that caused by mere fasting.[358]

The fat and especially the birefringent lipid content of the cortex diminishes during C-avitaminosis [359] and the chemically determinable cholesterol content falls below normal.[360] At the same time, those lipids of the nuclei, which are

[349] Deane and McKibbin B1349/46, Deane and Shaw B30043/47, 96879/47, McQueeney et al. B4907/47.
[350] Selye and Stone B30224/49, Skelton B40001/50.
[351] Skelton B40001/50, Ralli B43691/49.
[352] Deane and Shaw B30043/47, 96879/47.
[353] Wickson and Morgan 99852/46.
[354] Grégoire B38970/49.
[355] Bellows and Chinn B25557/43, Christensen 77229/40, B25555/42, Engel and Salmon B25556/41, György and Goldblatt B25553/40, Jervis A55990/42.
[356] Deane and Olson B18259/48.
[357] Baldwin et al. B443/44, Iwabuchi 13759/22, Lockwood and Hartman 15573/33, May A9548/37, Morelli and Gronchi 23294/27, Murray and Morgan 99851/46, Rondoni 5965/22, Rondoni and Montagnani B23143/15.
[358] La Mer and Campbell 6892/20.
[359] Bessey et al. 38938/34, Iwabuchi 13759/22.
[360] Randoin and Michaux 20561/26, Morelli et al. 19156/28.

demonstrable by Weigert's myelin stain, also decrease.[361] It has been claimed that if malnutrition is avoided, the lipid content of the cortex actually increases; [362] this may indicate some degree of resistance. However, the latter finding requires confirmation.

The ascorbic acid content of the adrenals is considerably diminished in scorbutic guinea pigs, as judged by the histochemical reactions with silver nitrate,[363] the 2-6-dichlorophenol indophenol reaction,[364] the 2,6-dibromophenol indophenol reaction.[365] the methylene blue reaction [366] and bioassay procedures.[367] Simultaneously, the dehydro-ascorbic-acid:ascorbic-acid ratio rises.[368] In the adrenals the fall in ascorbic acid is much more intense than in other tissues.[369]

Allegedly, the corticoid hormone content of the adrenal also diminishes in scorbutic guinea-pigs,[370] but this claim was based on data obtained with a not entirely specific bioassay method.

The chromaffinity and adrenaline content of the adrenal medulla are likewise considerably decreased in scorbutic guinea-pigs; [371] this is accompanied by degenerative changes [372] and functional insufficiency of the medulla.[373]

Administration of ascorbic acid prevents the development of all these changes in guinea-pigs kept on otherwise scurvy-producing diets.[374]

Conversely, in species which are relatively independent of exogenous ascorbic acid, such as the cat,[375] rabbit [376] and rat,[377] diets deficient in this vitamin cause little if any change in adrenal structure.

Avitaminosis-D likewise tends to cause G-A-S changes in the adrenals, according to observations in the rabbit,[378] rat [379] and man.[380]

Avitaminosis-E produces hypertrophy and hyperplasia of the adrenals in the rat,[381] but in this case the change is rarely very pronounced.

If *pteroylglutamic acid* deficiency is produced in rats by treatment with amino-teropterin the adrenals enlarge considerably, while the thymico-lymphatic organs involute.[382] Here again we are presumably dealing with a G-A-S response.

The hypertrophy and hyperplasia of the glomerulosa produced by *sodium* deficient diets [383] as well as the glomerulosa atrophy caused by excess Na

[361] Henriksen 26841/25.
[362] Innes 27933/34.
[363] Galvao and Cardoso 27627/34, Giroud and Leblond 19755/34, 29918/34, 31436/35, Hamilton 15050/33, Quick 5591/33, Siehrs and Miller 28602/34.
[364] Birch et al. 7893/33, Harris and Roy 4276/33.
[365] De Caro 16237/33, Svirbely 9647/33, Svirbely and Szent-Györgyi 7232/33.
[366] v. Euler 7895/33, Malmberg and v. Euler 32106/35, Nespor A8303/37, Weitzenberg A9819/38.
[367] Cardoso 27629/33, Galvao and Cardoso 27627/34.
[368] Martini and Bonsignore 31642/35.
[369] McKee et al. B37719/49.
[370] Giroud et al. 98774/39-40.
[371] Iwabuchi 13759/22, Rondoni 5965/22, Rondoni and Montagnani B23143/15.
[372] Innes 27933/34.
[373] Murray and Morgan 99851/46.
[374] Jacobsen 53492/35.
[375] Giroud et al. 33833/35.
[376] Giroud et al. 33833/35, Malmberg and v. Euler 32106/35, Weitzenberg A9819/38.
[377] Daoud et al. 38866/36, Giroud et al. 33833/35, Malmberg and v. Euler 32106/35.
[378] Matsuda 11123/30.
[379] Glanzmann 29001/34, Maggi and Miglietta 30828/35, Sekiguchi 22002/30.
[380] Guassardo 38940/30.
[381] Bisceglie 25468/27, 19391/28, Blumenfeld 27772/34.
[382] Higgins and Woods B40212/49.
[383] Deane et al. B23212/48.

administration [384] appear to be specific changes not directly related to the G-A-S. Conversely excess *potassium* administration to rats, results in an adrenal enlargement very similar to that caused by other stressors.[385] Yet under certain circumstances potassium overdosage can cause a rather selective enlargement of the glomerulosa in the rat.[385a]

Systematic studies on rats receiving high-sodium and/or high-potassium diets, showed lipid depletion in the inner zones of the cortex. This "could be considered to be a non-specific reaction, a part of the general-adaptation-syndrome". Desert Kangaroo rats revealed no corresponding adrenal changes on similar diets, presumably because they are congenitally less sensitive to dehydration".[385b]

Subcutaneous injection of a 25% NaCl solution in the dog produces *"dehydration shock"* with focal necrosis, leucocytic infiltration and hyperemia of the adrenal. These changes are very similar to those seen in other types of non-specific damage and appear to be closely related to the G-A-S.[386] The same is true concerning the loss of lipids from the inner cortex of *thirsting* rats.[387]

In summary, it may be said that all types of severe malnutrition, due to quantitatively or qualitatively inadequate diets, appear to cause G-A-S manifestations in the adrenals. Yet in certain instances (e.g., pantothenic acid deficiency, Na deficiency or overdosage, protein deficiency) the effect of mere systemic stress may be modified by specific corticotrophic actions.

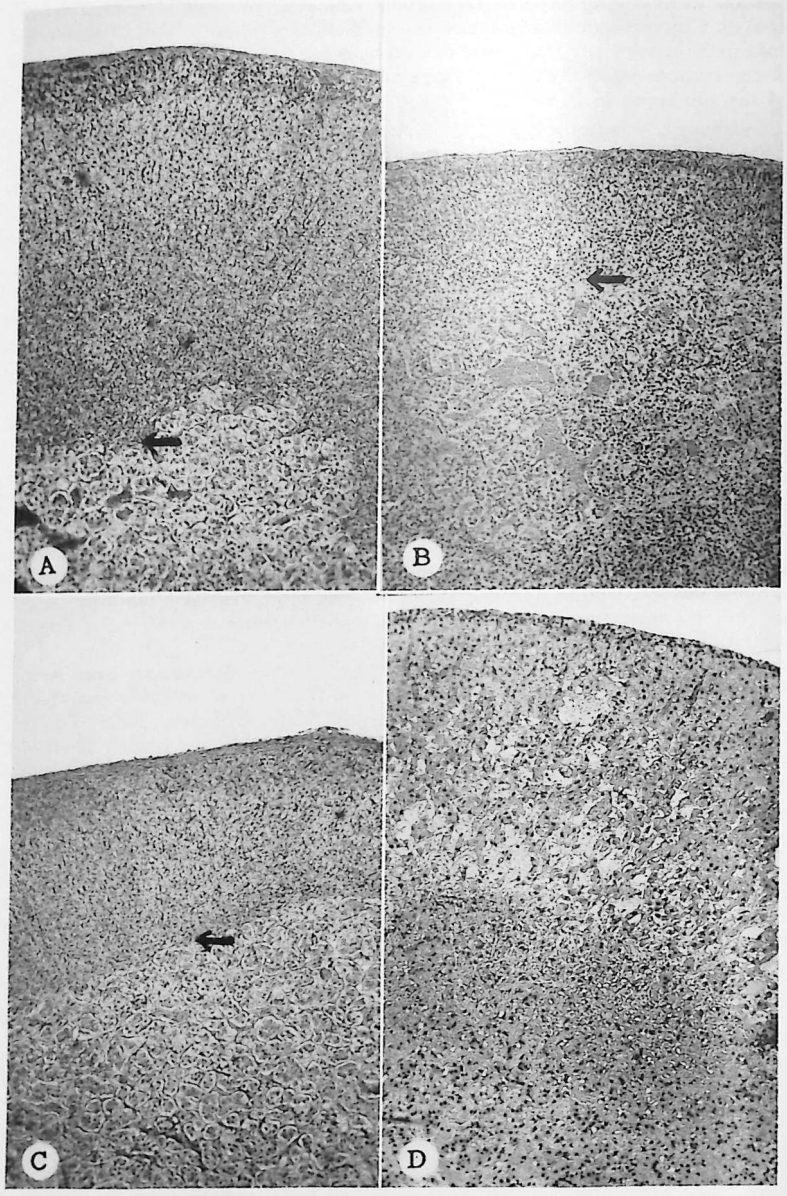
Stimuli Influencing the Adrenals During the G-A-S. — Hypophysectomy in itself, that is, without exposure to stress, causes very severe involution of the adrenal cortex. The glomerulosa is least, the reticularis most markedly affected, but all layers participate in this atrophy to some extent. As previously stated, a short time after removal of the anterior-lobe, the lipid content of the cortex is high, but later, when the atrophy becomes increasingly more severe, the lipids gradually disappear together with the other cytoplasmic constituents of the cortical cells,[388] e.g., ascorbic acid,[389] plasmalogen, fluorescent and birefringent granules.[390] This involution is not due to the usually decreased food intake of hypophysectomized rats since it remains uninfluenced by forced feeding.[391]

An actual increase in adrenal cholesterol after hypophysectomy can allegedly occur in the rat,[392] but this claim requires confirmation.

It has been shown in the rat that after hypophysectomy, the adrenal cortex no longer responds with the usual enlargement and lipid granule discharge upon exposure to *various alarming stimuli* such as trauma, toxic doses of drugs, emotional stress or acute starvation.[393]

Subsequently many investigations confirmed the view that the presence of the anterior-lobe is indispensable for the normal response of the adrenal cortex to stress.

[384] Bacchus B47104/50, Badinez and Croxatto B23939/48, B23940/48, Selye and Stone B30224/49.
[385] Badinez and Croxatto B23939/48, B23940/48, Jarpa and Croxatto B33754/48.
[385a] Bacchus B47104/50.
[385b] Nichols B44434/49.
[386] Davis A37428/41.
[387] Nichols B36281/49.
[388] Selye **94572/49.**
[389] Tyslowitz A56561/43.
[390] Deane and Greep 93399/46.
[391] Levin A71832/44.
[392] Levin B32055/45.
[393] Selye 36032/36, 66551/36, 38798/37, **B1204/46.**



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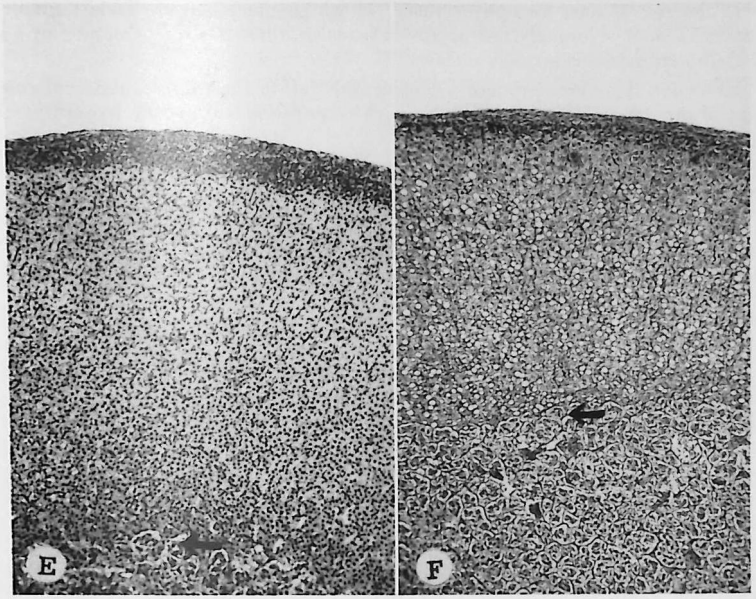


Effect of hypophysectomy and of various steroid hormones upon adrenal cortex. — **A.** Adrenal of a normal 3-month-old male rat. Note normal width of glomerulosa, fasciculata and reticularis zones. In this and following figures cortico-medullary junction is marked by arrow (adrenal weight 44 mg.). — **B.** Adrenal of similar rat 28 days after hypophysectomy. Note profound atrophy of the cortex, which affects all layers, but especially the fasciculata and reticularis. The medulla remains normal (adrenal weight 15 mg.). — **C.** Adrenal of similar rat receiving increasing doses (0.5 to 3 mg./day) of desoxycorticosterone acetate during 3 months. Note pronounced involution of cortex, while medullary cells remain normal (adrenal weight 23 mg.). — **D.** Adrenal of similar rat treated with estradiol (100 γ/day during 9 months). Note enlargement of entire cortex which takes up the whole visual field. There is marked hyperemia with great dilatation of cortical sinusoids. The glomerulosa, however, is inconspicuous (adrenal weight 122 mg.). — **E.** Adrenal of similar rat treated with small doses of testosterone (implantation of one 14 mg. pellet of methyl-testosterone one month prior to autopsy). Note extreme density of glomerulosa zone (adrenal weight 30 mg.). — **F.** Adrenal of similar rat receiving large doses of a testoid (10 mg. of methyl-testosterone/day during 3 months). Note density of glomerulosa and atrophy of cortex. The latter is studded with vacuolated "signet-ring cells" which are very characteristic of rats chronically overdosed with large amounts of testoids (adrenal weight 28 mg.). (After Selye 94572/49.)

Thus, it was found that the adrenal enlargement, as well as the ascorbic acid and cholesterol discharge produced by *x-irradiation* [394] and the cortical hypertrophy normally caused by forced *muscular exercise* in the rat are prevented by hypophysectomy.[395]

In guinea-pigs and rats, *toxic fatty-acid mixtures* cause pronounced adrenocortical enlargement. This response was ascribed to the A-R and proved to be preventable by hypophysectomy.[396]

[394] Patt et al. B33711/48, Tyree et al. B33116/48.
[395] Hajdu et al. A72012/42, A72232/42, Ingle 75145/38.
[396] Freud et al. 71309/38.

In the rat, a sham hypophysectomy (in which the pituitary is left intact) causes an A-R. Normally this operation leads to adrenal enlargement, but not if the anterior-lobe is actually removed.[397]

Extensive skin *burns* produce a considerable fall in the total cholesterol content of the adrenals in rats, while no such response is seen after hypophysectomy.[398]

Severe *hemorrhage* elicits a sharp fall in the ascorbic acid and total cholesterol concentration of the adrenal in intact but not in hypophysectomized rats.[399]

A similar decrease in the ascorbic acid and cholesterol concentration of the rat adrenal produced by exposure to *cold, painful stimuli, trauma,* is likewise prevented by hypophysectomy,[400] as is the adrenal enlargement normally seen after *starvation,*[401] that caused by feeding excessive amounts of *cholesterol,*[402] or *HCl* [403] and the "compensatory hypertrophy" of the remaining adrenal after *unilateral suprarenalectomy.*[404]

Allegedly, the proliferation of the glomerulosa in rats kept on *Na-deficient* diets likewise fails to be prevented by hypophysectomy,[405] but since this conclusion was based on very few experiments, it requires confirmation.

It has been stated that extensive *damage to the hypothalamus* prevents the adrenal atrophy normally elicited by hypophysectomy in the dog,[406] but here again, further research will be necessary before drawing definite conclusions since the hypophysectomy — though extensive — was admittedly incomplete.

Curiously in the pigeon, the adrenal cortex appears to be relatively independent of the pituitary. After injection of formaldehyde, there is enlargement of the cortex (with proliferation of mitochondria, an hypertrophy of the Golgi apparatus and a decrease in lipoid, cholesterol and water-insoluble ketone content of these cells) which is not prevented by hypophysectomy.[407] Perhaps in birds the activity of the cortex is less dependent upon ACTH than in mammals, due to some *species difference* in the corticotrophic mechanism.

Following a single injection of purified *ACTH* to hypophysectomized rats, the ascorbic acid and cholesterol content of the adrenal diminishes within a few hours — the former more rapidly than the latter.[408] After repeated daily injections of this same principle, however, there is an increase in the ascorbic acid [409] and lipid [410] content of the hypophysectomized rat's adrenal. If a single dose of corticotrophin is given more than three days after hypophysectomy, the ascorbic acid and cholesterol discharge becomes sluggish and then disappears.[411] This is probably due to the intense involution of the cortical cells, which renders them relatively insensitive.

In hypophysectomized rats neither LAP [412] nor purified corticotrophin [413] cause a greater adrenal stimulation on high than on low protein diets. Presumably dietary protein is necessary only for the elaboration of ACTH from its precursors by the anterior-lobe, not for its peripheral action upon the cortex.

397 Foglia and Houssay A56602/42.
398 Harkins 91182/44, Harkins and Long 87814/45, Long 98425/47.
399 Long 98425/47. Wilhelmi and Long B19257/48.
400 Long 98425/47.
401 D'Angelo et al. B19839/48, B17658/48.
402 Hajdu et al. A72232/42, A72012/42.
403 Hajdu et al. A72232/42.
404 Golla and Reiss A37560/41.
405 Deane et al. B23212/48.
406 Keller and Bruhn 77538/40.
407 Miller and Riddle A57528/42.
408 Long 98425/47.
409 Munson and Koch 92844/46.
410 Reiss et al. 64624/36.
411 Long 98425/47.
412 Henriques et al. B27603/49.
413 Moya et al. B4168/48.

Only in acute experiments on hypophysectomized rats did glucose enhance the discharge of cholesterol by ACTH from the adrenal cortex. Even here sugar failed to affect the simultaneous excretion of ascorbic acid.[414]

The x-zone of the mouse adrenal, which partially involutes after hypophysectomy, is not restored by ACTH although the other zones become normal. Conversely, hypophyseal (but not chorionic) LH maintains only the x-zone after hypophysectomy.[415] This is further evidence of the relative independence of the x-zone from other regions of the cortex.

Since *folliculoids* are highly effective alarming stimuli, their action upon the adrenal has been the subject of considerable study. Hypophysectomy prevents the usual corticotrophic action of natural and artificial folliculoids in the rat.[416] The characteristically intense loss of lipid granules, normally elicited by folliculoids, also fails to occur after removal of the pituitary.[417] Even in hypophysectomized rats, whose adrenals were maintained at an approximately normal weight level by a pituitary extract, simultaneous treatment with estrone did not influence the adrenal weight. This was deemed noteworthy because, in intact animals, simultaneous treatment with pituitary extract and estrone caused greater adrenal enlargement than either preparation alone.[418]

Other investigators claimed that some corticotrophic action is demonstrable if the adrenal structure is only partially maintained with low doses of pituitary corticotrophin.[419] However, even here the response was extremely slight.

Studies with radio-active "labeled" phosphate suggested that after hypophysectomy in the rat, the specific activity of the inorganic phosphate increases, but that of the acid-soluble organic phosphorus remains unchanged after treatment with folliculoids. From this it was concluded that after hypophysectomy "estrogen has an effect on the adrenals, but that this effect is not an indication of increased metabolism in the gland".[420]

Neither *progesterone* [421] nor Δ^5*-pregnenolone* [422] nor *DCA* [423] exert any effect upon adrenal structure in hypophysectomized rats, but large doses of *testosterone* propionate (and other testoids) appear to delay the usual adrenal atrophy.[424] The ability of testosterone to cause involution of the "x-zone" in the mouse adrenal remains demonstrable after hypophysectomy. Hence, this is apparently also a direct effect.[425] Of course any such direct action upon the adrenal cortex is likely to influence the response to ACTH and may act as a "conditioning factor" modifying the corticotrophic effect.

Since *adrenaline* liberation plays an important rôle in emergency reactions, our earliest studies concerning the G-A-S were already concerned with its possible corticotrophic action. It was found that, unlike in intact rats, even toxic doses of adrenaline failed to cause adrenal hypertrophy after hypophysectomy.[426] It was subsequently shown that the adrenal-lipid changes [427] as well as the depletion in ascorbic acid and cholesterol seen after adrenaline injection in intact rats, can likewise not be obtained after hypophysectomy.[428]

414 Constantinides et al. B38913/49.
415 Jones B33010/49, B44039/49.
416 Christensen 87545/44, Pinto 82666/41, Selye et al. 32001/35. Vogt 93902/45.
417 Selye et al. 32001/35.
418 Selye and Collip 66617/36.
419 Pinto 82666/41.
420 Gemzell B24892/48.
421 Leonard A94489/44, Winter A36510/42.
422 Selye and Clarke A55978/43.
423 Leonard A94489/44.
424 Leathem 85231/44, Leonard A56340/42, A94489/44.
425 Jones B36430/49.
426 Selye 36032/36.
427 Vogt 93902/45.
428 Long 98425/47.

Thyroxine also fails to produce its usual adrenal enlarging effect after hypophysectomy in the rat.[429] In the pigeon, however, the presence of the pituitary is apparently not indispensable for the corticotrophic action of the thyroid hormone.[430]

Insulin likewise causes adrenal enlargement with typical A-R changes in the hypophysectomized pigeon. All this agrees with the view that in this bird, the pituitary is not essential for the mediation of stress effects upon the adrenal cortex.[431]

It is well known that in intact animals hypophyseal **corticotrophin** causes enlargement of the adrenal cortex, due to hypertrophy and hyperplasia of the cortical cells.[432] The action of ACTH on cortical storage products, however, is greatly influenced by the time factor.

It has been shown, both in the rat and in the guinea-pig, that a single injection of purified ACTH produces a rapid fall in the ascorbic acid and a somewhat more delayed decrease in the cholesterol content of the adrenals, within a few hours. However, about 24 hours after the injection, the concentration of both these adrenal constituents returns to or even above normal.[433] In one series of experiments, purified ACTH was given to rats at 6 to 8 hour intervals over a period of 18 hours to 12 days. After 24 hours of treatment (the animals being killed 6 hours after the last injection), corticotrophin caused a depletion of sudanophilic, plasmal, birefringent and fluorescent granules as well as enlargement of the adrenal cortex, while upon more continued ACTH treatment, the concentration of all these granules rose above the initial level. The authors state that: "Cytochemically, none of the adrenal glands of animals treated with the hormone showed any alteration in the morphology or ketosteroid content of the zona glomerulosa. However, in the short term experiments, the fasciculata broadened and the ketosteroid content declined, reaching a minimum at 18 hours (alarm reaction of Selye). The extent of the reaction depended on dosage and on the size of the animals. By 24 hours the ketosteroids had begun to be replenished. In the animals receiving hormone for many days, the fasciculata was broad; in the first 8 days the ketosteroids were increased above normal (resistance phase of Selye), but by 12 days they had begun to disappear from the inner part of the fasciculata (exhaustion phase of Selye)".[434]

As we have stated in other connections, our experiments in the rat led us to slightly different conclusions. We found that even in short term (24-48 hours) experiments on rats, large doses of ACTH can stimulate the growth of the glomerulosa,[435] and cause an increase in sudanophilic lipids and plasmal,[436] although, at the same time, the ascorbic acid and cholesterol concentration of the gland falls below normal. Only immediately after a single ACTH injection is there a slight decrease in sudanophilia.[437] Perhaps this difference in the results obtained is due to the unusually high doses of ACTH which we employed. In any case, it is evident that after 24 - 48 hours of treatment — when exposure to non-specific stress would have caused a depletion of adrenal-lipid granules — large doses of ACTH have an opposite effect. Hence, the action of alarming

[429] Swann A30182/39.
[430] Miller and Riddle A30224/39.
[431] Miller and Riddle A36498/41.
[432] Selye **94572/49.**
[433] Ducommun and Mach B43388/49, Long 98425/47, Munson and Koch 92844/46, Sayers et al. 86963/46.
[434] Bergner and Deane B23875/48.
[435] Selye 94572/49.
[436] Selye and Stone B30224/49.
[437] Ducommun and Mach B43388/49, Fortier et al. B38281/50.

stimuli cannot be merely ascribed to a rise in ACTH production. It was suggested that an unknown peripheral factor, present during the A-R, conditions the response of the adrenal cortex so that a persistent lipid discharge ensues.

Extensive histochemical studies (Sudan black, plasmal, phenylhydrazine, Schultz reaction) in rats lead to the suggestion that even a single dose of ACTH "may produce cyclic changes, with repeated emptying and filling of the reticularis". However, the individual variations were great and it has been suspected that the variability of response may have resulted from the simultaneous development of a G-A-S due to incidental stressors.[438]

Unilateral nephrectomy and high *Na* diets greatly increase the hyalinosis-producing and hypertensive effect of crude corticotrophic pituitary extracts (e.g., LAP), yet these procedures do not appear to exert any specific influence upon the adrenal enlargement caused by such preparations. This is in agreement with the concept that partial nephrectomy and Na sensitizes the kidney to mineralo-corticoids, but has no direct effect upon the adrenal-cortical response to injected corticotrophin. Only if the cardiovascular and renal lesions produced by LAP become severe, is there any indication that these sensitizing procedures augment the cortical stimulation. Here, apparently, the stressor effect of the resulting hyalinosis (and not the specific direct action of partial nephrectomy and Na as such) is responsible for the exaggeration of the cortical response.[439]

Simultaneous treatment with *thyroxine* greatly augments the corticotrophic effect of LAP in the rat; [441] *thyroidectomy* diminishes it, without abolishing it completely.[442] These experiments also suggest that thyroid hormone, perhaps through its effect upon metabolism, merely sensitizes the adrenal to corticotrophic stimulation.

Extensive investigations in the rat have shown that the corticotrophic effect of LAP is also greatly increased by synthetic diets rich in *protein*.[443] This was likewise found to be true in rats kept on simple, natural diets. Thus in animals receiving only skeletal or cardiac muscle, "purina fox chow", peas, lentils, corn, lima beans or rice, the adrenal enlargement obtained by a given dose of LAP corresponded fairly closely to the protein content of these food substances.[444] This relationship was especially striking in rats kept on synthetic diets in which casein was the only source of protein. On diets containing 5 to 50% casein, the adrenal enlargement produced by a given dose of LAP was directly proportional to the protein content of the food; yet some corticotrophic action was demonstrable even on the lowest (5%) protein intake.[445]

As previously stated, it had also been shown that chronically *undernourished* rats develop a so-called "pseudohypophysectomy" syndrome, with pronounced adreno-cortical involution,[446] while complete starvation causes the usual A-R enlargement of the cortex. Rat pituitary implants elicited little adrenal enlargement in such "psuedohypophysectomized" (undernourished) rats, while

[438] Yoffey and Baxter B41280/49.
[439] Hall and Selye B22454/45, Selye A75044/44, B1204/46, B1433/48, Selye and Stone B29495/49.
[441] Selye et al. B229/45, B124/45.
[442] Hay B1216/46, 86717/45.
[443] Dontigny et al. 99356/48, Henriques et al. B27603/49, Prado et al. 96100/47, Selye B1204/46, B1212/46, 94572/47, Selye and Stone B30224/50, B29495/49.
[444] Selye and Stone A95909/46.
[445] Selye and Stone B30224/50.
[446] Mulinos and Pomerantz A33348/40, A36788/41, A36530/41, A36729/41, Mulinos et al. A17221/39, Pomerantz and Mulinos 74677/39.

they proved highly active in this respect in completely starved animals.[447] Presumably these undernourished rats failed to respond properly, because they were kept on a small amount of comparatively low protein diets, while the completely starved rats could suddenly liberate enough endogenous protein catabolites to sensitize their adrenals to the hypophyseal implants. Thus the slow protein depletion of chronic undernutrition could inhibit, while acute starvation with marked protein catabolism would facilitate ACTH production, due to differences in the availability of amino acids.

Further work showed that *various proteins* differ in their ability to sensitize the rat for the corticotrophic action of LAP. For instance, lactalbumin or zein are considerably less effective than egg-albumin or casein.[448]

LAP-treated animals normally consume very large amounts of food, due to somatotrophin and thyrotrophin in the LAP. It is important to note, therefore, that even in rats in which *overeating* was prevented by paired feeding, the corticotrophic effect of LAP remained proportional to the protein concentration of the food.[449]

On protein-free synthetic diets, in which equivalent amounts of nitrogen were administered in the form of various *protein-hydrolysates* [450] or mixtures of *purified amino-acids*,[451] LAP caused the same cortical enlargement as on protein-rich food.

Contrary to the results obtained with impure preparations, the adrenal enlargement elicited in the rat with purified ACTH, is independent of the carbohydrate, fat and protein contents of the diet.[452] This further emphasizes that the amino-acids are only required for the elaboration of ACTH, not for its peripheral action upon the adrenal.

By varying the type and amount of *carbohydrate* and *fat* in synthetic diets containing a given concentration of casein, it was demonstrated that, in chronic experiments, sensitization to LAP is largely independent of fats and sugars.[453] Yet in acute experiments, glucose enhances the discharge of cholesterol (without affecting the elimination of ascorbic acid) from the adrenals during ACTH administration.[454]

In *summary*, it may be said that the corticotrophic action of impure anterior-lobe extracts is greatly augmented by diets rich in protein, while that of purified ACTH appears to be independent of the diet. The sensitizing action of protein upon the corticotrophic effect of crude anterior-lobe extracts is not due to the protein molecules themselves but to the constituent amino-acids. The latter are required for the production of ACTH by the anterior-lobe, not for the responsiveness of the cortical cells.

In rats simultaneously treated with LAP and *testoids*, the "fatty metaplasia" of the cortical cells, which can be elicited to some extent by testoids alone, becomes extraordinarily pronounced.[455] Apparently there is a peripheral synergism between testoids and ACTH within the adreno-cortical cell itself.

Lymphoid and myeloid metaplasia is often noted in experiments and spontaneous diseases causing extensive *tissue necrosis*. This change is likewise

[447] Mulinos and Pomerantz A36729/41.
[448] Hay et al. 96831/48.
[449] Hay and Seguin B1220/46.
[450] De Grandpré et al. B3479/48. Selye B1433/48.
[451] Henriques et al. B24140/49.
[452] Ingle et al. B2709/47.
[453] Hay et al. 96831/48.
[454] Constantinides et al. B38913/49.
[455] Selye and Stone B29495/49, B30224/50, B29075/50.

enhanced by simultaneous LAP administration. In fact, under the influence of LAP plus tissue necrosis-producing agents, the entire inner fasciculata and reticularis of the rat's adrenal is occasionally transformed into more or less typical myeloid tissue. The concomitant fatty metaplasia of the stroma helps to reproduce the structure of normal bone-marrow in the zone surrounding the adrenal medulla. This reaction is further enhanced by the simultaneous administration of thyroxine. Here, again, it has been assumed that LAP sensitizes the adreno-cortical cell itself to a direct action, in this case that of tissue-degradation products and thyroxine.[456]

While LAP (or purified ACTH) proved highly effective in preventing the lipid granule discharge which is normally produced in the cortical cells by *folliculoids*, the ascorbic acid and cholesterol content of the adrenals fell to even lower levels in rats treated with LAP plus stilbestrol than in those receiving either of these preparations alone. The loss of cytoplasmic lipid and plasmal granules occasioned by non-specific stress (e.g., trauma, nervous stimuli) is less markedly — if at all — inhibited by similar corticotrophic preparations.[457] Since ACTH antagonizes the effect of folliculoids upon the sudanophilic adrenal-lipids, this action of these steroids cannot be merely mediated by the discharge of endogenous ACTH.

The cortical enlargement seen in LAP-treated rats is not prevented by *DCA*, but under the influence of such dual treatment, colloid deposition occurs in the cortical cells. This may be a manifestation of hormone storage at a time when hormone production is stimulated, but its discharge inhibited.[458]

The well known "compensatory hypertrophy" of the remaining adrenal seen in rats subjected to *unilateral adrenalectomy* is greatly facilitated by diets rich in protein. Here, as in the G-A-S, protein presumably enhances ACTH production.[459]

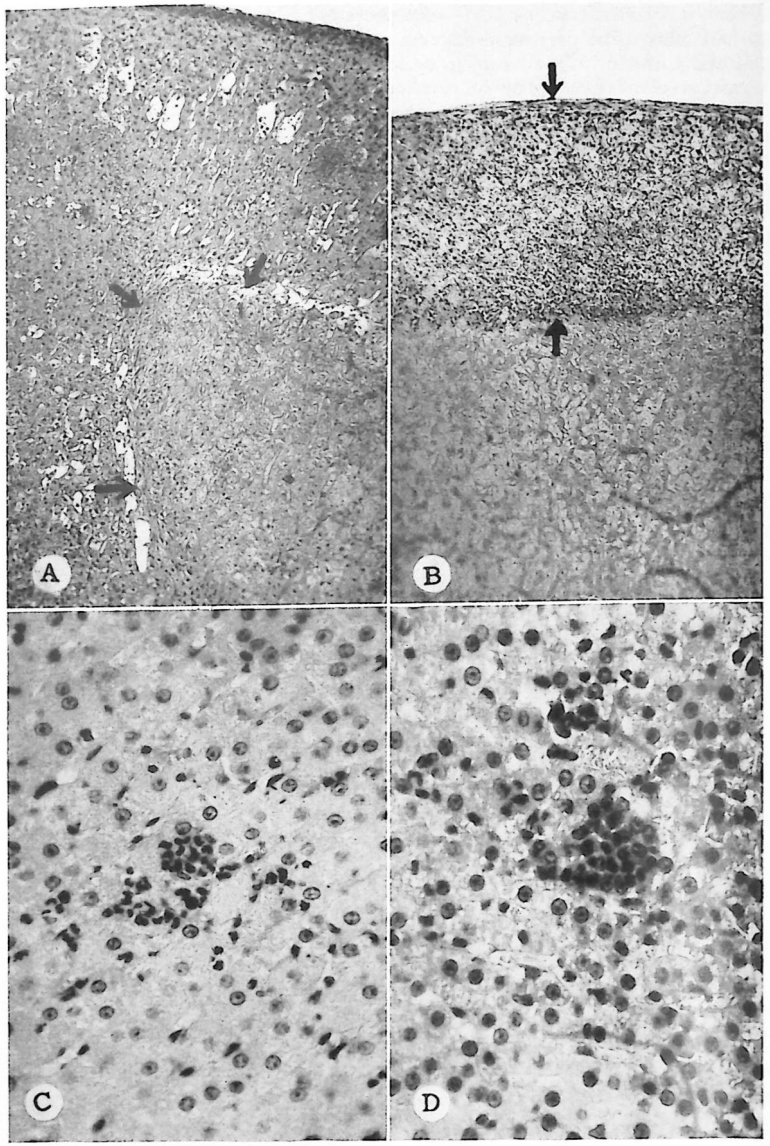
Anterior-lobe hormones other than ACTH do not appear to exert any marked effect upon the adrenals. **Somatotrophin** stimulates suprarenal tissue, but only in proportion to its "growth hormone" effect on any cell.[459a]

LH appears to be necessary for the maintenance of the reticularis in those strains of mice in which there is a definite "X-zone".[459b]

Thyrotrophin allegedly enlarges the adrenals in starved, but not in fed, guinea-pigs.[440] Perhaps thyroid hormone (here liberated under the influence of thyrotrophin) merely sensitizes the adrenals to the action of endogenous ACTH, e.g., that produced under the influence of starvation.

In intact rats treated with toxic doses of **adrenaline**, adrenal enlargement occurs simultaneously with other manifestations of an A-R.[460] While in acute experiments on rats, the adrenal-lipid content is diminished, chronic treatment with adrenaline causes lipid accumulation in the adrenal cortex.[461] The ascorbic acid and cholesterol content of the gland likewise diminishes following adrenaline treatment in rats.[462] Thus the action of adrenaline does not differ significantly from that of other stressors. Furthermore, the adrenal enlarge-

[456] Selye and Stone B29495/49, B29705/50, B30224/50.
[457] Selye and Stone B30224/50, Skelton et al. B27602/49.
[458] Selye et al. B124/45, Selye and Stone B30224/50.
[459] Moya et al. B4168/48.
[459a] Selye 35935/ND.
[459b] Jones B44039/49.
[440] D'Angelo et al. A37897/41.
[460] Selye 36032/36, 66551/36.
[461] Vogt 93902/45, Bacchus B47103/50.
[462] Long 98425/47.



Effect of anterior-lobe extracts upon the adrenals. — **A.** Adrenal of an adult male rat receiving 20 mg. of lyophilized anterior-pituitary tissue daily during 30 days. The animal was sensitized to the corticotrophic action of the extract by castration, unilateral nephrectomy and a high-sodium diet. Note great enlargement of the cortical cells, dilatation of the sinusoids and partial necrosis of the cortex (arrows) which is presumably due to adrenal periarteritis nodosa (adrenal weight 283 mg.). — **B.** Adrenal of a similarly treated rat. Here, the necrosis destroyed both adrenals almost completely, except for a thin subcapsular rim of cortical cells (arrows). These pictures show that anterior-pituitary extracts can not only stimulate the adrenal cortex, but, in the event of overstimulation (perhaps by producing adrenal periarteritis nodosa) cause necrosis with subsequent hypocorticoidism. — **C.** and **D.** High magnification of a region from the adrenal cortex of a similarly treated rat. Note "round-cell infiltration islets" consisting of small lymphocytes and polymorphonuclear leukocytes. There appear to occur transitional stages between these blood cells and the epithelial elements of the cortical cell columns. Similar infiltration islets are seen in rats bearing large, necrotic tumors or those injected with decomposing protein material. (After Selye 94572/49.)

ment produced in rats by various alarming stimuli is not inhibited by adrenergic blocking agents such as dibenamine, although that provoked by adrenaline is prevented by this drug.[462a] From this it was concluded that stressors cannot affect the adrenal cortex solely through the liberation of adrenaline. The interpretation of these data is somewhat difficult since under certain circumstances the ascorbic acid discharge caused by adrenaline was likewise not inhibited by adrenergic blocking agents (dibenamine, ergotamine, TEA) in the rat.[462b] However, here these drugs may have been given in too large doses, since they themselves caused a marked discharge.

During the first week of life, adrenaline does not cause a fall in the ascorbic-acid content of the adrenals. Since injected ACTH is already effective at this time it was concluded that, in the very young, the anterior-lobe fails to produce corticotrophin, in response to stress, although the adrenal is sensitive to corticotrophic stimulation.[462c]

Nor-adrenaline also decreases the ascorbic acid content of the rat adrenal, but it is less effective than adrenaline.[462d]

Chronic overdosage with pure **corticoids** or cortical extracts causes "compensatory atrophy" of the adrenal cortex in various species of mammals.[463] In rats chronically treated with comparatively small doses of DCA, it was found that although adaptation occurs to many actions of this steroid, the compensatory atrophy of the adrenals persists. This has been interpreted as an example of "dissociated adaptation" to a hormone action.[464]

Simultaneous treatment with DCA and excess NaCl causes especially pronounced atrophy of the glomerulosa in the rat adrenal.[464a]

In the adult fowl, DCA exerts the same depressing action upon the adrenal development as in mammals, but in very young birds, this effect was not detectable.[465]

The cholesterol content of the rat adrenal may allegedly rise above normal following DCA treatment, but this is an inconstant finding.[466]

The stimulation of the adrenal cortex, which normally occurs under the influence of various *alarming stimuli* (e.g., formaldehyde injections, cold, atropine, trauma, muscular exercise) is markedly inhibited by pre-treatment

[462a] Seifter B32930/49,
Tepperman and Bogardus B29439/48.
[462b] Ronzoni and Reichlin B47023/50
[462c] Jailer B44799/49.
[462d] Ronzoni and Reichlin B47023/50.
[463] Selye and Albert A38071/42,
Selye and Beland A57605/43,
Selye and Dosne A32151/40,
Selye and Hall A56583/43,
Selye et al. B124/45,
Selye **A32884/40. 94572/49.**
[464] Selye A36209/41.
[464a] Bacchus B47104/50,
Knowlton et al. B43547/49.
[465] Selye A56607/43.
[466] Levin B32055/45, B364/45.

with DCA.[467] This same inhibitory effect has subsequently been confirmed after intense *muscular exercise,*[468] treatment with *toxic tissue extracts,*[469] *folliculoids* [470] and *anoxia.*[471] The adrenal stimulation occasioned by acute *starvation* is apparently not, or only slightly, inhibited by cortical extracts or DCA in the guinea-pig, although it is markedly counteracted in the rat.[472]

The decrease in the ascorbic acid concentration of the adrenal normally produced by exposure to various alarming stimuli (such as cold, hemorrhage, heat, histamine, adrenaline or typhoid bacilli) is also inhibited by purified corticoids or cortical extracts.[473] Yet in rats exposed to very severe cold, even toxic doses of DCA failed to inhibit the loss of adrenal-ascorbic acid. From this, it was concluded "that during severe stress, corticotrophin discharge is conditioned by factors other than mere lack of corticoids".[474]

It is certainly true, however, that only in very exceptional instances is overdosage with corticoids completely ineffective in preventing an adrenal enlargement caused by stress. Thus, the adrenal lesions characteristic of *pantothenic acid deficiency* do not appear to be prevented by moderate doses of DCA in the rat,[475] nor is the adrenal enlargement caused by thyroxine [476] or the stimulation of the glomerulosa seen in this same species during *sodium deficiency,* inhibited by simultaneous DCA overdosage.[477]

Gluco-corticoids, such as cortisone, cause much more pronounced adrenocortical atrophy, than DCA, as judged by observations in the rat and mouse.[477a]

The **renal pressor substances,** produced in the rat by the "endocrine kidney" technique, cause adrenal enlargement whenever the resulting intoxication becomes a severe systemic stress. The *protein* or the *Na* concentration of the diet [478] fails to influence this adrenal response significantly, but *testosterone* diminishes it markedly.[479]

In rabbits the hypertension produced by renal ischemia causes adrenocortical hyperplasia with increased lipid storage. The possible relationship between these changes and our concept of the diseases of adaptation has been discussed.[480] Similar adrenal changes occur in rats in which nephritis has been produced by anti-kidney serum.[480a]

It is interesting that **gonadectomy** often elicits the development of adrenocortical adenomas or even carcinomas in either sex, especially in certain hereditarily predisposed strains of mice.[481] In other species, e.g., the rat, ovariectomy reduces the normally larger adrenal cortex of females approximately to the size characteristic of the male.[482] The relationship of these

[467] Dalton et al. 78098/40, Dosne and Selye 81963/42, Selye A31129/40, Selye and Dosne A37249/42, Selye et al. A32768/40.
[468] Beznak and Korényi A57235/41, Ingle 75145/38, Korényi and Hajdu A56945/42.
[469] Riml A39402/40.
[470] Selye A32884/40, Albert and Selye A37637/42.
[471] Langley and Clarke 83179/42.
[472] D'Angelo et al. B19839/48, B17658/48, B32728/49, B32991/49.
[473] Gray and Munson B47258/50, Sayers and Sayers 98805/47, **B37770/49.**
[474] Moya and Selye B19381/48, Selye B1433/48.
[475] Mushett and Unna A37733/41.
[476] Selye et al. B229/45, B124/45.
[477] Deane et al. B23212/48, Selye and Stone B29495/49, B30224/50, Selye et al. B19413/49.
[477a] Antopol B47052/50, Selye 35935/ND.
[478] Selye and Stone B18527/48.
[479] Selye and Stone B19379/49.
[480] Rosselli del Turco and Matteini B37480/47.
[480a] Knowlton et al. B43547/49.
[481] Wooley **B37778/49.**
[482] Selye **94572/49.**

responses to the G-A-S has not yet been clarified, but it is obvious that gonadal hormones can condition the reactivity of the adrenal cortex.

The cortical changes produced by **folliculoids** deserve special attention. The earliest pertinent studies were performed with impure extracts and are difficult to evaluate because the toxic contaminating substances acted as stressors. However, experiments with the first available pure compound of this group (estrone) clearly showed that folliculoids cause marked loss of lipid material from the cortex.[483] It soon became evident furthermore that, in very large doses, even pure folliculoids also cause other manifestations reminiscent of the A-R (adrenal enlargement, thymico-lymphatic atrophy, increased catabolism, etc.).[484] Yet the adrenal changes differ somewhat from those seen upon exposure to other alarming stimuli. The lipid discharge is particularly marked and long lasting, there is intense hyperemia of the entire cortex with almost hemangioma-like dilatation of the sinusoids and often liquefaction necrosis of cortical cells with pronounced edema. Both natural and artificial folliculoids produced essentially the same reaction in the mouse and rat.[485]

In very young rats, neither estradiol [486] nor stilbestrol [487] caused any adrenal enlargement. The cause of this relative insensitivity to folliculoids, at an early age, is still not understood. Curiously however, in the fowl — which may be regarded as phylogenetically "young" — estradiol also failed to elicit adrenal hypertrophy.[488]

Studies with labelled phosphorus in the rat show that folliculoids have a marked effect upon the acid-soluble organic phosphate content of the adrenal cortex. This change being similar to that produced by ACTH, has been interpreted as a metabolic manifestation of increased cell activity.[489]

The cholesterol content of the rat adrenal is not influenced by small [490] but is diminished by very large [491] doses of folliculoids. At the same time the ascorbic acid content also falls.[492]

Simultaneous treatment of rats or mice with folliculoids and *testoids* results in a diminution of the cortical enlargement normally produced by the former.[493]

In addition to the testoids (and the corticoids whose action has already been discussed above) *luteoids* and several *other steroid hormones* can counteract the adrenal enlargement normally produced by folliculoids.[494]

Testoids can also exert rather specific actions upon the adrenal cortex. In the mouse, they selectively induce an involution of the reticularis (the so-called "x-zone") and diminish the total width of the cortex. In the rat adrenal, they tend to increase the cellularity of the glomerulosa and cause capsular fibrosis as well as a pronounced diminution of weight.[495] This is usually accompanied by fatty metaplasia of cortical cells.[496] In the fowl, testoids also cause involution of the adrenals.[497]

[483] Selye et al. 32001/35.
[484] Luri et al. B31933/49, Selye et al. 38815/36.
[485] Gangitano B41887/48, Selye et al. 38815/36, Selye A8610/37, A18206/39.
[486] Selye and Albert A37751/42.
[487] Timiras B18852/48.
[488] Selye A56607/43.
[489] Gemzell B24892/48.
[490] Gemzell B24892/48.
[491] Levin B32055/45, B364/45, Skelton et al. B27602/49.
[492] Skelton et al. B27602/49.
[493] Albert A37132/42, Albert and Selye A37637/42, Selye A32884/40, A56607/43, Selye and Friedman A34228/41.
[494] Albert and Selye A37637/42, Selye A32884/40.
[495] Selye **A32884/40, A18308/39.**
[496] Selye and Stone B30224/50, Selye et al. A58747/43.
[497] Selye A56607/43.

Only if very high doses of testosterone are given does the rat adrenal fail to involute; indeed, it may become enlarged if the testoid overdosage causes severe systemic stress.[498] This is especially noteworthy since — contrary to current opinion — testoids are even more effective than DCA in inhibiting the adrenal enlargement normally caused by *alarming stimuli*. The intensity of their anti-corticotrophic effect was demonstrated in rats in which systemic stress was produced either by formaldehyde injections [499] or by very high doses of thyroxine.[500]

The fact that in the rat crude testis extracts can cause adrenal enlargement, is hardly surprizing since, in this case, the impurities probably act as alarming stimuli.[501]

Luteoids and several **other steroids** cause adrenal involution both in the rat [502] and in the fowl,[503] perhaps because they possess some degree of corticoid or testoid activity.

In view of the clinical use of **insulin** in the shock-therapy of mental disease, it is worthy of mention that the hypoglycemia produced by toxic doses of this hormone has long been known to cause intense loss of chromaffin granules with adrenaline discharge from the adrenal medulla. This may be accompanied by marked vacuolization and actual disintegration of cells similar to that seen after exposure to other stressors. The reaction depends upon the integrity of the adrenal nerves, as it is prevented by *denervation*.[504] Large amounts of *glucose* likewise prevent this loss of chromaffinity,[505] hence, it is generally assumed that the reaction is due to the decrease in blood sugar and mediated by the medullary nerves. The cholesterol content of the rabbit's adrenal likewise diminishes under the influence of insulin overdosage.[506]

We have already mentioned that **thyroidectomy** tends to inhibit the corticotrophic action of LAP (while thyroxine enhances it).

Whether thyroidectomy in itself has any significant effect upon the cortex has long been debated, because contradictory results were obtained in various species. In the rat — which is comparatively insensitive to parathyroidectomy — the removal of the thyroids (with the enclosed parathyroids) causes an involution of the adrenals. This is much more obvious in females than in males,[507] perhaps because females normally have a larger cortex so that its involution results in a relatively more pronounced change in the total weight of the gland.

The ascorbic acid content of the rat adrenal allegedly rises after thyroidectomy.[508] Other experiments on rats suggest that both after thyroidectomy and after thiouracil treatment, the fasciculata atrophies and its sudanophilic lipids, plasmal, birefringent and autofluorescent granules tend to disappear.[509]

The adrenal enlargement during an A-R produced in the rat by exposure to *cold* [510] or by *formaldehyde* injections [510a] is diminished but not prevented by thyroidectomy. This may well be due to the characteristic diminution of all metabolic processes in thyroid deficiency.

[498] Selye A35221/41.
[499] Selye A31129/40.
[500] Selye and Stone B30224/50, Selye et al. B124/45.
[501] Simonnet 99953/47.
[502] Selye and Albert A38086/42, Winter A36510/42.
[503] Selye A56607/43.
[504] Hillarp 93731/46, Selye **94572/49.**
[505] Loeb et al. 9347/31.
[506] Chamberlain 22539/30, 11091/30.
[507] Selye 38798/37.
[508] Sas A1959/36.
[509] Deane and Greep B3167/47.
[510] Brolin 91168/46.
[510a] Selye 38798/37.

Overdosage with **thyroid hormone** increases the weight of the adrenal, mainly — if not entirely — due to cortical enlargement.[511] There is also an increase in the number of mitoses, especially in the fasciculata.[512] This has been considered to be the consequence of a G-A-S developed under the influenced of overdosage with this hormone, especially since after prolonged administration, adaptation occurs and the adrenal tends to return towards normal.[513]

It has been claimed that thyroid feeding increases the cholesterol content of the adrenals in the guinea-pig,[514] while in the rat, thyroxine treatment decreases it.[515] The latter response was considered to be part of a defense mechanism against the hormone.

More recent cytochemical studies on the rat suprarenal led to the conclusion that thyroid feeding causes especially marked hypertrophy of the fasciculata. During the first week, this is accompanied by an increase and later by a decrease in sudanophilia, plasmal, birefringent and fluorescent granule content, as well as considerable cytolysis.[516] Perhaps the initial change corresponds to the resistant, the final to the exhaustion phase of the G-A-S, but this requires further proof.

The ascorbic acid content of the guinea-pig adrenal was reported by some [517] as above, by others [518] as below normal after thyroid treatment. A reduction in adrenal-ascorbic acid has also been noted in thyroid-fed rabbits,[519] and rats.[520] Yet in some experiments on the rat, opposite results were obtained.[521] These apparent contradictions may well be ascribed to the fact that (depending upon the dose, length of treatment and species differences in sensitivity) the authors observed their animals in different stages of the G-A-S. In one such study on rats it was clearly demonstrated that under the influence of continuous thyroxine treatment the ascorbic acid first decreases and secondarily rises [522] presumably because, after the A-R, the stage of resistance supervened.

In view of the close interrelations between the thymus and the adrenals, it is noteworthy that **thymectomy** causes no significant adrenal change in the rat.[523] The fact that intrapleural administration of **thymus extract** resulted in adrenal enlargement,[524] could hardly be ascribed to any specific "thymus principle" and is almost certainly due to the resulting A-R.

There is no doubt that **nervous stimuli** play an important rôle in the response of the adrenal during the G-A-S. It has been clearly shown that denervation of the adrenals (e.g., by periarterial sympathectomy or splanchnicotomy) prevents the loss of chromaffin granules which otherwise occurs in the A-R. There are only very few agents which can cause loss of chromaffinity, or otherwise demonstrable adrenaline discharge, following adrenal denervation. Acetylcholine is a notable exception, but since this substance is the direct humoral transmitter of secretory stimuli to the chromaffin cells, its behaviour is understandable.[525] Potassium and nicotine are other agents allegedly capable

[511] Durey B36312/49, Kaden et al. A707/37, Miller and Riddle A30224/39, Swann A30182/39, Selye **94572/49.**
[512] Schmidt 79397/37.
[513] Kendall and Ingle 68707/37.
[514] Sakai 14310/29.
[515] v. Abelin 86927/44.
[516] Deane and Greep B3167/47.
[517] Mosonyi 35212/37, Paal and Brecht A1954/37.
[518] Nespor A1955/36.
[519] Nespor A1955/36.
[520] Svirbely 67334/36.
[521] Paal and Brecht A1954/37.
[522] Wallace and Reineke B37726/49.
[523] Hashimoto and Freudenberger 76844/39.
[524] Tislowitz and Chodkowska 36624/36.
[525] Hillard **93731/46**, Selye **94572/49.**

of causing adrenaline discharge by direct action upon the denervated adrenal.[526] In any case, most stresses cause adrenaline discharge as a result of splanchnic stimulation, even if exceptional agents can affect the medulla through humoral means.

Conversely, the cortex does not appear to receive any secretory nerves and fails to respond to splanchnic stimulation or splanchnicotomy.[527]

Experiments on rats with transplanted adrenal cortices likewise suggest that adrenal-cortical function is independent of direct nervous stimulation.[528] Furthermore, the hypertrophy of adrenals, under conditions of decreased barometric pressure, is not affected by subdiaphragmatic vagotomy.[529] The ascorbic acid content is not influenced by splanchnic stimulation, even in the adrenal medulla, as shown by experiments in the dog and cat.[530]

It has been shown with particular clarity, in a systematic investigation on rats, that during exposure to non-specific stress, the adrenal cortex is independent, while the medulla is dependent, upon the integrity of the adrenal nerves. Upon exposure to cold, heat, hemorrhage or toxic doses of insulin, the loss of cortical lipids was the same in intact controls and in animals whose splanchnics and upper lumbar sympathetic chains were removed on both sides. Yet, the latter group did not respond to these stressors with the usual adrenaline discharge.[531]

Some investigators claimed to have produced adrenal-cortical atrophy following suprarenal denervation.[532] Others stated that in rats the adrenal enlargement caused by stress (e.g., muscular work, injection of acid, unilateral adrenalectomy), is inhibited by removal of the celiac ganglion.[533] However, in all these cases it is difficult to exclude the possibility of coincidental interference with the adrenal vessels. As we have stated above, normally, adrenal denervation has no effect upon the response of the cortex during the G-A-S.

In accordance with this interpretation, it was found that the ascorbic acid depletion of the rat adrenal, caused by a standard stress (e.g., cold, intraperitoneal injection of CCl_4), is not prevented by *adrenergic blocking agents*, such as dibenamine or tetraethylammonium.[534] Indeed it could even be shown that "the histological changes of the alarm reaction in the thymus and the adrenals, provoked by epinephrine were reversed by dibenamine but those provoked by colchicine were not".[534a] Any theory postulating that the emergency discharge of adrenaline is responsible for the stimulation of corticotrophin secretion during stress, would have to take these negative findings into account.

It has been mentioned above that various *anesthetics* can cause A-R changes in the adrenals. Yet, under certain circumstances, barbiturate anesthesia prevents the discharge of adrenal ascorbic acid, which normally follows upon exposure to cold, in the rat. It does not prevent this effect of heat or hemorrhage. In these same experiments barbiturate anesthesia prevented the hyperglycemic effect (ascribed to adrenergic discharge) of all these stressors. It

[526] Hermann A18032/38.
[527] Hillarp **93731/46**, Selye **94572/49**.
[528] MacFarland 96804/44.
[529] Hailman A69737/44.
[530] Giroud and Santa A30561/39.
[531] Vogt B17483/47, B26537/47.
[532] Snell et al. A58087/36, Ljvraga **75106/39**.
[533] Otto and Sass-Korsak A15466/38, Beznak et al. A15465/38.
[534] Tepperman and Bogardus B29439/48.
[534a] Seifter et al. B32930/49.

was concluded that adrenaline cannot be indispensible for the discharge of ACTH.[534b]

There is considerable disagreement concerning the rôle of the *pituitary stalk* during the G-A-S. Some experiments in the rat suggest that severance of the stalk prevents the corticotrophic effect of stress, while in others there was no such inhibition.[535] In dogs, pertinent data are also contradictory.[536] It must be kept in mind that isolated destruction of the pituitary stalk is a technically difficult operation; it is often accompanied by accidental lesions in the hypophysis, due to direct interference with the gland or its nutritive vessels. Hence, the occasional finding of adrenal-cortical atrophy after stalk transection must be viewed critically.

Some pertinent observations were made on partially hypophysectomized rats (in which the posterior lobe and the stalk were removed, but small anterior lobe remnants were left intact), others on rats whose pituitary was transplanted into the anterior chamber of the eye. Such experiments showed that exposure to stress (trauma, cold, histamine) can still stimulate the adrenal cortex to enlarge and to discharge its lipids and ascorbic acid even when connections with the hypothalamus no longer exists.[537]

Thus, it appears that neither denervation of the adrenal cortex itself nor severance of the connections between hypophysis and hypothalamus prevent the usual adreno-cortical response during the G-A-S.

Heredity and constitution undoubtedly also have an important effect upon suprarenal responses. The wild Norway rat has much larger adrenals than the inbred, albino laboratory rat. This is due mainly to a difference in the development of the cortex.[538] It has been suggested that more frequent exposure to stress in the case of the wild rat may be responsible for this difference and the phenomenon was interpreted in terms of the G-A-S concept.[539] Curiously, wild Norway rats, kept under sheltered laboratory conditions from birth, had slightly smaller adrenals than recently captured specimens, although their glands were still much larger than those of domestic rats. First generation crosses between wild and domestic Norways, however, had adrenals only slightly larger than those of pure domestic rats.[540]

It has also been claimed that in high-strung "nervous" strains of rats, the adrenal weight is greater than in more passive strains.[541]

These findings are particularly significant as regards the interpretation of the "diseases of adaptation". It is well known that only certain patients respond to stress with a syndrome suggesting hyper- or dys-corticoidism. It is very probable that here differences in genetic constitution play an important rôle.

The rat adrenal responds normally to ACTH, even at a very early age. However, alarming stimuli (e.g., cold, adrenaline) fail to cause an adrenal-

[534b] Ronzoni B47024/50.
[535] Brolin 91168/45, Dempsey and Searles A56587/43, Dempsey and Uotila A34573/40, Uotila A19997/39, B5016/39, A31211/40, A31212/40.
[536] Beattie 4685/32, Bodo and Marine A95837/46, Findley **B36596/49**, Hume B33420/49, Keller and Beckenridge 99997/47.
[537] Cheng et al. B38333/49, B45616/49, Fortier and Selye B37371/49.
[538] Donaldson B32481/24, Hatai A10936/15, Nichols B29974/48, Rogers and Richter B4924/48.
[539] Nichols B29974/48, Rogers and Richter B4924/48.
[540] Rogers and Richter B4924/48.
[541] Freudenberger B32482/32, Yeakel and Rhoades A35655/41, A31156/39.

ascorbic acid discharge during the first week, presumably because the anterior-hypophysis does not yet react to stress by an increased ACTH elaboration.[541a] This may also explain why very young rats show little, if any, cortical enlargement following overdosage with folliculoids.[541b] Many additional observations, listed in various sections of this book, confirm that ACTH-discharge during stress is deficient during the first days of life.

The influence of the **diet** upon the reaction of the suprarenals during stress has previously been discussed in other connections. Let us merely re-emphasize here that *fasting* during the A-R stage, greatly increases the loss of cortical lipids, cholesterol and ascorbic acid. Administration of readily digestible food, especially *carbohydrate-rich* diets, have an opposite effect.[542]

In acute experiments the corticotrophic effect of burns (judged by adrenal size, cholesterol and ascorbic acid) was not significantly altered in rats kept on *protein-deficient* diets.[543] However, here the stressor action may have been so great that further accentuation became impossible. During the later stages of the G-A-S, the adrenal enlargement produced by stress is roughly proportional to the protein content of the food. This effect is not dependent upon the integrity of the protein molecule, since protein hydrolysates and mixtures of pure, essential amino-acids likewise increase the responsiveness of the adrenal during stress. Perhaps amino-acid mixtures facilitate the production of corticotrophin by the anterior-lobe. Diets rich in *sodium* tend to specifically inhibit the development of the glomerulosa, but otherwise they exert no important influence upon the adrenal response during the G-A-S, although they greatly sensitize the organism to the toxic effects of mineralo-corticoids (e.g., hypertension, nephrosclerosis, hyalinosis).[544]

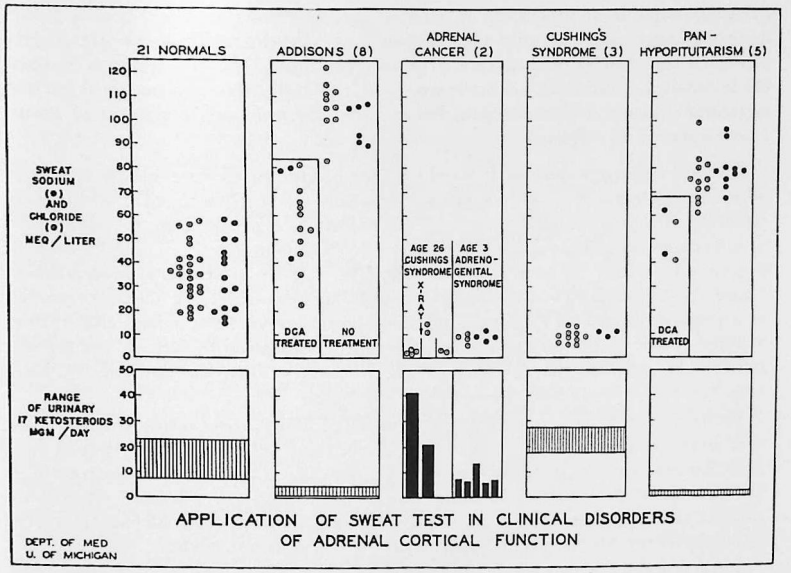
It has been claimed that *ascorbic acid* administration inhibits the adrenal hemorrhages otherwise produced by diphtheria toxin in the guinea-pig,[545] as well as the adrenal enlargement and cholesterol discharge caused by cold in the guinea-pig and rat.[546] On the other hand, the cortical hypertrophy normally induced by thyroxine in the rat, is allegedly not prevented either by excess ascorbic acid or by *thiamine*.[547]

Adrenal Diseases of Adaptation

Hypocorticoidism. — In a sense Addison's disease may be interpreted as a disease of adaptation.[548] It would be superfluous to survey its clinical features, since this has just been done in an excellent monograph, in which the relations of this disease to the G-A-S have also been discussed.[549]

It is obvious that adreno-cortical deficiency, no matter how produced, interrupts the hormonal defense reaction to stress at the adrenal level and thus diminishes resistance, because corticoid production can no longer be increased when necessary. If the disease is caused by a local pathologic process developing in the adrenals (e.g., tuberculosis, syphilis, bilateral destructive tumors) we may speak of a primary disease in an organ of the adaptive system. If, on the other hand, the adrenal is damaged because of exhaustive overstimulation during a G-A-S, the lesion may be regarded as a secondary disease of adaptation. In experimental animals, bilateral suprarenal necrosis has often been observed following chronic treatment with LAP or prolonged exposure to stress. In an effort to correlate these findings with clinical observations, it has been stated that "the comparatively frequent occurrence of bilateral adrenal necrosis, which is conducive to secondary infection of the adrenals and eventually leads to the development of Addison's disease, may perhaps be explained on the basis of such a tissue collapse caused by prolonged overstimulation".[550]

[541a] Jailer B44799/49, B47152/50.
[541b] Selye and Albert A37751/42, Timiras B18852/49.
[542] Selye **B1204/46.**
[543] Sayers B35911/49.
[544] Dugal and Leblanc B44850/49, Henriques et al. B26250/48, Knowlton et al. B43547/49, Leblond and Dugal A72918/43, Selye 36032/36, 36031/36, 38798/37, B1204/46, 94572/47, B17771/38, A8406/38.
[545] Torrance A30233/39.
[546] Dugal and Thérien B23325/48, Thérien and Dugal B32840/49, Thérien et al. B39699/49.
[547] Kaden et al. A707/37.
[548] Selye 94572/49, B1204/46.
[549] Thorn **B41761/49.**



Correlation between adrenocortical activity and NaCl excretion through the sweat. Note that in patients with Addison's disease or pan-hypopituitarism, NaCl losses through the sweat are above normal unless DCA treatment is instituted. In hypercorticoidism (adrenal cancer, Cushing's syndrome) NaCl excretion through the sweat is subnormal. The urinary 17-KS excretion generally parallels the degree of NaCl retention, both being indices of hypercorticoidism. (After Conn B46371/49.)

In man, Addison's disease can occur following exposure to intense stress. The selective localization of pathogenic organisms (e.g., tuberculosis, syphilis) in both adrenals, may perhaps be the consequence of local tissue breakdown which creates a "locus minoris resistantiæ".[551] Long standing wound infection, following burns has been reported to cause Addison's disease associated with amyloidosis,[552] perhaps through some similar mechanism.

[550] Selye A75044/44.
[551] Selye **94572/49.**
[552] Levenson et al. B24308/47.

Of course any stressor may cause a purely functional "relative hypocorticoidism", if the corticoid production is not commensurate with the increased requirements occasioned by the damaging agent.[552a] Here, we may further distinguish between relative deficiency in all or only in some members of the cortical hormone group. (cf. below).

Significantly, in many diseases there is a decrease in the blood-sodium concentration accompanied by an increase in melanin formation, such as are also noted in Addison's disease. It has been shown that, in vitro, the oxidation of various hydroxyphenols to melanin is inhibited by ascorbic acid, especially in the presence of NaCl. Lack of NaCl accelerates melanin formation under such conditions, perhaps because it facilitates the oxidation of ascorbic acid. Hence, it was suggested that in Addison's disease, as well as in many other disorders capable of producing at least relative hypocorticoidism, melanin formation is augmented because the "melanogens" (hydroxyphenols) are poorly protected by ascorbic acid against oxidation.[553] Should this be correct, at least the melanosis of Addison's disease would be especially dependent upon certain metabolic changes (hyponatremia, fall in blood-ascorbic acid) known to result from exposure to stressors.

Adrenal hyperactivity. — It would be redundant to devote much space to adrenal hyperactivity as a disease of adaptation. It is obvious that any lesion resulting in a purposeless, continuous increase in the production of corticoids, or adrenergic substances, could vitiate the development of a normal G-A-S in response to stress. If such a derangement be due to a primary proliferation (tumor or hyperplasia) of the cortex or medulla, it would have to be regarded as a primary disease of this organ or adaptation. Conversely, when the hyperactivity of the cortex or medulla is the result of exposure to stress, the condition would fall into the category of the secondary diseases caused by maladaptation.

In the preceding pages of this section we listed many observations suggesting that stressors can cause an excessive or abnormal production of corticoid and medullary hormones; additional pertinent observations have been discussed in the chapter on the pituitary in connection with Cushing's syndrome. It will be recalled that often the latter is not due to a primary derangement of the pituitary, but to primary neoplasms or hyperplasias of the adrenal cortex.

Little is known as yet about the conditions which can cause a deviation from the normal proportion between mineralo- and gluco-corticoid hormones during stress. We suspect "conditioning factors" which qualitatively influence the corticotrophic discharge of the anterior-lobe, or the response of the adrenal cortex to a standard ACTH stimulation. In any event, many observations suggest that such a derangement in the $\frac{\text{gluco-corticoid}}{\text{mineralo-corticoid}}$ quotient can cause disease.

It is quite conceivable that a dysfunction of this type may lead to a pathogenic predominance of either among these two main groups of corticoids. This could result in secondary disturbances (e.g., the tendency to develop hypertension, hyalinosis, rheumatoid and rheumatic changes, gout or diabetes) without there being any obvious abnormality in the total amount of corticoids

[552a] Kappert B42767/47, Selye B1204/46. [553] Lea B26358/45.

produced or excreted, and indeed without any major structural change in the adrenals themselves.

It is especially significant that primary hyperplasia or neoplasia, in the adrenal cortex or medulla, so frequently lead to hypertension, arteriosclerotic changes, diabetes and other derangements, which we would interpret as diseases of adaptation. Here, there is no doubt about an etiologic relationship between the adrenal change and the peripheral disturbance since generally ablation of the diseased adrenal effects a cure.

Undoubtedly, in the majority of these "degenerative" diseases the adrenals are not conspicuously abnormal, nevertheless, extensive systematic surveys suggested that adrenal cortical and/or medullary hyperplasia, is very common for instance in cardiovascular and renal diseases. This has been interpreted as further proof in favor of our view according to which these are diseases of adaptation.[554] We shall come back to this later in connection with the pathogenesis of arteriosclerosis, pariarteritis nodosa, hypertension, nephrosclerosis, etc.

Pancreas

Systemic stress. — The first systematic studies conducted to examine the **characteristic** effects of alarming stimuli (formaldehyde, morphine, atropine, adrenaline, spinal shock, surgical shock, cold, exercise) upon the structure of the pancreas, revealed merely that during the A-R stage the gland loses its normal whitish color; it becomes pink and translucent so that the Langerhans islets are readily distinguishable by the naked eye. The latter appear in the form of white spots situated along the course of the larger blood vessels. Histologic sections showed that the acinar cells lose their secretory granules, becoming round and small. Only in the immediate vicinity of the Langerhans islets do the acinar cells retain their secretory granules, forming an eosinophilic "halo" of almost normal excretory cells around the endocrine-tissue accumulations. Often the impression is gained that acinar or duct cells are transformed into endocrine cells. There is no doubt that, during the A-R, the relative proportion of islet cells to acinar cells changes in favor of the former, however, this is largely due to the fact that the intense catabolic phenomena affect almost only the acinar cells of the pancreas.[555]

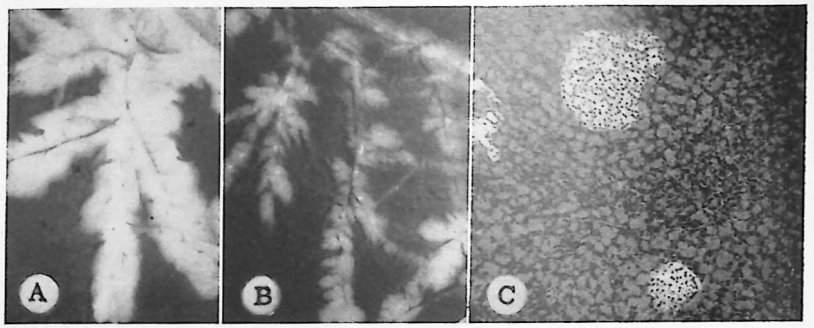
In dogs, an acute hemorrhagic pancreatitis may occur after stimulation of the cervical or thoracic sympathetic nerve chains. Hence, purely **nervous** stimuli are also capable of eliciting such inflammatory changes.[556]

Chronic **starvation** causes atrophy of the pancreas, in man, frequently accompanied by numerous pyknotic cell-lesions in the exocrine acini.[556a]

Essentially similar changes have been elicited by treatment with toxic doses of various **drugs.** For instance, intense loss of zymogen granules from the pancreas of the cat has been noted after chronic *atropine* intoxication.[557] However, this could have been largely due to specific pharmacologic actions of this autonomic drug especially since zymogen discharge and "halo" formation has also been seen in cats after vagus stimulation or intravenous injection

[554] Mosinger B30627/48.
[555] Selye 38798/37, A8406/38.
[556] Reilly **99381/42.**
[556a] Overzier B45391/48.
[557] Arima 32274/18.

of *choline chloride*. Although the resemblance of this change to that characteristic of the A-R was emphasized, "halo" formation in this latter case was nevertheless regarded to be a specific vagus effect.[558] Yet, toxic doses of *guanidine derivatives* also cause similar changes, often accompanied by intense hyperemia, fat necrosis, perivascular leucocytic infiltrations and sometimes frank inflammation of the pancreas in the dog.[559] In man, fatal *colchicine poisoning* was found to cause some damage to the acinar cells, while there were "pictures suggesting the new formation of Langerhans islets from exocrine acini".[560]



Pancreas during the G-A-S. — **A.** Normal pancreas — macroscopic view of the pancreas of a normal rat. — **B.** Pancreas in A-R — macroscopic view of the pancreas of a rat similar to that shown in Fig. A, but having received toxic doses of atropine. Note the distinctly visible white Langerhans' islets along the blood vessels. The pancreatic lobules are atrophic and translucent. — **C.** Pancreas in A-R — section through the pancreas of a rat, in which an alarm reaction was produced by excessive, forced muscular exercise. Note that acinar tissue remains normal only in a halo-like area around the two Langerhans' islets. Here, it contains numerous (eosinophilic) secretory granules. The remaining acinar tissue shows no sign of secretion and is atrophic. (After Selye B1204/46.)

In rabbits, given intravenous injections of allyl-formiate, "serous pancreatitis" is of common occurrence.[560a]

Another series of observations has been summarized as follows: "an alarm reaction was produced experimentally in rats, dogs and rabbits with large doses of *colchicine, aminopyrine, selenium compounds and other drugs*. It was found that all these alarming stimuli can cause loss of zymogen granules and in severe cases, even focal necrosis of the pancreas".[561]

A patient, who received thiouracil for angina pectoris, suddenly developed intense abdominal pain and collapse. A hard, greatly enlarged pancreas was found at laparotomy,[561a] but it is not known whether this corresponded to a non-specific acute pancreatitis.

Conspicuous damage to the Langerhans islets has been noted, in association with A-R changes, during severe diphtheria in man and after diphtheria-toxin treatment in the guinea-pig. This was held responsible for some of the accom-

[558] Sergeyeva 72174/38.
[559] Dische and Goldhammer 19784/33.
[560] Dustin 94160/41.
[560a] Papayannopoulos B45313/49.
[561] Ehrich and Seifter B31789/48.
[561a] Barclay and Leatham B45641/46.

panying derangements in carbohydrate metabolism.[562] Perhaps here again, conditioning factors determine which part of the organ will be most affected during stress.

Electric shock can also cause pancreatic necrosis, a fact whose possible medico-legal significance has been emphasized.[563]

The extraordinarily frequent and pronounced involvement of the pancreas both during acute (A-R) and chronic (replicas of "diseases of adaptation") exposure to stress suggests that comparable pancreatic lesions in man may find their explanation in derailments of the adaptation mechanism.

Stimuli Influencing the Response of the Pancreas During the G-A-S. — Certain **anterior-lobe extracts** increase the development of Langerhans islet tissue in the pancreas. Since at the same time, the acinar tissue is also slightly increased, it has been concluded that here, the response is specific and not merely due to an A-R.[564]

It is highly probable that the so-called "diabetogenic hormone" and "pancreatotrophic hormone" actions are actually due to somatotrophin. Depending upon conditioning factors such anterior-lobe preparations either stimulate or "exhaust" and destroy the Langerhans' islets.[565] Thus the level of somatotrophin production would play an important rôle in determining the response of the pancreas to stress. Unfortunately this aspect of the G-A-S problem has not yet received much attention.

Curiously, unlike the mineralo-corticoids or the "endocrine kidney" (see below) **LAP** is comparatively ineffective in producing severe vascular lesions in the pancreas, or any other organ outside the kidney.[566] Perhaps LAP increases both mineralo- and gluco-corticoid production and the latter tend to antagonize this particular effect of the former.

Chronic treatment of rats with toxic doses of **DCA**,[567] or **desoxocortisone** [568] causes especially pronounced vascular changes in the pancreas. In the acute stage, these tend to produce edema, pancreatic necrosis and inflammatory changes, while in later phases, they result in scar formation with fibrosis. Cortisone can prevent these changes.

Essentially similar, but even more rapidly developing pancreatic lesions are produced by the **"endocrine kidney"**.[569]

Pancreatic Diseases of Adaptation

In the preceding pages we enumerated many observations showing that stress, or overdosage with those hormones whose production is increased during the G-A-S, can cause acute involution of the pancreas with edema, widespread vascular lesions and necroses. These changes are often accompanied by the formation of inflammatory granuloma tissue and the view has repeatedly been expressed, on the basis of animal experiments, that acute **pancreatic necrosis** and **pancreatitis** in man may also result from a derangement of the G-A-S.[570]

[562] Prosperi B41943/49.
[563] Glazer B2401/45.
[564] Richardson and Young 70318/37.
[565] Selye **94572/49.**
[566] Selye B1204/46, 94572/49.
[567] Selye B1204/46,
Selye et al. A58748/43.
[568] Selye B43385/50.
[569] Selye 94572/49,
Selye and Stone 94202/46.
[570] Ehrich and Seifter B31789/48,
Selye B1204/46.

Certain clinical observations tend to confirm this view. It has been noted that pancreatic necrosis can result from a generalized arteritis [571] such as is caused by mineralo-corticoid overdosage. Furthermore, pancreatitis (sometimes accompanied by parotitis) is frequently observed in men suffering from hunger edema,[572] or various acute infectious diseases [572a] and, occasionally, after thiouracil intoxication.[572b]

Diabetes as a disease of adaptation has been discussed elsewhere (p. 263). Let us add that since that chapter was written, the reduced glutathione and uric acid content of the blood was found to be usually normal in diabetics,[572bb] but evidence of an increased corticoid production and the participation of the G-A-S mechanism has been strengthened.[572bc]

Thyroid

Systemic stress. — Changes in thyroid structure are not particularly characteristic of the G-A-S. In the rat, there appears to be a slight tendency towards thyroid atrophy during an A-R, caused by **alloxan** [572c] **formaldehyde** injection [573] and during **starvation.**[574] Of course exposure to cold is highly effective in stimulating the morphologic development [575] and radio-iodine uptake [576] of the rat thyroid, but this is a specific response designed to maintain the body temperature. However, some degree of apparently non-specific thyroid stimulation has been noted even in the rat under certain experimental conditions, for instance, after production of **frost-bite** by local cooling [577] and after **burns.**[578] Studies with radio-iodine led to the conclusion that in rats "apparently various stresses lead to an increased production of thyroid hormone, but there was also an increased rate of utilization of it".[579]

Conversely, in the guinea-pig — which is notoriously sensitive to thyrotrophic stimuli — **diphtheria toxin** [580] and many **other stressors** cause thyroid hyperplasia.[581]

The thyroids of rabbits with **artificial fever,** due to diatherm or radiotherm treatment, often show colloid depletion with hyperplasia of the lining epithelium.[582]

Stimuli Influencing the Response of the Thyroid During the G-A-S. — It has been claimed that **transection of the pituitary stalk** prevents the thyrotrophic effect of exposure to cold in the rat.[583] It will be remembered, however, that the thyroid stimulation by cold is part of a specific adaptive response; it helps to maintain body temperature by raising the B.M.R. Hence this reaction is not, strictly speaking, part of the G-A-S. As previously mentioned (cf. Adrenals ← Nervous Stimuli, p. 345) in rats exposed to cold, transection of the pituitary stalk does not prevent the adreno-cortical enlargement which is undoubtedly characteristic of the G-A-S.

The development of intracellular colloid-droplets in the thyroid epithelium of the rat is normally due to the endogenous formation, or exogenous administration, of thyrotrophin. This change also occurs under the influence of various toxic stressor substances (e.g., toxic doses of typhoid vaccine, histamine, pilocarpine). These toxic compounds allegedly exert their thyrotrophic effect even after hypophysectomy,[584] but this important claim requires confirmation.

Data concerning the effect of **adrenaline** upon the thyroid are somewhat conflicting. In man, adrenaline appears to increase the uptake of radio-iodine by the thyroid. This was considered to be an indirect effect mediated by the hypophysis-adrenocortical system, since the response was absent in patients with Addison's disease or hypopituitarism. These experiments would indicate that the adrenal cortex augments the thyrotropin stimulating action of epinephrine.[584] However, in the intact rat, adrenaline considerably decreased the uptake of radio-iodine by the thyroid, while after adrenalectomy, the same hormone caused a pronounced increase. In the dog, the inhibitory effects of the adrenal were manifest only after several days of adrenaline treatment. "This apparently represents a species difference . . .".[584b] In the future experiments along these lines, it would be desirable to determine the radio-active iodine uptake at different time-intervals after initiation of adrenaline administration, especially if we accept the view that the hormone may act merely by causing an A-R.[584c] In this event, the thyroid response — as most other changes during the G-A-S — may be triphasic and could accordingly be reversed during the countershock phase. This possibility would be particularly likely if the adrenaline-effect were mediated through the adrenal cortex, as some investigators assume (cf. below). In any event, the data strongly suggest that, during the G-A-S, the response of the thyroid is considerably influenced by the adrenals.

Adrenocortical extract and **DCA** do not appear to affect significantly the uptake of radio-iodine by the rat's thyroid.[584d] Yet, in patients with Addison's disease, the uptake of radio-iodine by the thyroid is low and rises (up to four-fold) following treatment with **cortisone** or adreno-cortical extract. Hence, it was suggested that corticoids facilitate the release and/or action of thyrotrophin,[584e] but preliminary experiments on rats suggested that cortisone inhibits the thyrotrophic effect of adrenaline, as judged by this criterion.[584f] Indeed in normal man and in addisonians, the initial rise in radio-iodine uptake is also followed by a marked depression if treatment with cortisone be continued over four days.[584g] In mice cortisone causes thyroid atrophy.[584h]

Experimental **renal hypertension** is claimed to cause signs of "intense hyperfunction, with the eventual development of exhaustion" in the thyroid of the rabbit. These phenomena have been discussed in relation to the G-A-S,[585] but the exact nature of this purported relationship has not been elucidated.

Thyroid-Diseases of Adaptation

Hyperthyroidism. — It has been noted that hyperthyroidism is often elicited by a **psychic trauma** [586] and is then quite amenable to psychotherapy.

[571] Aufdermaur B34905/47.
[572] Trautmann and Kanther B37154/47.
[572a] Papayannopoulos B45313/49.
[572b] Barclay and Leatham B45641/46.
[572bb] Stock and Currence B47653/50.
[572bc] McArthur et al. B47652/50. Sprague et al. B47651/50.
[572c] Arvy and Gabe B44853/49.
[573] Parchkis et al. B46261/50. Selye 38798/37.
[574] Meites and Reed B27700/49.
[575] Selye **94572/49.**
[576] Schachner et al. B32891/49.
[577] Zenow B28100/44.
[578] Rumyantsev B30295/44
[579] Williams et al. B43573/49.
[580] Prosperi B41943/49.
[581] Selye 66551/36, **B1204/46, 94572/49.**
[582] v. Haam and Frost A30282/39.
[583] Dempsey and Searles A56587/43. Dempsey and Uotila A34573/40, Uotila A30203/39.
[584] Dvoskin B25917/48.
[584a] Reiss et al. B35918/49.
[584b] Soffer et al. B36930/49.
[584c] Paschkis et al. B46261/50.
[584d] Paschkis et al. B46261/50.
[584e] Reiss et al. B35918/49.
[584f] Soffer et al. B36930/49.
[584g] Reiss et al. B46967/50.
[584h] Antopol B47052/50.
[585] Rosselli del Turco and Matteini B37480/47.
[586] Delay et al. B43381/49, Means **A32629/37-38,** 86393/44, Mittelmann B323/35, Moschcowitz B2549/45-46, Ogilvie B36284/49, Rabboni B31300/47, Wilensky B3270/46.

It has repeatedly been stated that in times of war, the incidence of hyperthyroid goitre increases [587] presumably due to emotional stress.[587a] The term "Kriegsbasedow" has been used to designate this condition in the German literature.[588] Yet, during the second World War for instance, it was noted that although the incidence of goitre increased greatly in some countries, it decreased in others. An analysis of these data led to the conclusion "... that environmental factors (as in the alarm reaction) must play some etiologic rôle. What the factors may be, nutritional insults, psychic trauma or a combination of these, is not clear".[589]

In **undernourished** patients, and especially in those suffering from hunger-edema, the thyroid tends to store colloid and appears to be hypofunctional.[589a]

The beneficial effect upon the course of hyperthyroidism of removing a focus of **infection** [590] for instance a chronically inflamed appendix [591] likewise suggests some relationship to the G-A-S. In this connection it has been emphasized that infections, surgical **trauma** (even at a distance from the thyroid), **asthma**, etc. may make a preexistent "latent" hyperthyroidism manifest, or may produce a thyroid crisis.[592] In any event, it is undoubtedly true that various stressors such as emotional shock, infections, exposure to cold, etc., may precipitate hyperthyroidism in predisposed individuals.[593]

Perusal of the pertinent literature leaves the impression that the thyrotrophic effect of stress — like so many other manifestations of the G-A-S — is largely dependent upon incidental conditioning factors (e.g., heredity, diet, age, sex). Thus, an A-R may elicit thyrotoxicosis in "constitutionally predisposed" individuals.[593a] In agreement with this interpretation, one of the most prominent students of thyroid disease concluded that: "I surmise that Graves' disease is somewhat analogous to the adaptation syndrome of Selye except that it is pathological. Perhaps tentatively we might call it a 'maladaptation syndrome' and look on it as a type of response that persons of certain constitutional pattern make when they encounter certain adverse circumstances in living".[593b]

Conversely, hyperthyroidism appears to sensitize the body to the stressor action of various agents, and in particular to the production of "serous inflammation".[593c]

Some **relationship between the adrenal cortex and the development of hyperthyroidism** has been suspected for a long time,[594] but pertinent data are rather contradictory. Thus, one investigator came to the conclusion that the adrenal cortex is usually hypoplastic in patients who died of hyperthyroidism and "if adrenal hypoplasia is characteristic of 'thyroid storm', one may also wonder whether this hypoplasia indicates a failure of adaptation of the organism in the sense of Selye.[595] Another worker claims that "in thyrotoxicosis

[587] Anonymous Editorial **B24161/47.**
Brull **B3031/45.**
Iversen B46863/48, B46859/49,
Meulengracht B44979/49,
Vartiainen B39569/46.
[587a] Grelland B35519/46, Kroch B45082/49,
Rabboni B31300/47,
Schürmeyer and Lagen B45146/47,
Volpe and Zannini B46724/46.
[588] Gattig B29162/44.
[589] Means A32629/48.
[589a] Overzier B45391/48,
Schürmeyer and Lagen B45146/47.
[590] Goia **B25571/46.**
[591] Gallegari B43603/49.
[592] Wilensky B3270/46.
[593] Means **A32629/48,**
Selye **B1204/46, 94572/49.**
[593a] Piulachs and Canadell B46331/50,
Perrault and Vignalou B24170/47,
Taptas B24872/48.
[593b] Means B44084/49.
[593c] Eppinger B37085/49.
[594] Williams **98462/47.**
[595] Le Compte B33139/49.

some of the adrenal changes probably are manifestations of a chronic alarm reaction".[596]

Any effort to find a unifying interpretation for all pertinent observations should also take into account that ACTH and cortisone tend to decrease the B.M.R. and may exert a beneficial effect in hyperthyroidism, especially during a crisis.[596a] They also diminish exophthalmos. Interestingly, among hyperthyroid patients on whom laparotomies were performed for various reasons "contrary to the findings after surgical operations on the thyroid gland, was a group of six whose eyes decreased in prominence after operation".[597]

All these apparently contradictory observations appear compatible with the view that gluco-corticoids help resistance during a thyroid storm and counteract the toxic manifestations of hyperthyroidism. A preëxistent latent adreno-cortical insufficiency may therefore predispose to severe complications in Grave's disease and particularly, to the development of exophthalmos. Hence, it is not unexpected that many patients who die during a thyroid crisis have hypoplastic adrenal cortices, while cortisone and ACTH are beneficial in combatting this complication. If the adrenal cortex is efficient, it undergoes hyperplasia and will thus compensate for the increased corticoid requirement. In this sense, it would largely depend upon the relative proportion of thyrotrophin and ACTH production during stress whether an alarming stimulus would tend to produce hyperthyroidism, or mitigate its complications.

The gluco-corticoids may act upon exophthalmos in particular, through the same mechanism which is also responsible for their beneficial effect upon rheumatoid granulomas. In both cases they apparently help the catabolism of readily dispensable tissue stores of mesenchymal cells and diminish lymph-stagnation and edema.

Hypothyroidism. — Several investigators regard the so-called "thyrotoxic crises" as manifestations of an acute thyroid hormone deficiency. It has been noted that while various stressors (e.g., operations) may elicit a thyrotoxic crisis, they also tend to cause a strongly negative iodine balance, even in normal persons.[598] Infections, traumas, emotional excitement, etc., allegedly increase the "consumption" of thyroid hormone. This leads to "hypothyroxinemia" most readily in patients with Grave's disease, because their thyroid is usually very poor in hormone stores. Therefore, "the hypothesis must be envisaged that hypothyroxinemia can elicit malignant hyperthermic crises following infections or traumas, even in normal individuals".[599]

This type of response has been interpreted as a derailment of the A-R characterized by a particularly severe hyperthermia and tachycardia apparently due to an insufficient thyroid hormone production. In such instances thyroid hormone treatment seems to be of great benefit.[600] A sudden exhaustion of the iodine and thyroid hormone reserves during exposure to stress is thus claimed to be a common cause of derailments of the G-A-S mechanism in man.[601] Yet, the etiology of the thyroid crises is still very incompletely understood and

[596] Williams 98462/47.
[596a] McArthur et al. B45558/47,
Moseley and Merrill B46968/50,
Reiss et al. B46967/50.
[597] Dobyns B28621/45.
[598] Waldenström **B29000/45.**
[599] Mahaux 89939/45.
[600] Romani B41073/49.
[601] Romani and Recht B37860/ND.

many observations suggest that an excess production of thyrotrophic or thyroid hormone may be involved.[601a]

The possible relationship between myxedema and the hyalinoses, should also be considered here. In both there are abnormal deposits of proteinaceous material in the extracellular spaces of mesenchymal tissues. Even paramyloidosis may be a related phenomenon, e.g., the "pseudomyxedema paramyloidosum".[601b]

Testis and Male Accessory Sex Organs

Systemic stress. — Involution of the testis and the male accessory sex organs is a very **characteristic** effect of exposure to systemic stress. The mature spermatogenic cells are particularly sensitive, but in the case of intense and prolonged exposure, all elements of the seminiferous tubules, except the Sertoli cells and the most immature elements of the spermatogenic series (e.g., spermatogonia, primary spermatocytes), disintegrate and many polynuclear giant-spermatocytes appear in the tubular lumina. The Leydig cells also involute and the testis assumes an almost embryonic appearance. Curiously, the normally undeveloped mammary glands of men may enlarge considerably, perhaps due to some derangement in the intermediary metabolism of steroid hormones.[602]

Involution of the testis and accessory sex organs has been seen to occur in the rat under the influence of **traumatic** shock, simultaneously with other manifestations of the A-R, such as thymus involution and adrenocortical enlargement.[603] Similar changes occur in the testes of rabbits, after ligature of the common bile-duct.[603a]

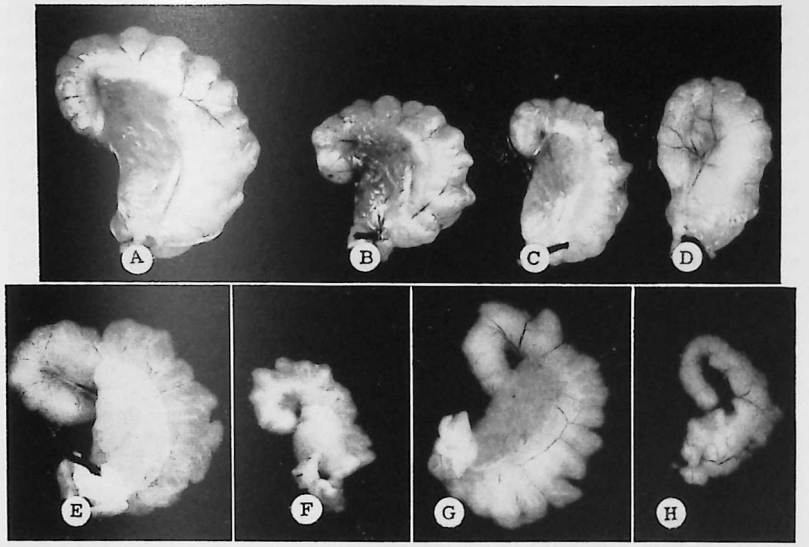
In the past, ignorance of this non-specific effect of stress has repeatedly led to false conclusions concerning the endocrinologic consequences of various operations. For example, it has been thought that the testicular atrophy seen after removal of the head-appendages from cockerels is due to a specific endocrine derangement. However, subsequent systematic investigations led to the conclusion that the gonadal changes "... are likely to be after-effects of the complex changes, which are known to be produced by traumatic shock and by the consequent alarm-reaction".[604]

Exposure to extremes of **temperature** exerts similar effects. Thus, in rabbits exposed to *heat* (diatherm or radiotherm) "necrosis of germinal epithelium, with edema and hemorrhage in the interstitial tissues, was found in the testicles of the animals exposed from 8 - 40 hours to high fever. The nuclei of the germinal epithelium showed changes varying from simple pyknosis to complete lysis. Giant cells with dense peripheral nuclei and hyaline cytoplasm were frequently present. Acidophilic cell debris filled the lumina of the tubules. The changes seemed to affect the spermatids first, the spermatocytes second, and the spermatogonia last. Frequently an intact layer of spermatogonia could be found in tubules in which all other elements were destroyed. The interstitial cells showed only a slight swelling with some vacuolar degeneration."[605]

[601a] McArthur et al. B45558/47, Selye 94572/49.
[601b] Miescher B36161/45.
[602] Selye B1204/46, 94572/49.
[603] Foglia and Houssay A56602/42.
[603a] Rosselli del Turco and Matteini B37479/49.
[604] Landauer A38215/42.
[605] v. Haam and Frost A30282/39.

Similar lesions were observed in the testes of men who died during fever therapy.[606]

It is true that the seminiferous epithelium is more heat-sensitive than most tissues; however, these effects are not specifically due to heat only, since we found that exposure to *cold* causes identical lesions in the testicle of the rat.[607]



Effect of G-A-S upon seminal vesicles of the rat. — **A.** Seminal vesicle of normal rat killed as control for B, C and D in which an A-R was produced by exposure during 48 hours to the stressor effect of: — **B.** transection of the spinal cord at the level of the 7th cervical vertebra, — **C.** exposure to cold (+2 C°), — **D.** repeated forced muscular exercise while food was withdrawn. — **E.** Control for F. — **F.** Seminal vesicle of rat exposed to cold during 15 days and exhibiting manifestations of the resistant phase. Note that decrease in the size of this accessory sex organ (presumably due to diminished LH formation) can occur even during resistant phase, presumably due to "shift in pituitary hormone production". — **G.** Control for H. — **H.** Seminal vesicle of a rat exposed to cold during 30 days and exhibiting manifestations of the exhaustion phase. Note that here the involution is particularly severe. (After Selye 35935/ND.)

Ionizing radiations, such as x-rays, produce essentially similar lesions in the testes of various animals and man. These changes are particularly severe if the testis itself is exposed, but they also occur if intense systemic damage is caused by exposure of other somatic regions to the effect of the rays.[608] They were noted for instance among the Japanese exposed to the effect of the atomic bombs.[609] Here "the testes showed intense changes in almost every cadaver. As early as the fourth day, when the parenchyma had a normal appearance grossly, the histologic sections presented marked injury of the germinal epithelium, numerous cells of which were necrotic and free in the tubules and

[606] Gore and Isaacson B41903/49.
[607] Selye 35935/ND.
[608] Selye 94572/49.
[609] De Coursey B38048/48.

even in the rete testis. The number of mitoses was small. Sertoli's cells were increased in number. Mature spermatozoa were found even in later specimens with no spermatogenesis. Apparently uninjured spermatozoa appeared in the seminal vesicles. In the second month, gross examination revealed little. A few necrotic germ cells remained, but most had disappeared, and phagocytic or infiltrating inflammatory cell activity was absent. A few bizarre cells still approximating the basal membrane appeared to be spermatogonia. Sertoli's cells were more numerous. The tubules had started to shrink. At this time also the interstitial cells of Leydig were so prominent that some interpreters considered them hyperplastic. Some of the small interstitial vessels showed the most marked vascular change of any part of the body. Beneath the distinct, thin endothelium was an eccentrically located mass of eosinophilic, homogeneous, refractile material that almost occluded the lumen. This change was often best seen near the tunica albuginea and was present also in the third and fourth months. The interstitial tissue was less, but still prominent. The basement membranes were quite thick, wavy and acellular. The tubules, more atrophic at this stage, were often hyalinized. Elsewhere Sertoli's cells had replaced the germ cells, which were rare. In the third and fourth months the state of nourishment was poor and specimens from the Dachau prison camp in Germany have been described as showing similar testicular changes".[610] Yet, even the testicular lesions caused by neutron bombardment are reversible, if the damage is not too severe.[610a]

In various animal species ionizing radiation produced the same changes. Here again the great radio-resistance of the interstitial cells was very striking.[613]

Nervous stress likewise causes characteristic G-A-S changes in the testis. Thus, intense degeneration of the seminiferous epithelium, with the formation of polynuclear giant spermatocytes, has been noted in men who committed suicide or were executed. Here, the emotional strain preceding death was considered to be the responsible stressor agent.[611]

In paraplegic men, excessive development of the breasts may occur and it was concluded that: "it is not unlikely that the adaptation-syndrome with its consequent hypopituitarism, might be instrumental in bringing about hypogonadism, and thereby contribute to the pathogenesis of gynecomastia in paraplegia due to traumatic injuries of the spinal cord".[612]

Somewhat comparable lesions were observed in rats exposed to **anoxia**;[614] this was accompanied by infertility as long as exposure was continued.[615] The response is reversible, however, since testis structure and fertility returned to normal following an adequate rest period.[616] It is also noteworthy that in the case of discontinuous exposure to mild reduction in atmospheric pressure, the testis weight may remain normal, although the seminal vesicles involute considerably and fertility is reduced.[617] Curiously, the sensitivity of the interstitial tissue to anoxia appears to vary considerably in different species. It is allegedly great in the mouse and very slight in the rabbit.[618] The males of various animal species and men become sterile when transferred to high alti-

[610] Anonymous B28192/48, B26330/48.
[610a] Robinson and Engle B46040/49.
[611] Selye **94572/49.**
[612] Cooper and Hoen B36868/49.
[613] Bloom B31225/48.
[614] Altland B24783/46.
[615] Altland B24782/48.
[616] Altland B24782/48, B39237/49.
[617] Altland B24781/47.
[618] Buraczewska B39662/48.

tudes (e.g., in the Andes). In agreement with the G-A-S concept, fertility tends to return after a period of adaptation.[619]

It has long been known that many **spontaneous diseases** of man can also result in testis atrophy. This is often accompanied by the formation of polynuclear spermatocytes, with disintegration of spermatids and spermatozoa. Systematic studies of this reaction led to the conclusion that they are probably part of the G-A-S [620] and should not be ascribed to specific actions upon the male gonad. This interpretation has also been considered in connection with the pathogenesis of *cardiac infantilism* [621] and *hepatic infantilism*.[621a]

The testis involution tends to be particularly severe — and is often accompanied by gynecomastia, decrease in axillary hair and diminished libido — in patients suffering from *Laënnec's cirrhosis*. Here, the participation of a specific effect is difficult to exclude since the liver plays such an important rôle in the detoxification of steroid hormones. Yet, it is noteworthy that in most of these cases with testicular atrophy, autopsy also revealed a marked decrease in the adrenal lipids, such as occurs during certain stages of the G-A-S.[622]

Suffice it merely to mention that various **drugs**, given in doses capable of producing a G-A-S, cause similar testicular involution. This has been found to be the case in rats after administration of *formaldehyde* [623] or *nicotine*,[624] in guinea-pigs exposed to *carbon monoxide*,[625] in rabbits given *ascaris toxin* [626] and in many other intoxications.[627]

The fact that various **dietary insufficiencies** cause a similar type of sex organ involution is too well known to deserve a detailed discussion here. While certain deficiencies (e.g., E-avitaminosis) undoubtedly exert a specific effect upon testicular structure, most types of malnutrition appear to affect the male gonad merely due to the development of a G-A-S.[628]

This may explain the frequent occurrence of testis atrophy, loss of libido and gynecomastia among inmates of concentration camps.[629] In one series of 300 **undernourished** prisoners of war, 15 were found to have testicular atrophy and all had complete loss of libido and potency. 36 had manifest gynecomastia at the time of observation while another 12 had had it before. Curiously, the gynecomastia often appeared or was aggravated immediately upon return to a normal diet, but after the general condition of the patient improved, the gynecomastia disappeared. The participation of deranged hepatic function in the pathogenesis of this gynecomastia has been considered but could not be definitely proven.[630]

Lack of certain **amino-acids** (e.g., tyrosine, phenylalanine) also produces testicular lesions in the rat. These are essentially the same as those which we consider to be characteristic of the G-A-S. It is noteworthy, however, that the authors who described these observations did not interpret them in this sense.

[619] Monge B27662/48.
[620] Moricard B30942/48
[621] Rosselli del Turco and Matteini B37835/48.
[621a] Rosselli del Turco and Matteini B37835/48, B37479/49.
[622] Lloyd and Williams **B24306/48.**
[623] Selye A31127/40, Selye and Friedman A34228/41.
[624] Wilson et al. A18094/38.
[625] Cameron B32988/49.
[626] Simonin B12416/22.
[627] Selye **94572/47.**
[628] Selye **94572/49.**
[629] Jacobs B25095/48, B45781/48, Koecher B37757/49, Overzier B36851/49, B45391/48, Steinbrinck B27374/48, Trautmann and Kanther B37154/47, Uehlinger B24304/47, B27612/48.
[630] Salter et al. B24286/46.

They suspected that, for instance, the polynuclear giant spermatocytes in the seminiferous tubules of tyrosine-deficient animals are specifically due to lack of this amino-acid.[631] Of course it is tempting to ascribe a change caused by tyrosine deficiency directly to the lack of this food constituent and to postulate its indispensability for the formation of normal spermia. Yet, in the light of the G-A-S concept, the testicular lesion is not due to lack of tyrosine per se, but to the adaptive adjustment elicited by the resulting stress. It is clear that here — as in so many similar instances — the interpretation of the observed facts is completely altered if we take the G-A-S into account.

It is especially noteworthy that, for instance in rats, **overfeeding** likewise can cause testis and seminal vesicle atrophy, possibly due to the resulting G-A-S.[632]

Stimuli Influencing the Response of the Testis and Male Accessory Sex Organs During the G-A-S. — It is generally assumed that systemic stress produces testicular atrophy, due only to a diminution of gonadotrophin secretion. In agreement with this assumption, **hypophysectomized** animals show most severe involution both of the seminiferous epithelium and of the Leydig cells; in them the process is not further aggravated by exposure to non-specific stress.[633] However, hypophysectomized animals spontaneously take little nourishment and tend to lose weight. Hence it is of special importance to note that in rats force-fed with approximately normal quantities of food after hypophysectomy, the involution of the testes and accessory sex organs was not influenced, although the body weight increased.[634]

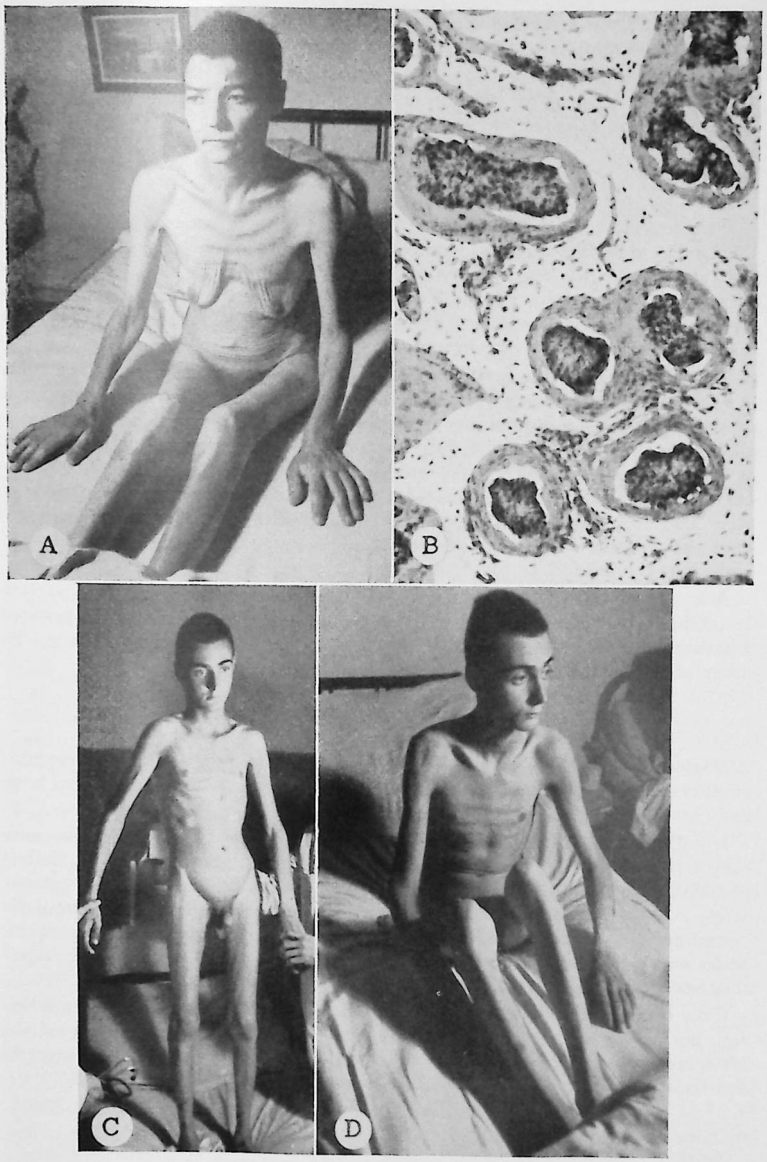
The possible influence of **hypophyseal stalk transection** upon the testicular involution during the G-A-S (e.g., that caused by exposure to cold) has been investigated. The interpretation of pertinent results is difficult, however, because the operation in itself often tends to cause testis involution.[635] Perhaps this is due to the stress of the operation or to incidental lesions to the anterior-lobe: further work will be necessary to clarify this point.

ACTH, allegedly inhibits the development of the seminal vesicles and prostate, in testosterone-treated castrate rats,[635a] but this may merely reflect the general catabolic actions of the resulting gluco-corticoid discharge. Certain impure corticotrophic preparations actually stimulate the growth of the accessory sex-organs, even after castration, presumably because they increase the production of testoids by the adrenal cortex.[635b]

Administration of anterior pituitary **gonadotrophins** restores the testis even in the hypophysectomized animal. FSH is necessary for the maintenance of the spermatogenic epithelium, LH for the structural integrity and endocrine secretion of the Leydig cells.[636] Suitable mixtures of FSH and LH maintain the testes of rats exposed to a variety of systemic stresses.[637] **Growth hormone,** on the other hand, appears to aggravate the testicular involution, for instance, during the stress of partial starvation.[638]

Spermatogenic steroids (e.g., testosterone, Δ^5-pregnenolone) inhibit the involution of the seminiferous epithelium normally caused by non-specific stress (e.g., formaldehyde injections, folliculoids). In the case of **testoids,**

631 Scott et al. B33026/49.
632 Ingle and Nezamis 98817/47.
633 Selye **94572/49.**
634 Levin A71832/44.
635 Brolin 91168/45.
635a Hase and Schindel B43389/49.
635b Selye 94572/49.
636 Selye **94572/49.**
637 Selye 35935/ND.
638 Quimby B19203/48.



Involution of sex organs during starvation in man. — A. 28-year-old female, concentration camp inmate with severe cachexia. Note marked atrophy of the breasts. — B. Testis of 23-year-old concentration camp inmate with hunger edema. Note marked involution of seminiferous tubules and Leydig cells. — C. and D. 19-year-old concentration camp inmate with infantilism and cachexia. (After Hottinger et al. B31235/48.)

this is true only if large doses are given. None of the spermatogenic steroids prevent the involution of the Leydig cells.[639]

Even in rats not exposed to stress, small doses of testosterone cause testis atrophy while large doses have an inverse effect.[640] It is not within the scope of this book to examine the cause of such peculiar dose-effect interrelations among the testoids, especially since we discussed them elsewhere.[641] They are mentioned here only to emphasize that a spermatogenic effect during the G-A-S can only be expected from high doses of testoids.

Overdosage with **DCA** causes involution of the seminiferous epithelium and the Leydig cells in various experimental species. In animals especially sensitized to this mineralo-corticoid by unilateral nephrectomy or high sodium diets, there may also develop serious vascular changes and intense edema of the testis.[642] DCA, desoxocortisone or cortisone exert no stimulating effect upon the accessory sex-organs of male castrate rats.[642a]

It is particularly noteworthy that in **castrate male** rats the production of an A-R with marked suprarenal hypertrophy is unaccompanied by any stimulation of the accessory sex organs. "It is concluded that the adrenal cortical hypertrophy, so characteristic of the alarm-reaction, is not accompanied by increased sex hormone production".[643] Yet estrone apparently can stimulate the accessory sex organs of orchidectomized rabbits to undergo changes similar to those elicited by small doses of testoids; hence in this species we must admit "the possibility of an indirect production of endogenous testoids due to stimulation of the adrenal cortex by estrogen".[644]

Allegedly the testicular lesions caused by starvation in the rabbit are partially inhibited by **vitamine E,** but not by **vitamine A.**[645] It remains to be seen whether vitamine supplements would influence the testis damage caused by other stressors.

Testicular Diseases of Adaptation.

Various types of hypogonadism are probably due to a diminution of gonadotrophin secretion during stress, when the pituitary has to produce large amounts of ACTH to maintain life.

It will not be necessary to discuss such derangements in detail here, since they have already been considered in the preceding pages. Let us merely reiterate that, in man, the most common consequence of exposure to systemic stress are: loss of libido and potency, involution of the testis with particularly severe degenerative changes in the more mature elements of the spermatogenic series and a tendency to develop gynecomastia while the typically male accessory sex organs involute.

Only severe and prolonged stress can induce the picture of actual eunuchoidism, but many common, minor "psychosomatic" sexual derangements of the male are probably the result of abnormal adaptive responses to the stresses and strains of daily life and therefore primarily diseases of adaptation.

[639] Selye A31127/40, **94572/47,** Selye and Albert A38086/42, Selye and Friedman A34228/41.
[640] Selye A35221/41.
[641] Selye **94572/49.**
[642] Selye A55847/42, B1204/46, Selye and Hall A56583/43.
[642a] Selye B41762/49, 35935/ND.
[643] Albert A55477/42.
[644] Bern B38384/49.
[645] Chevrel-Bodin and Cormier B37153/48, B36311/49.

Ovaries, Female Accessory Sex Organs, the Sexual Cycle, Pregnancy and Lactation

Systemic stress. — Experiments in the rat suggest that the **characteristic** response of the female sex organs to systemic stress (e.g., muscular exercise, qualitatively or quantitatively inadequate diets, toxic doses of various drugs) manifests itself mainly by *ovarian atrophy* and more or less permanent *anestrus.* These changes are related to the G-A-S, since upon continued exposure to stressors, the ovary returns towards normal and vaginal cycles reappear as soon as adaptation becomes adequate. The change was ascribed to the well-known "shift in anterior-lobe hormone production", which consists in a diminution of gonadotrophin secretion at a time when a greatly increased elaboration of ACTH is indispensable for the maintenance of life under stress. During the anestrus of the G-A-S, the ovarian atrophy may become just as severe as after hypophysectomy. Even the "wheel cells" characteristic of severe hypophyseal insufficiency tend to appear in the theca. On the other hand, though the anestrus be permanent, follicle maturation and corpus luteum formation may continue in animals which are not especially severely damaged. Under these conditions, usually only one or two (instead of the normal 10-12) follicles are transformed into corpora lutea at each ovulation. Apparently this *"anestrus ovulation"* is a counterpart to the so-called "anovular cycle". Corresponding changes in women have been designated as *"amenstrual ovulation".*[646]

It is interesting that in certain fishes, such as the bitterling (Rhodeus Amarus), *nuptial coloring* and lengthening of the *ovipositor* occur under the influence of various non-specific stressors (e.g., intoxications with drugs, exposure to cold). These changes can also be produced by various steroids and they have been used as the basis for the bioassay of endocrine principles (e.g., corticoids, folliculoids, luteoids). However, the results of systematic investigations concerning these tests have been summarized as follows: "As there is a marked resemblance between the observations of Selye in mammals and those in the bitterling, the hypothesis is suggested, that in the bitterling, experimental ovipositor lengthening is the visible expression of an alarm reaction".[647] This interpretation does not imply that the ovipositor lengthening (or the nuptial coloring) is independent of steroid hormones, but merely that such indicators cannot be regarded as specific of certain steroids since similar hormones are endogenously liberated as part of the G-A-S.

It is highly probable that in women, decreased gonadotrophin production with the resulting ovarian atrophy, derangements or complete cessation of the *menstrual cycle,* and in milder cases, at least *a delay in puberty or acceleration of the menopause,* also occur during the G-A-S as a result of the "shift in anterior-lobe hormone production".[648]

Statistical studies reveal that in the course of the last 100 years the average human life span has been prolonged by about 6 to 8 years, puberty accelerated (from 16.5 to 14.6 years of age) and the menopause retarded (from 40 to 48 years of age). This is ascribed to the fact that living conditions have improved

[646] Selye A18343/39, 74721/39.
[647] van Koersveld B19396/47, B38414/48, B30935/49.
[648] Bieler **78340/40.** Selye **94572/49,** B1204/46.

drug acts by eliciting a G-A-S, but curiously, the adrenals are not noticeably enlarged [668] so that some specificity in the effect of this drug must be considered.

Picrotoxin, given in large doses, induces ovulation in rabbits.[669] It remains to be seen whether this is a specific effect since electrical stimulation, or treatment with various other acutely toxic drugs, may likewise elicit a single ovulation before the ovary undergoes atrophy.[670] Special importance has been attached to the observation that *dibenamine* blocks the discharge of gonadotrophin from the anterior-lobe which normally occurs after treatment with folliculoids,[671] but even the specificity of this blocking action has been questioned.[672]

Perhaps the most systematic studies along these lines have been performed with *folliculoids*, which, if given in large doses at the right period of the cycle, will elicit a single ovulation, but subsequently induces ovarian atrophy.[673] The possible relationship of this biphasic reaction to the G-A-S would deserve further study.

Malnutrition (whether qualitative or quantitative) is notoriously conducive to ovarian atrophy and cessation of the sexual cycle. Here again, the change has long been recognized as being due to the "hypophyseal shift" incident to the G-A-S.[674]

It will also be recalled that ovarian atrophy is part of the *"pseudo-hypophysectomy"* syndrome which results from chronic undernutrition in rats. Observations in this species led to the conclusion that: "the starved rats reacted as if they had been hypophysectomized in that ovaries, uteri and vaginal epithelium underwent marked atrophy. They did not differ from hypophysectomized rats as concerns their potential capacity to respond to exogenously administered gonadotrophins since administration of rat pituitary suspension, rich in gonadotrophins, restored ovarian, uterine and vaginal cells to normal. Therefore, the conclusion that the circulating blood was low in gonadotrophin content seems warranted".[675] Judged by observations on chronically undernourished rats it appears that the gonadotrophin content of the anterior-lobe actually increases while the ovaries involute and the estrus cycle ceases. Presumably the discharge of gonadotrophins is even more markedly impeded by stress than their production.[676]

In the case of the so-called *"war amenorrhea"* (closely related to "Fluchtamenorrhoë", "Arbeitsdienstamenorrhöe" or "Ghettoamenorrhöe" of the German investigators),[677] it is often difficult to determine the relative rôle played by undernutrition, emotional upsets and other stressors. Most investigators agree, however, that this phenomenon is due to a systemic stress effect.

Such amenorrhea and ovarian atrophy was often seen among inmates of various concentration camps during the second World War.[678] According to

[668] Cranston B27853/45, Noble and Plunkett B39692/49, Plunkett and Noble B39695/49.
[669] Kasdon B33142/49.
[670] Selye **94572/49.**
[671] Everett et al. **B33144/49.** Sawyer et al. B33143/49.
[672] Nickerson B33150/49.
[673] Selye **94572/49.**
[674] Selye 74721/39, **A18343/39.**
[675] Maddock and Heller **B17565/47.**
[676] Rinaldini B36690/49.
[677] Overzier B27372/48, Sweeney et al. B2459/47.
[678] Bass B26564/47, Copelman B38868/48. Heynemann B34571/48, Hirscher B45240/48, Horvath et al. B38867/48, Overzier B27372/48, Sendrail and Lasserre B37450/48, Stieve A57136/42, Stroink B39349/47, Uehlinger B24304/47, **B27612/48.**

one survey in the women's camp at Theresienstadt, 54 cent cent of the 10,000 inmates ceased to menstruate, 60 per cent in the first month of the imprisonment, 35 per cent in the second and 8 per cent in the third month. In one small group of women who were better housed and not in danger of their lives, only 25 per cent had amenorrhea. Menstruation usually returned spontaneously after some time, although the nutrition became worse. After about 18 months, 94 per cent of the women recommenced menstruation.[679] These observations again suggest that the amenorrhea is connected with the "alarming effect" of the stress (malnutrition, fear) and vanishes after adequate adaptation has been acquired.

Systemic investigations during the second World War also revealed the great frequency of "war amenorrhea" in Holland.[680] It was found that: "the severe undernutrition of the winter of 1944-45 in Northwestern Holland was marked by the following effects upon pregnancy and the fetus: (1) amenorrhea and infertility were so common as to reduce strikingly the expected number of births; (2) infants conceived before the hunger months, but born during them, were significantly below the expected weight and length." In this series, lactation was not manifestlv affected nor was there an increase in the incidence of pregnancy toxemia, stillbirths or neonatal deaths. The frequency of congenital malformations and premature birth was slightly, but not significantly, increased.[681]

Curiously, the ovarian atrophy and infertility due to senescence is delayed in mice temporarily kept on a restricted caloric intake.[682] Here, one gains the impression that the interruption of sexual life, due to undernourishment, merely "saved" fertility for a later time.

Stimuli Influencing the Response of the Female Sex Organs During the G-A-S. — Both in animals and in man, **hypophysectomy** completely abolished the sexual cycles, due to a severe involution of the ovaries. Since systemic stress causes ovarian involution by diminishing the gonadotrophin secretion of the hypophysis, its effect is not demonstrable after ablation of the pituitary. On the other hand, all these deficiencies can be corrected in hypophysectomized animals by adequate gonadotrophin therapy.[683]

Contrary to earlier claims,[684] **transection of the pituitary stalk** greatly affects ovulation, pregnancy and lactation in the rat, as well as in various other species.[685] It is interesting, however, that "the depressing action of cold upon the reproductive cycle and the ovary is abolished by pituitary stalk section" in the rat.[686] This was interpreted to mean that severance of the connection between hypophysis and hypothalamus influences the rate of production of gonadotrophic hormones in the rat.

Gonadotrophins exert their normal stimulating effect upon the rat ovary even when the latter became severely atrophic as a result of starvation [687] and other alarming stimuli (e.g., muscular exercise, qualitative or quantitative malnutrition).[688]

[679] Bass B26564/47.
[680] Smith B26642/47.
[681] Smith B23097/47.
[682] Carr et al. B32717/49.
[683] Selye **94572/49.**
[684] Dempsey and Uotila A34573/40.
[685] Harris B47511/49, Selye **94572/49.**
[686] Dempsey and Uotila A34573/40.
[687] Carr et al. B32717/49. Maddock and Heller B17565/47, Rinaldini B36690/49.
[688] Selye A18343/39.

Experiments on **ovariectomized** rats indicate that the responsiveness of the vagina to folliculoids is not significantly influenced by the G-A-S.[689] Hence, we may conclude that the sensitivity of the sex organs is not markedly depressed by systemic stress and their atrophy is conditioned mainly by a diminution of gonadotrophin (and subsequently ovarian hormone) secretion. However, certain observations on ovariectomized rats, given threshold doses of estradiol, suggest that the uterine response to this folliculoid is somewhat inhibited following injection of corticoids or corticotrophin and immediately after exposure to severe stress, such as cold or partial hepatectomy. The possibility has therefore been envisaged that large quantities of corticoids produced at times of intense systemic stress might counteract the peripheral effects of folliculoids. Yet the inhibition of folliculoid activity immediately after partial hepatectomy was not completely prevented by adrenalectomy, hence it is probably, at least in part, due to loss of liver tissue.[690]

In ovariectomized rats in which an A-R was produced by subcutaneous injection of formaldehyde, the uterus and vagina showed no signs of stimulation even when the adrenal-cortical enlargement became very manifest. "It is concluded that the adrenal-cortical hypertrophy, so characteristic of the alarm reaction, is not accompanied by increased sex hormone production".[691]

In **partially ovariectomized** rats the compensatory hypertrophy of the remaining gonad is prevented by the "spinal shock" which ensues after transection of the spinal cord.[692]

It has been claimed that **adrenalectomy** inhibits the formation of atretic follicles in x-ray treated rats, even if the ovary is directly exposed to the rays.[693] This observation is so unexpected, however, that it would require confirmation.

Overdosage with **corticoids,** particularly with cortisone, causes complete ovarian atrophy, with "wheel-cell" formation in the rat. This is presumably due to an inhibition of hypophyseal gonadotrophin secretion.[693a]

Ovarian Diseases of Adaptation

From the preceding discussion it is evident that the development and function of the ovary is inhibited by systemic stress. Certain types of **delayed puberty,** e.g., "cardiac infantilism", have been related to the G-A-S and may be regarded as diseases of adaptation,[694] in this instance, adaptation to the cardiac defect.

If exposure to stress commences after the onset of puberty, temporary **amenorrhea** and diminished fertility can ensue (for literature see preceding pages).

Pregnancy Diseases of Adaptation

Certain similarities between the syndrome produced by overdosage with mineralo-corticoids and **eclampsia** have raised the suspicion that the latter may also be a *disease of adaptation.*[695] In both instances, there is a renal

[689] Selye A18343/39.
[690] Szego and Roberts B24576/48.
[691] Albert A55477/42.
[692] Aron et al. B37807/48.
[693] Ickowicz B17562/47.
[693a] Selye 35935/ND.
[694] Rosselli del Turco and Matteini B37835/48.
[695] Parviainen et al. B44269/49, B46924/50, B46923/50, Selye B1204/46.

type of hypertension and widespread hyalinosis which tend to be aggravated by an excess of sodium. Significantly, rest — and indeed protection against even the mildest stressors, such as light or noise — has empirically been found to be of value in the treatment of eclamptic women.

The non-specificity of the glomerular lesions in eclampsia has long been noted.[696] The similarity between the organ changes observed in animals treated with "menstrual toxin" and those characteristic of the A-R has also been emphasized. Furthermore, treatment with *corticoid* extract is allegedly beneficial in patients suffering from eclampsia (cf. p. 127). Hence, it was concluded "that adrenal cortical exhaustion may play a part in the alarming rapidity with which clinical manifestations may increase in severity in the preeclamptic patient. Up to a certain point, overactivity of the adrenal cortex may combat the 'toxin' as in the first stages of the 'alarm reaction'...".[697]

There are many other observations suggesting some degree of hypocorticoidism. Thus, it has been found that in cases of fatal eclampsia the adrenals are often small.[698] Eclampsia may even occur in women suffering from Addison's disease. In one such patient who received DCA treatment, the manifestations of the toxemia did not disappear after withdrawal of the steroid therapy, yet, it was concluded that in such instances DCA is contraindicated.[699]

The urinary elimination of ACTH has so far not shown any great deviations from the normal in eclamptic women,[700] but systematic studies with specific tests have not yet been performed.

Excretion of "formaldehydogenic" corticoids in the urine allegedly rises, especially in edematous toxemic women. "Although this conclusion cannot be considered established until a larger series of patients has been studied, the findings may afford a partial explanation for the similarity of pre-eclampsia to desoxycorticosterone intoxication".[701] On the other hand, the gluco-corticoid elimination (as judged by the glycogen-deposition test) is subnormal in eclamptics as compared with normal pregnant women,[702] though during the crises it may rise to very high levels.[702a]

Pregnancy enhances the susceptibility of the rat to renal damage produced by anti-placenta serum. The nephritis so produced is further intensified by DCA. Indeed, the pressor and nephrotoxic action of anti-placenta serum is augmented by DCA, even in the non-pregnant rat. However, unlike in human toxemias of pregnancy, emptying the uterus did not prevent the progress of these renal and hypertensive lesions in the rat. "For this reason, the observed increased susceptibility of the kidney of the pregnant rat, to the action of nephrotoxic serum and DCA, is perhaps more analogous to the acceleration of chronic nephritis in human beings, which is frequently observed during or following intercurrent pregnancy".[702b]

An attempt has also been made to correlate pregnancy toxicosis with the G-A-S through the so-called *"exaggeration phenomena",* the sudden exaggeration of previously existing latent changes by some sudden stress. However,

[696] Christian A56705/42.
[697] Smith and Smith 81127/41.
[698] Fauvet A58136/36.
[699] Cohen B43624/48.
[700] Fauvet and Munzner B10442/37.
[701] Tobian B18628/48.
[702] Venning and Browne B43464/ND.
[702a] Devis and Eeckhoudt B46892/49, B44570/49.
[702b] Loeb et al. B41168/49.

this interpretation has not yet been developed in sufficient detail to permit its adequate evaluation.[703]

Attention has also been called long ago to the remarkable similarity between the syndrome of eclampsia and that produced experimentally in animals by *vasopressin* overdosage.[704] In the rat, the toxic actions of this hormone are greatly augmented by simultaneous administration of folliculoids; since the latter are produced in large amounts during gestation, this was again interpreted as suggesting some relation between the toxicoses of pregnancy and vasopressin production.[705] An attempt has been made to connect the vasopressin theory of eclampsia with the G-A-S. It has been pointed out that during the siege of Budapest (1944-45), when the population withdrew to air-raid shelters, the incidence of eclampsia rose from 2.5% to 10.6%. On the basis of indirect evidence, this was ascribed to an increased vasopressin formation resulting from exposure to stress,[705a] but further data would be required to prove this point. It is interesting, however, that under similar war-time conditions in Italy, a "war nephritis" with hypertension has been described in people who were forced to live underground during long periods of time; here again, the condition was interpreted as a disease of adaptation.[705b]

Other observations pointed to *anterior-lobe hormones* as possibly important factors in the pathogenesis of eclampsia. It was emphasized that in eclamptics, the anterior-lobe basophils tend to conglomerate into large clumps, "in the light of recent evidence which indicates a distinct relation of the basophils to hypertension and to hyperplastic changes in the adrenal cortex, these observations may be significant".[706]

Allegedly it is possible to reproduce an experimental disorder resembling toxemia in pregnant rabbits by giving crude anterior-pituitary extracts, or partially purified LH, during the later part of gestation. Here fatty degeneration and bilateral cortical necrosis were found in the kidney; some necrotic lesions were also seen at the cortico-medullary borderline of the adrenals.[707] However, the blood-pressure dropped and the entire clinical picture was admittedly not identical with that of clinical pregnancy toxicosis.

Various other investigations pointed to a *humoral origin* of eclampsia.[708] Thus, the great pathogenic rôle played by angiospasm has been emphasized and the view was expressed that the word "toxin" in respect to toxemia of late pregnancy "will probably in time be supplanted by the word hormone".[709] This view received confirmation by clinical tests with TEA, which, "by blocking the autonomic nervous system at the ganglia, eliminated neurogenic tone but does not lessen humoral tone, the results suggest that the hypertension of toxemia of pregnancy is supported by an excessive degree of humoral tone".[710]

It has also been asserted that "nephrin" (a pressor substance of the kidney not identical with renin, adrenaline, tyramine, hydroxytyramine or vasopressin) is present in the blood in excessive amounts during eclampsia.[711]

It would not be within the scope of this review to discuss the entire extensive literature on the possible humoral origin of pregnancy toxicoses, especially

[703] Wilensky B3270/46.
[704] Hofbauer **B23092/46.**
[705] Byrom **A8247/37. A9905/38.**
[705a] Kekete B44856/49.
[705b] Bassi B37375/46.
[706] Hofbauer B23092/46.
[707] Greene A30174/39.
[708] Pigeaud and Dumont B24548/47.
[709] Whitacre et al. B38031/47.
[710] Brust et al. B29409/48.
[711] Enger B19358/47.

since this has recently been done elsewhere.[712] Nevertheless, we wish to point out that mineralo-corticoid intoxication probably simulates eclampsia more closely than any other experimental procedure so far employed and that there is considerable evidence pointing to a diminished gluco-corticoid production in women suffering from eclampsia. The therapeutic efficacy of synthetic gluco-corticoids has not yet been adequately investigated, but it would certainly deserve attention, because a derangement in $\frac{\text{gluco-corticoid}}{\text{mineralo-corticoid}}$ quotient appears to participate in the pathogenesis of this disorder. Undoubtedly, the placenta is the source of the pathogenic humoral stimulus, since its removal from the body is so rapidly followed by the disappearance of the symptoms. It remains to be seen, however, whether the humoral agents act merely as allergens whose toxicity is not adequately neutralized by gluco-corticoids, or whether the placenta actually produces toxic amounts of mineralo-corticoids. Apparently here, as in so many other allergic or hyperergic diseases, the principal cause of the derangement is a disproportion between the amount of toxic allergen produced and the ability of the adrenal to cope with these by increased gluco-corticoid production.

Theories Concerning the Participation of the Endocrine Glands in the G-A-S

The endocrine glands play a very important and rather complex rôle in the development of the G-A-S and its diseases. In this chapter we shall make no effort to quote all pertinent data, since an extensive survey of the relevant literature has already been given in the preceding pages. Here we merely plan to attempt an integration of the known facts into a dynamic concept of the endocrine interrelations during stress, citing but a few sample papers in which the various theoretical problems have been formulated from different points of view.

Unquestionably, for many students of this field, one of the most confusing tenets of the G-A-S theory is **that the same systemic reaction to stress should be capable of eliciting so many apparently unrelated "diseases"** under different conditions. It is difficult to understand at first why exposure to stress can lead either to hypo- or to hypertension, to a loss or an increase in adrenal-lipids, to dilatation or constriction of peripheral vessels and so forth, all through the same reaction to stress. It is perhaps even more confusing that at will, certain typical manifestations of the G-A-S (or some of its pathologic derailments) can be inhibited, while others are exaggerated, in an individual exposed to a standard stress. A recent symposium concerning this general subject illustrates this confusion. It was summarized as follows: "in conclusion we must accept the 'alarm reaction' and the resulting phenomena produced; we must admit that in some way, the hypophysis and the adrenal cortex may be concerned in this reaction; but we are still obliged to hold reservations regarding the concept of 'diseases of adaptation'. There is abundant evidence indicating that the adrenal cortex, although concerned in the 'alarm reaction', may not be essential for all the signs and symptoms which follow stress".[713]

[712] Smith and Smith **B17982/48.**
[713] Loeb et al. B36597/49.

In discussing the theory of resistance to systemic stress (cf. p. 196) we placed special emphasis upon the fact that any stressor causes both *systemic damage* and *systemic defense* in addition to its own *specific actions*. The clinical picture resulting upon exposure will obviously depend upon the summation of all these actions on each individual target organ. The picture is further complicated by the fact that the systemic defense reactions are transmitted through a number of intermediate stations, whose responsiveness is largely dependent upon *conditioning factors*, such as heredity, the availability of metabolites necessary for their function and so forth. Only if all these modifying influences are kept in mind can the essence of the G-A-S concept really be grasped.

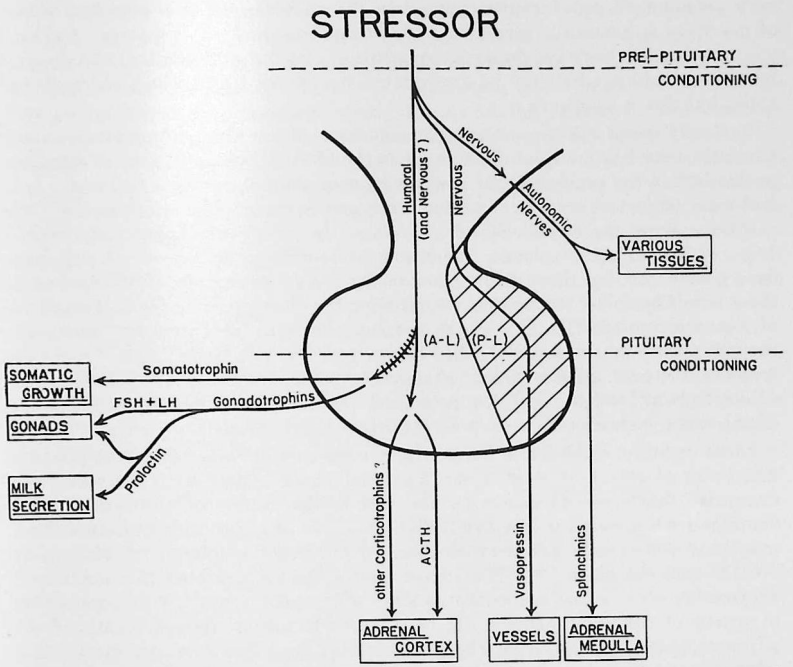
Let us illustrate this with an example taken from every day life. In the electric network of a city, the result of generating current will be light, cold, heat, motion, sound, etc., depending upon the condition of the receptor organs (the electric light bulbs, refrigerating plants, heaters, radio receivers, gramophones, bells, etc.) and upon the integrity of the wires which conduct the current to them. It is a matter of common observation that, during dark hours much of the current will be used to generate light, during the winter season to produce heat, during the summer to refrigerate and so forth. Nevertheless no one will doubt that the underlying basic mechanism is always the same and that all these responses are initiated by switching on the current in the central electric plant.

It is in the same sense that we should like to interpret the G-A-S response to stress as being basically the same irrespective of the stressor agent. It makes no difference who switches on the current and whether he does it with his hands or with some instrument; the result will always be the same. Similarly, it is immaterial which stressor is used to set the G-A-S mechanism into motion. The result will always be essentially the same, although the manifestations of the response will largely depend upon the many modifications in the basic picture which can be introduced by such factors as: 1) the specific actions of the stressor, 2) the integrity and responsiveness of each intermediate station in the transmission of the response to the peripheral target organs, 3) the responsiveness of the target organs themselves. If these conditioning factors are kept in mind, it will not be surprizing to note that certain specific properties, of either the stressor or the subject, may greatly modify the manifestations of the resulting G-A-S and largely determine which, if any "disease of adaptation" will ensue.

In the following pages we shall attempt to discuss the main theoretical problems involved in the interpretation of the mediation of systemic stress responses through the endocrine system. Special attention will be given to those conditioning factors which may qualitatively alter the course of this response.

The Action of Stressors Upon the Hypothalamus and the Hypophysis. — It is obvious that if a stressor agent elicits a normal G-A-S response it must first reach the centers of the two coördinating systems responsible for setting this defense reaction into motion. These are the hypothalamus, as a center of the vegetative nervous system, and the anterior-hypophysis, as the chief coördinator of the endocrine glands. As we have stated many times in this book, the identity of this *first mediator* is not known, but there is some indication

that certain stressors (e.g., pain, emotions), may affect the anterior-lobe by way of the hypothalamic centers.[713a]



Stress, for instance that elicited by trauma to a circumscribed region of the body, acts upon the **hypothalamic centers** partly through afferent nerves coming from the injured region (since denervation of the injured region diminishes autonomic responses to systemic stress) and partly through humoral substances (since such denervation does not completely abolish these autonomic responses). From the hypothalamus the impulse is mediated through the *autonomic nerves* to various tissues (e.g., blood vessels, glands) but it is especially important that in such instances there occurs an intense splanchnic discharge which leads to the liberation from the **adrenal medulla** of *adrenergic substances*. This response is not mediated through the hypophysis-adrenocortical axis.

Secondly, the nerve centers of the hypothalamus send impulses through the *stalk of the pituitary* to another endocrine organ, whose activity is regulated by secretory nerves, namely the **posterior-lobe.** It produces an excess amount of *vasopressin* (or "antidiuretic hormone") which influences the blood-vessels and urine production through humoral means during stress situations.

It is not known whether purely humoral stimuli can affect the posterior-lobe directly. After transection of the stalk, this part of the pituitary undergoes

[713a] Hume and Wittenstein B46961/50, Harris and de Groot B47142/50.

almost complete involution and hence it can certainly not be stimulated by humoral means. Nevertheless, it is noteworthy that excess sodium causes very pronounced proliferative changes in the posterior-lobe, a reaction which of necessity is humorally mediated, at least through part of its course. Perhaps it acts only upon the hypothalamus by virtue of circulating chemical substances; from here the impulse may be transmitted by nerves descending through the stalk, but this is unproven.

Systemic stress exerts particularly important effects upon the **anterior-lobe.** From the very beginning of our interest in the G-A-S, we paid special attention to this link in the production of stress responses since it appears to be the first, and most important step, in initiating hormonal defense. Yet, here again, little is known about the mechanism of mediation. A variety of *"toxic metabolites"* (e.g., acetylcholine, histamine, adenosine, protein degradation products) have been considered, but there was no convincing reason to assume that any one of these would be solely responsible for initiating the characteristic G-A-S response of the anterior-lobe.[714] This negative conclusion was accepted by most subsequent investigators, some of whom suggested that the basic factor "... is the inability to resist certain violent changes in the concentration of distribution of electrolytes, and we feel that potassium should be included as at least one of the 'toxic metabolites' postulated by Selye".[715]

More recently, the adrenal hormones themselves were considered as possible mediators of this first step in the hormonal chain reaction. The view was expressed that since *adrenaline* is liberated in the course of the well known "emergency discharge of the sympathetic nervous system" this hormone itself may have the specific property of inducing the anterior-lobe to discharge its ACTH into the blood.[716] "The stimulation of the elements of the autonomic nervous system, with concomitant release of epinephrine, that occurs under a variety of conditions, appears to be a major factor in the activation of the adrenotrophic secretion from the anterior-lobe".[717] There is no doubt that adrenaline is liberated during emergencies and it is equally certain that this substance can cause an ACTH discharge, indeed we used it routinely as an "alarming stimulus" in some of our earliest investigations concerning the G-A-S.[718] Hence, the release of adrenaline can undoubtedly favor an ACTH discharge at times of stress. It is unlikely, however, that this is the major (or only) factor responsible for the corticotrophic response during the G-A-S. Firstly, adrenaline did not prove to be more active in stimulating the adrenal cortex than other compounds causing a comparable degree of stress; [719] secondly, blockade of the adrenergic responses by such substances as dibenamine or TEA, does not prevent the corticotrophin discharge following exposure to stress.[720] It is true that certain adrenolytic compounds, e.g., dihydroergocornine, have been claimed to block most of the effects of adrenaline or sympathetic stimulation, without inhibiting an adrenaline-induced ACTH discharge (estimated by the eosinopenia and lymphopenia). Indeed, on the basis of these observations, combined treatment with adrenaline and dihydroergocornine has been recommended as a substitute for ACTH treatment in man.[720a] However, dibenamine fails to inhibit the adrenal enlargement caused by an alarming

[714] Selye 38798/37, B1204/46.
[715] Kendall and Ingle 68707/37.
[716] Long B1736/47, Zeckwer B19293/48.
[717] Long B1736/47.
[718] Selye 36032/36.
[719] Selye 36032/36, 38798/37.
[720] Tepperman and Bogardus B29439/48.
[720a] August and Gubner B4445/49.

stimulus (colchicine) without preventing that elicited by adrenaline itself.[720b] Hence, the stimulation of ACTH discharge, during an A-R, cannot be ascribed solely to adrenaline liberation.

According to another theory, the increased consumption of *corticoids* by the peripheral tissues is the adequate stimulus responsible for the discharge of ACTH during the A-R.[721] This view was mainly based upon the observation that pretreatment with corticoids tends to inhibit the adreno-cortical response to stress. Lack of corticoids is certainly conducive to increased ACTH production. Indeed, such lack (for instance, after unilateral adrenalectomy) is the cause of the compensatory hypertrophy which occurs in the remaining adrenal tissue. Conversely, exogenous administration of excess corticoids causes "compensatory cortical atrophy" through this same auto-regulatory interplay between the adrenal cortex and the anterior-lobe. Gluco-corticoids are much more effective in this respect than mineralo-corticoids, but both kinds of hormones produce some adreno-cortical involution.[722] It is highly probable, however, that this kind of auto-regulation is effective only in the near physiologic range of blood-corticoid levels. Under conditions of extreme stress, the adrenal cortex does show signs of increased activity, even in animals simultaneously receiving extraordinarily large amounts of DCA.[723] It is conceivable that if still larger amounts of the particularly active gluco-corticoids were used, the inhibition could be complete under any condition of stress, but this has not yet been demonstrated. In any event, we have no objective proof that corticoids are "consumed" more rapidly during stress than at rest; [724] indeed, a perfect auto-regulatory mechanism of this sort would be incompatible with the increased presence of corticoids in the blood and urine of individuals exposed to stress. If any excess in the amount of circulating corticoids would automatically diminish ACTH production, a rise in corticoid levels during the G-A-S would become impossible.

This intensive search for a mediator — which would be produced by injured cells and after having reached the pituitary would induce it to produce ACTH — may be doomed to failure because *perhaps no single substance is responsible for this effect.* It is generally agreed that a great variety of stressors eventually act through a common pathway, namely, the anterior-lobe. At present we have no reason to believe that the pathway is common at a higher level. It is quite possible that any derangement in the biochemical constitution of the blood (toxic substances, hormones, deficiency of certain vitally important metabolites, etc.), as well as nervous stimuli reaching the anterior-lobe cells directly through nerve fibers, may liberate ACTH from some labile combination in the cell and stimulate its increased production.

Whatever the mediating mechanism may be, it is highly probable that the degree of pituitary response during stress is dependent upon *pre-pituitary conditioning factors.* Constitution and heredity, the state of adaptation (due to previous exposure to stress), the application of sedatives or excitants can all respectively increase or diminish the intensity of the stress itself. Thus they influence the hypophysis-adrenocortical response by increasing or decreasing the degree of stress that follows a standard type of exposure.

[720b] Seifter et al. B32930/49.
[721] Sayers and Sayers B18350/48, 98805/47.
[722] Selye A32884/40, **94572/49.**
[723] Selye B4165/48.
[724] Selye **94572/49.**

Response of the Anterior-lobe. — As we have seen, upon exposure to stress, the anterior-lobe responds with an increased ACTH production.

The chemical steps through which this hormone is made are not known, but there is some evidence that it is prepared from **precursors** which are present in crude anterior-pituitary preparations, such as LAP. Thus, a standard dose of LAP is more effective in causing adreno-cortical enlargement in intact than in hypophysectomized animals.[725] Perhaps precursors present in the anterior-lobe tissue can not be transformed into active ACTH outside the pituitary, hence only the preformed ACTH of the LAP remains effective after ablation of the hypophysis.

Many observations show that various anterior-pituitary extracts differ qualitatively in the kind of corticotrophic action which they exert.[726] Similarly, in clinical medicine, hyperactivity of the adrenal cortex may be accompanied by qualitatively different structural alterations in the suprarenals and distinct functional derangements in the peripheral organs. This raised the question whether in addition to the corticotrophin, now available in pure form, there would exist **several corticotrophins** which may exert predominantly gluco-corticotrophic, mineralo-corticotrophic or testo-corticotrophic effects.[727] It has been pointed out, for instance, that in gonadectomized (male or female) rats, an A-R causes no stimulation of the accessory sex organs, although there is conclusive evidence to show that the production of life-maintaining corticoids (presumably gluco- and mineralo-corticoids) is greatly increased.[728] Since the adrenal cortex can produce testoids and folliculoids, it follows that under conditions of stress, it does not produce all its hormones in set proportions.

This view received further support from clinical observations showing that the 17-KS excretion does not parallel the corticoid excretion during the A-R. However, some investigators brought forth evidence against the assumption of several corticotrophins,[729] and it was emphasized that a chemically pure ACTH preparation can cause sodium and water retention (mineralo-corticoid effects), hyperglycemia and glycosuria (gluco-corticoid effects), as well as an increased 17-KS excretion (testo-corticotrophic effect). Hence, it was felt that there is no need to assume the existence of qualitatively different corticotrophic principles.[730] On the other hand, it has definitely been proven now for most of the available pure gluco-corticoids that they also possess some mineralo-corticoid properties and that in the course of their intermediate metabolism they may be degraded into 17-KS compounds. In the light of these observations, the above data remain compatible with the assumption that the ACTH preparation merely stimulated the adrenal to produce an excess of gluco-corticoids and that the other effects were merely a secondary consequence of this.

The final proof of the existence of several corticotrophins will have to await their actual isolation in pure form,[731] but it should be stated now that there are indubitably several qualitatively different corticotrophic effects. This may be due to the production of different corticotrophic hormones or to the peripheral conditioning of the actions of a single principle, for instance, at the adrenal level (see below).

[725] Selye 35935/ND.
[726] Selye **94572/49**, B39702/49, B39703/49.
[727] Selye B1212/46, **94572/49.**
[728] Albert A55477/42.
[729] Sayers and Sayers B18350/48.
[730] Forsham et al. B17987/48.
[731] Sayers and Sayers B18350/48.

Simultaneously with the increased discharge of ACTH during stress, there is a **"shift in anterior-lobe hormone production".** This results in a diminished somatotrophin and gonadotrophin production. The inhibition of *somatotrophin* secretion manifests itself by cessation of somatic growth in the young and increased protein catabolism in the adult. The diminution in the elaboration of *gonadotrophins* results in testicular and ovarian atrophy (due to lack of FSH, LH and prolactin). There is also cessation of milk secretion if the stress is applied during lactation (due to diminished prolactin production).[732]

The clinical condition of anorexia nervosa may lead to such a "shift" in which most anterior-lobe functions become subnormal, although corticotrophic stimulation may continue.[733] Only very few agents cause an inhibition of all anterior-lobe functions (e.g., chronic partial starvation on low protein diets, cortisone overdosage). These exceptions are due to the specific effects of stressors which tend to inhibit ACTH production through special mechanisms; they are not merely reactions to stress as such.

All the above-mentioned anterior-lobe responses are highly subject to **conditioning influences.** Thus, lack of amino-acids inhibits ACTH formation; administration of LAP increases the ability of the pituitary to produce corticotrophin in response to stress, presumably by furnishing precursors, etc.[734]

Although the administration of protein (or amino-acids) greatly increases ACTH production following exposure to stress or after administration of LAP in the intact rat, it does not significantly affect the actions of pure ACTH, nor does it influence the corticotrophic effect of LAP in the hypophysectomized animal. "It appears that the ability of high-protein diets to increase the corticotrophic effect (of stress or LAP) is dependent upon the integrity of the hypophysis".[735]

Response of the Posterior-lobe. — As previously stated, the posterior-hypophysis discharges vasopressin during certain stages of the G-A-S. This is principally, if not entirely, dependent upon the integrity of secretory fibers descending through the stalk. Up to the present little is known about agents which may condition the discharge of vasopressin, but the sodium and water intake probably play an important part in this reaction, since they regulate vasopressin production even in the absence of stressor agents.

Response of the Adrenal Medulla During the G-A-S. — During the G-A-S the adrenal medulla appears to discharge its adrenergic hormones mainly, if not entirely, as a result of **splanchnic stimulation.** There is some evidence that circulating acetylcholine, and perhaps also some other tissue metabolites, may likewise induce a hormone discharge from the chromaffin cells during the G-A-S, but pertinent data are quite inconclusive. In any event, there is no reason to believe that trophic hormones of the anterior-lobe would be involved. In essence, the adrenal medulla acts like the sympathetic nerve endings, only that it discharges hormones into the blood-stream and thus makes them available to all tissues, while the adrenergic nerves are more suited to produce high concentrations of such hormones in certain limited areas.

Conclusive evidence has now proven that the medulla — like the sympathetic nerve endings — liberates at least two qualitatively different adrenergic principles, namely, **adrenaline** and **nor-adrenaline.** It is probable that these

[732] Selye 36030/36. A18343/39, 74721/39.
[733] Sunderman et al. B25093/48.
[734] Selye B1212/46, **B1204/46.**
[735] Henriques et al. B27603/49.

are not always discharged in set proportions, but nothing is known as yet about the factors which condition the quality of this response at the adrenal level. In any case, the effect of such adrenergic principles may certainly be modified in the periphery, by certain adrenergic blocking agents which can selectively interfere with individual actions upon the receptor cells and thus lead to qualitatively different responses.

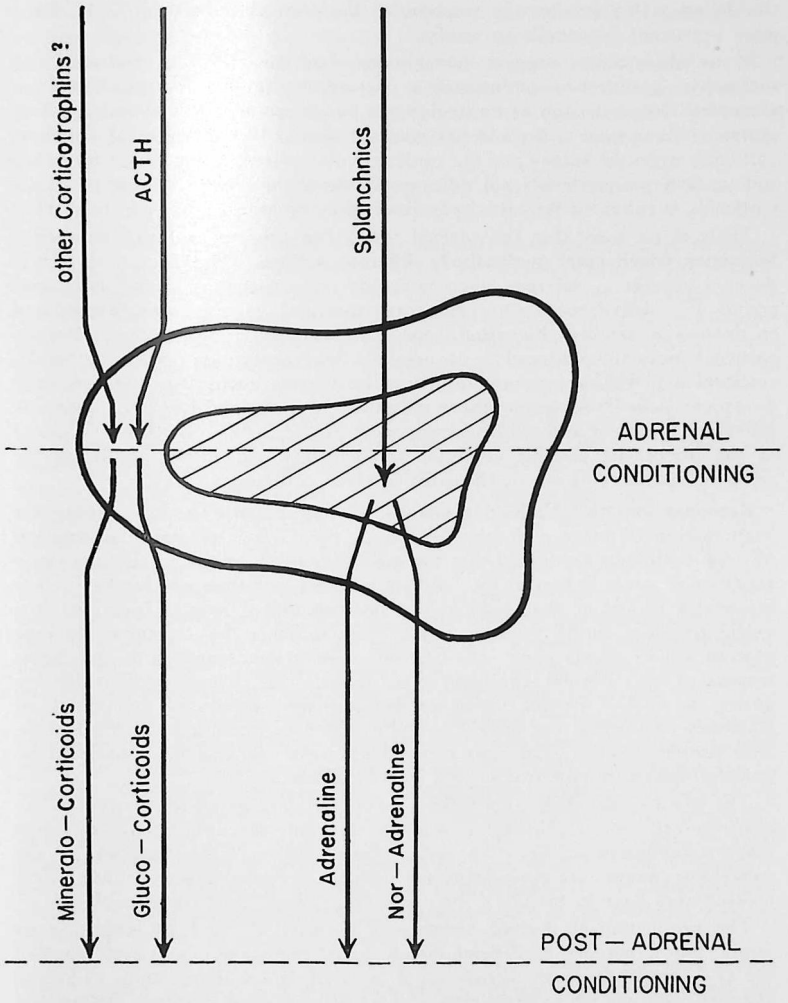
During the last fifteen years or so, interest has focused so much upon the defensive rôle of the corticoids that the part played by the medulla has been somewhat neglected. Data concerning the probable utility of this adrenergic discharge, in the frame of a systemic defense reaction, have been discussed elsewhere (cf. Resistance ← Adrenaline, p. 64). Let us merely recall here that more than thirty years ago, it had already been recognized that adrenaline discharged from the medulla under the influence of various infections and intoxications may help to prevent the usual "collapse of the cardiovascular system", which tends to occur under the influence of extreme stress.[736] In the course of the following two decades, this concept has been most fruitfully developed and extended by Cannon's investigations upon the "emergency discharge" of adrenaline.[737]

It is striking that so many actions of adrenergic substances are also characteristic of corticoids (e.g., hyperglycemia, hypertension, polyuria). Since the former produce these effects much more rapidly, while the latter have a more sustained effect, it is probable that the adrenergic discharge is meant to cope particularly with very acute needs, while the corticoids help resistance in the event of more prolonged exposure.

Response of the Adrenal Cortex. — The efficacy of corticoids in raising systemic resistance to stress as such, may now be considered as definitely established.[738] The close resemblance between the manifestations of adrenocortical deficiency and those of an intense A-R have been particularly emphasized. It was found that adrenalectomy exaggerates manifestations of pure damage during the A-R, while it prevents many hormonal responses characteristic of defense.[739] It has even been shown that there exists a direct dose: effect relationship between the amount of corticoids administered to an adrenalectomized animal and the degree of resistance thus imparted.[740]

In the preceding pages we listed many observations showing that the response of the adrenal cortex to stress is highly subject to **conditioning factors** which appear to act *at the level of the cortical cell* itself. Thus, exogenous administration of ACTH, or its endogenous formation under the influence of stress, can exert qualitatively very different effects upon the structure and function of the adrenal cortex (e.g., discharge or storage of lipid granules, fatty metaplasia, myeloid transformation, colloid storage in the cortical parenchyme). Special attention was given to the fact that continuous treatment with pure ACTH causes only a slight and very transitory discharge of adrenal-lipids followed by marked lipid storage, while in the A-R the discharge of lipids is much more pronounced and prolonged, indeed folliculoids may even produce a persistent degranulation of the cortical cells. "These observations show that the corticotrophic effect of folliculoids cannot be solely ascribed

[736] Marie 32348/18.
[737] Cannon B14905/39.
[738] Selye 67153/37, Gronchi 97044/41.
[739] Selye 67153/37.
[740] Selye and Schenker A15353/38.



to the liberation of anterior-pituitary corticotrophin".[741] Unless we assume that alarming stimuli, as well as folliculoid hormones, induce the pituitary to produce corticotrophins other than those present in the pure ACTH preparations now available, these findings would have to be interpreted as indications of a conditioning of ACTH actions at the adrenal level. It is possible that during the A-R and after treatment with folliculoids, some metabolites appear in the

[741] Skelton et al. B27602/49.

circulation which so alter the response of the cortical cells to ACTH that a more persistent degranulation ensues.

Many observations suggest, furthermore, that the action of the corticoids themselves is subject to conditioning *at post-adrenal levels*. To give but a few examples, the production of hyperglycemia by gluco-corticoids is enhanced by systemic stress, even in the adrenalectomized animal; [742] the effect of mineralo-corticoids upon the kidney and the cardiovascular system is increased by excess sodium and pre-existent renal damage; [743] the diabetogenic action of gluco-corticoids is enhanced by partial pancreatectomy or high carbohydrate diets.[744]

There is no doubt that the adrenal cortex can produce a large number of **hormones which exert qualitatively different actions.** The fact that it produces a number of different gluco-corticoids (e.g., cortisone, Kendall's "compound F", dehydrocorticosterone, corticosterone) is too well established to deserve a detailed discussion here. Less is known about the mineralo-corticoids normally produced by the adrenal. Several steroids possess mineralo-corticoid actions, for instance, desoxycorticosterone, acetoxy-pregnenolone,[745] desoxocortisone,[746] but among these, only the last mentioned has been definitely proven to represent a physiologic component of the cortex. Nothing is known as yet about the possible conditioning factors which might influence the selective discharge of one or the other of these corticoids.

Response of Other Endocrine Glands. — Our knowledge concerning the participation of other endocrine glands in the G-A-S is very incomplete. We have already mentioned that the **gonads** tend to undergo atrophy upon exposure to stress as part of the "shift in pituitary hormone production". It is reasonable to assume that a diminution or cessation of sexual functions is a useful response during systemic stress, since it helps the organism to concentrate all its efforts upon activities immediately concerned with the maintenance of life. The derangements of the sexual cycle, which tend to develop during the G-A-S, are not due to any hormone insensitivity of the gonads or accessory sex organs, but merely to a diminution of sex-hormone production. The atrophic ovaries of animals exposed to stress can still be stimulated by gonadotrophins, the diestrus vagina by folliculoids, etc.[747]

The effect of the G-A-S upon the hormone production of the **pancreas** has also received considerable attention in the preceding discussion. Since insulin plays a fundamental rôle in the regulation of intermediate metabolism, the pancreatic changes are presumably not without physiologic significance. Few investigators have so far given their attention specifically to this problem.

The production of **thyroid** hormone is likewise affected by exposure to stress, but it appears to depend largely upon conditioning factors whether the G-A-S will cause an increase or a decrease in its elaboration. Thyroid changes could not fail to affect resistance since the thyroid hormone determines the level of the B.M.R. and hence affects many of the most fundamental metabolic responses to stress.

The **parathyroids** do not show any very striking modifications which could be ascribed to the G-A-S as such. The parathyroid hormone is one of the most important regulators of calcium and phosphate metabolism. It presumably

[742] Selye and Dosne A37037/41.
[743] Selye **94572/49.**
[744] Hartman and Brownell **B36274/49.**
[745] Selye A36370/41.
[746] Selye B43385/50.
[747] Selye A18343/39.

participates in the pathogenesis of osteoporosis during the A-R (see below), but the disintegration of the organic bone-matrix, which is part of the catabolic impulse, can affect a discharge of minerals into the blood-stream, even independently of the parathyroids. These glands are not immediately dependent upon any trophic hormones of the anterior-lobe and their response during the G-A-S is largely governed by the calcium and phosphate content of the serum.

Summary of Observations Concerning the Participation of the Endocrine Glands During the G-A-S.

It is still not known through what mechanism stress initiates those defensive responses of the endocrine glands which are characteristic of the G-A-S. It may be taken as established, however, that both afferent nervous stimuli and blood-borne metabolic principles (originating in the directly damaged area) can affect the **hypothalamic vegetative centers** and induce an autonomic nerve discharge, which, through the splanchnics, reaches the adrenal medulla (cf. below).

These same stimuli can also influence the **posterior-lobe** presumably through the nerve fibers which descend from the hypothalamus through the stalk. Under their influence, the posterior-lobe cells secrete the antidiuretic and vaso-pressor principle, *vasopressin*.

Neither the autonomic nerves nor the stalk of the pituitary are necessary for the effect of most stressors upon the **anterior-pituitary.** It is possible that *impulses descending through the stalk* can induce the hypophysis to respond in a manner characteristic of the G-A-S. Yet, this response is not necessarily prevented by transection of the connections between the pituitary and hypothalamus, hence we must assume that humoral principles (toxic substances, hormones, deficiencies in vitally important metabolites, relative lack of corticoids) are more important under usual conditions.

Certain recent experiments suggest that the nerve centers in the posterior-hypothalamus may cause a discharge of ACTH from the anterior-lobe, through blood-borne metabolites which it receives through the hypophyseal portal vessels. The latter regenerate rapidly after stalk-transection (unless an impermeable membrane is placed between hypothalamus and pituitary), although the nervous connections are not re-established. This neuro-humoral transmission appears to be indispensable only in the case of an A-R elicited by certain neurogenic stimuli, since other stressors (e.g., exposure to cold) elicit an ACTH discharge, even after transplantation of the pituitary from the sella to another location.

Whatever the mediator may be, systemic stress causes the pituitary to respond with an increased production of *corticotrophin* and a decreased discharge of *somatotrophin* and *gonadotrophins*. This results in a stimulation of the adrenal cortex, accompanied by a diminution of somatic growth, an increased tendency to catabolism and a hypofunction of the gonads. During lactation there is also an inhibition of milk secretion. The gonadal atrophy is presumably due to a lack of FSH, LH and prolactin, the cessation of milk secretion, to a deficiency in prolactin. This rearrangement of the pituitary-secretion pattern during stress has been termed the *"shift in pituitary-hormone production"*. In man, it may lead to a syndrome of partial hypo-pituitarism, such as is seen in anorexia nervosa, starvation, chronic infections, intoxications, etc.

The response of the anterior-lobe to stress is largely dependent upon *conditioning factors*, for instance, the availability of amino-acids, which enhance ACTH production.

The **adrenal medulla** is stimulated by the splanchnics to produce adrenergic hormones, such as *adrenaline and nor-adrenaline*.

Nothing is known as yet about possible conditioning factors which may determine which adrenergic substance is predominantly produced.

The **adrenal cortex** is stimulated by ACTH and there is some evidence suggesting the existence of several *qualitatively distinct corticotrophins*. It is equally possible, however, that a single ACTH may cause qualitatively different responses in the adreno-cortical cells, depending upon *conditioning factors*. Thus, folliculoids, testoids, foreign proteins and corticoids may qualitatively alter the response of the adrenal cortex to a given corticotrophic preparation. Only the existence of several corticotrophins, or the production of distinct corticotrophic actions due to conditioning of the adrenal response to the same ACTH, could explain the variety of corticotrophic effects seen in organisms exposed to stress (predominance of mineralo-, gluco- or testo-corticoid actions).

Peripheral, post-adrenal conditioning to corticoids is also important during the G-A-S. Thus, an excess of sodium, pre-existent renal damage and blood-borne principles produced during the A-R greatly influence the response of peripheral target organs to the corticoids liberated during the G-A-S.

Among the other endocrine glands which undergo important changes upon exposure to systemic stress are the **gonads**, which (as we have stated above) undergo atrophy, as well as the **thyroid, pancreas** and the **parathyroids.** The responses of these latter glands, however, are very irregular because they depend so largely upon conditioning factors. Hence, and because these glands have not yet been systematically studied in connection with stress reactions, we know comparatively little about their rôle in the genesis of the G-A-S and its diseases.

Since the response of the endocrine system to stress is so largely dependent upon the reactivity of each individual gland, the hormonal reactions caused by stress are subject to great individual variations, although the basic pattern is always the same. The effect of conditioning factors (e.g., heredity, diet, pre-existent lesions in individual organs, previous exposure to stress) is mainly responsible for the fact that stress can cause such a large variety of apparently quite distinct **"diseases of adaptation".**

SKELETAL SYSTEM

Bones

Systemic stress. — Inhibition of somatic growth in young individuals and loss of weight (increased catabolism, decreased anabolism of tissues) at all ages, are **characteristic** components of the response to severe non-specific systemic stress. It has long been known that any kind of illness can delay the growth of children and cause osteoporosis in adults. Yet these phenomena have only recently been interpreted as due to the "shift in hypophyseal hormone production" typical of the G-A-S, and in particular to the decrease in somatotrophin secretion which occurs at times when ACTH production is maximal.[1]

Any protein deficiency may interfere with the formation of the organic bone matrix, the framework in which the mineral constituents of the skeleton are deposited. Catabolism of osteoid, or disturbances in its formation actually have been considered to be the principal cause of the *"osteoporosis of the alarm-reaction"* which occurs following trauma and other types of systemic stress in man.[2]

During the A-R the production of gluco-corticoids is greatly increased; these cause protein catabolism. Simultaneously there is a decreased elaboration of the testoids and somatotrophin, which have a protein-anabolic effect. Hence it has been postulated that this change in the hormonal equilibrium may be the major cause of bone dissolution during the G-A-S.[3] The osteoporosis of Cushing's syndrome, which also appears to find its explanation in a considerably increased gluco-corticoid production, has therefore often been compared to the osteoporosis of the G-A-S.[4]

Contrary to earlier views it is unlikely that immobilization (e.g., by disease) in itself could explain the severe osteoporosis of the G-A-S. Yet the above-mentioned hormonal factors are likewise not all important since during stress, general catabolism proceeds even in the absence of the hypophysis, adrenals and gonads. It is unlikely therefore that bone catabolism should be entirely dependent upon the hormones of these glands. Presumably here again — as in so many other instances — the hormones merely facilitate certain preëxistent metabolic processes.

Many kinds of systemic stressors cause growth inhibition or osteoporosis, simultaneously with other manifestations of the G-A-S. Among these are chronic **anoxia** as judged by observations in the rat.[5]

Bile-duct ligature inhibits the growth of young rabbits through the "shift in pituitary-hormone production" characteristic of the G-A-S.[6]

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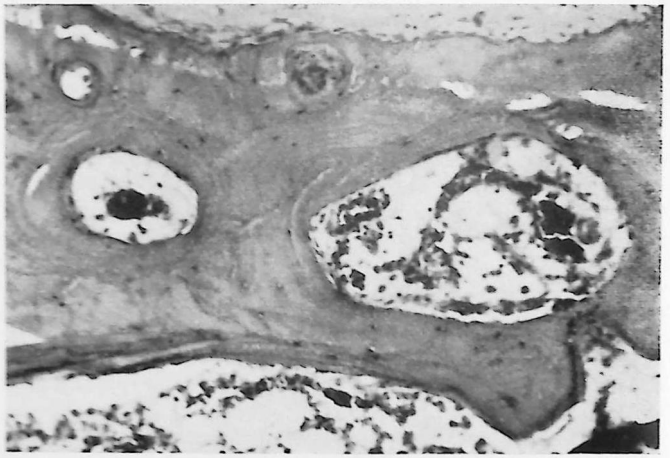
[1] Selye 38798/37, B1204/46, **94572/49.**
[2] Albright B309/43, Lichtwitz 99169/46, Rutishauser B18121/47.
[3] Albright and Reifenstein **B28570/48,** Reifenstein and Albright 96952/47.
[4] Albright B309/43, **B44727/47,** Lichtwitz 99168/47, Reifenstein and Albright 96952/47.
[5] Altland B26573/47, B24783/46, B24782/48, B33460/49.
[6] Rosselli del Turco and Matteini B37479/49.

The various disturbances of growth and skeletal structure which may develop in the course of many chronic spontaneous diseases of man have also been ascribed to the development of a G-A-S.[7] Here it would not be correct to speak of an "osteoporosis of the A-R", since the exposure to stress is prolonged. Such derangements may better be designated as *"osteoporosis (or dwarfism) of the G-A-S."* The so-called cardiac dwarfism is a case in point.[7a]

Various **nutritional deficiencies**[8] cause similar skeletal changes in rats. Drastic food restriction, begun in very young rats after weaning and continued throughout life, decreases the rate of proliferation and causes regressive changes in the epiphyseal and articular cartilages, but it prolongs the growth period.[9]

In young guinea-pigs, which receive a calorically restricted but balanced diet, growth of the junction-cartilages and ossification also proceed at a greatly diminished rate. Upon refeeding, however, the growth processes are readily resumed and temporarily they may even surpass normal.[10]

In times of war and famine, marked osteoporosis is frequently seen. The condition has variously been described as **"hunger osteopathy"**, "hunger osteosis" or "osteoporosis of famine". It is usually associated with various other manifestations of the G-A-S and undoubtedly corresponds to the above mentioned "osteoporosis of the alarm-reaction", which we would prefer to call "osteoporosis of the G-A-S".[11]



Hunger osteoporosis in man. Marked osteoporosis of a rib in a woman suffering from chronic starvation. Absence of osteoclasts or osteoid tissue proliferation. The Haversian canals are greatly dilated. (After Uehlinger B27612/48.

[7] Flosi B36498/48.
[7a] Lutembacher et al. B36154/45.
[8] Barnes et al. B27271/47, MacCay et al. B27272/43, Zucker and Zucker 93062/46.
[9] Samuels and Silberberg B26669/47.
[10] Silberberg and Silberberg 79644/40, A71383/43.
[11] Gsell B27611/48, Keys B37797/48, Keys et al. **B46730/50.** Justin-Besançon **B23346/39-45.** **B28524/43,** Piersotte **B3030/45.** Pompen et al. B45180/46.

It is perhaps not entirely irrelevant also to mention some **local effects** of non-specific damaging agents upon bones. Thus *freezing* causes local osteoporotic atrophy of the bone, which is accompanied by endarteritis obliterans and decomposition of the myelin sheaths of the nerves in the same region.[12] This is mentioned merely as yet another example of the often noted similarity between the systemic manifestations of general stress and the results of local non-specific damage.

Stimuli Influencing the Response of the Skeleton During the G-A-S. — Hypophysectomy causes cessation of growth in young animals and osteoporosis in adults. Conversely, **somatotrophin** (the growth hormone of the anterior-lobe) restores the skeletal structure of hypophysectomized animals practically to normal. It is generally assumed, therefore, that non-specific stress acts largely through the inhibition of somatotrophin secretion. Yet, **corticotrophin** and the **gluco-corticoids,** simultaneously with their protein-catabolic effects, also tend to cause growth inhibition and osteoporosis. Hence, presumably increased ACTH and gluco-corticoid production likewise participates in the "osteoporosis of the alarm-reaction", as outlined above.[13]

Among other hormones exerting important effects upon bone structure **parathyroid hormone** should also be mentioned. If it is given in high doses, it rapidly causes osteitis fibrosa and osteoclastic bone absorption, while prolonged treatment with low doses produces increased density of the bones and the development of a condition resembling "marble bone disease". Various derangements associated with hyperphosphatemia (e.g., renal lesions) stimulate the production of parathyroid hormone and the blood-phosphates are often increased during the G-A-S: hence, we must consider the possible participation of the parathyroids in the genesis of skeletal lesions during systemic stress.[14] Unfortunately, this possibility has not yet been investigated.

Folliculoids cause cessation of somatic growth in young individuals. Since this is accompanied by increased bone density, it hardly plays any important rôle in the skeletal changes characteristic of the G-A-S.[15] Nevertheless, it is of therapeutic interest that in Cushing's syndrome, folliculoids probably do have a beneficial effect upon the negative calcium balance.[16] It is also noteworthy that various steroids, especially testoids, tend to counteract the growth inhibition normally elicited by folliculoids.[17]

Small doses of **testoids** augment somatic growth and protein anabolism in the rat, especially among females.[18] This action upon N-metabolism and tissue growth also occurs in man and hence testoids have been recommended in the treatment of osteoporosis due to Cushing's disease or the A-R; the results are apparently encouraging.[19]

Skeletal Diseases of Adaptation

The so-called **"osteoporosis of the A-R"** which appears following acute exposure to systemic stress and the **"osteoporosis or dwarfism of the G-A-S"** seen after more prolonged exposure (cf. above) are obviously diseases of adaptation in the sense in which we defined these. Many types of **infantilism**

[12] Staemmler B29879/44, Vagliano B29862/47.
[13] Selye **94572/49.**
[14] Selye **94572/49.**
[15] Selye **94572/49.**
[16] Reifenstein and Albright 96952/47.
[17] Albert and Selye A37637/42.
[18] McEuen et al. 39157/37.
[19] Albright and Reifenstein B28570/48, Reifenstein and Albright 96952/47.

characterized by retarded somatic and sexual development, presumably also belong to this group as does the **hunger osteopathy**, or famine osteopathy, seen at times of war or starvation.

Here again, the extraordinary importance of conditioning factors must always be kept in mind. Obviously protein, calcium, phosphate, vitamin-D and many other substances are necessary for the normal development of bone tissue, furthermore, hereditary factors, the amount of exercise taken, as well as innumerable other circumstances can influence skeletal development. Consequently, in the pathogenesis of various osteopathies, the rôle played by maladaptation to stress as such varies considerably depending upon the intensity of the stress on the one hand, and the rôle played by specific conditioning factors on the other. In this sense, one may say that there is a gradual transition between the typical skeletal diseases of adaptation and osteopathies in which maladaptation to stress plays a negligibly small rôle. The subject has been discussed in great detail in relation to the syndrome of **"renal rickets"**. This has been interpreted as a disease of adaptation due to a derailment of the G-A-S, because a primary renal lesion causes hyperparathyroidism as a compensatory adaptive mechanism against the flooding of the blood with phosphates and an increased secretion of parathyroid hormone which in turn produces osteoporosis and bone fragility.[20] This undoubtedly means that we are dealing with a disease of adaptation, in the general sense of this term. Adaptation is involved in its pathogenesis, however, it is important to remember that renal rickets is not a maladaptation to stress as such, but rather a maladaptation specifically to a renal lesion. In this sense, it is comparable with other specific diseases of adaptation (e.g., allergies). While any such specific derangement would also cause stress and hence a G-A-S, it is well to keep in mind that these diseases are not primarily due to a derangement of the G-A-S. We feel that the concept of the diseases of adaptation would be weakened by the inclusion in this group of conditions in which maladaptation to specific derangements (not to systemic stress as such) is the major etiologic component.

Joints

Systemic stress. — Exposure to systemic stress does not in itself tend to cause joint diseases in normal animals or man. Perhaps the most **characteristic** direct effect of exposure to stress upon the joint structures is a sudden discharge of fat from the adipose tissue of the synovial villi, accompanied by edema, hyperemia and sometimes by multiple petechial hemorrhages.[21] Such lesions occurred quite consistently in our experiments, especially during the A-R and exhaustion phases, in a large variety of animals exposed to many kinds of stressors. It is quite possible that these changes would predispose the joint structures to the development of true arthritis. They may also be responsible for the painfulness and stiffness of the joints which accompanies many clinical syndromes of systemic damage, caused by exposure to cold, drugs, allergens, and infections, for instance during the prodromal period of infectious diseases.

Occasionally an arthritis, of rather non-specific appearance, may occur in rats chronically exposed to the systemic effects of **cold**,[22] but this is inconstant

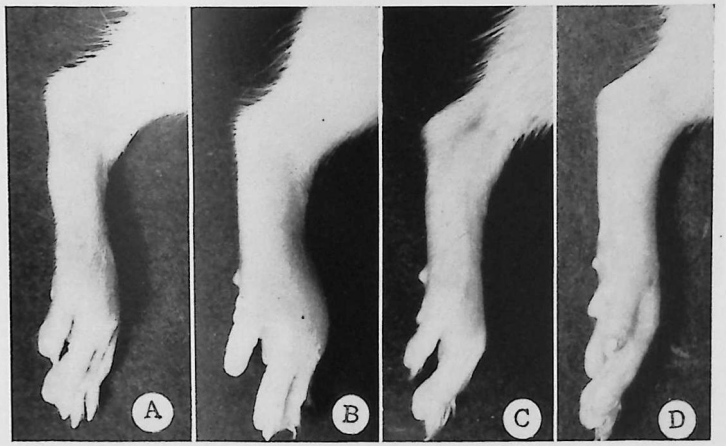
[20] Uehlinger B38385/49.
[21] Selye 35935/ND.
[22] Selye B1204/46.

and in any event, the direct effect of cold upon the joint structures is difficult to eliminate in such instances. The so-called "trench foot" or "immersion foot" of clinical medicine are also subject to this same criticism, especially since systematic studies concerning the local effect of freezing have revealed that upon local exposure to low temperature, inflammatory changes tend to develop particularly in the joint region.[23]

In rabbits treated with **horse serum** arthritides occasionally develop in conjunction with hypersensitivity lesions in the cardiovascular system.[24]

Sensitivity to **barbiturates** likewise may result in joint lesions. "Perhaps it will be possible to include barbituric rheumatism in the picture of the G-A-S".[24b]

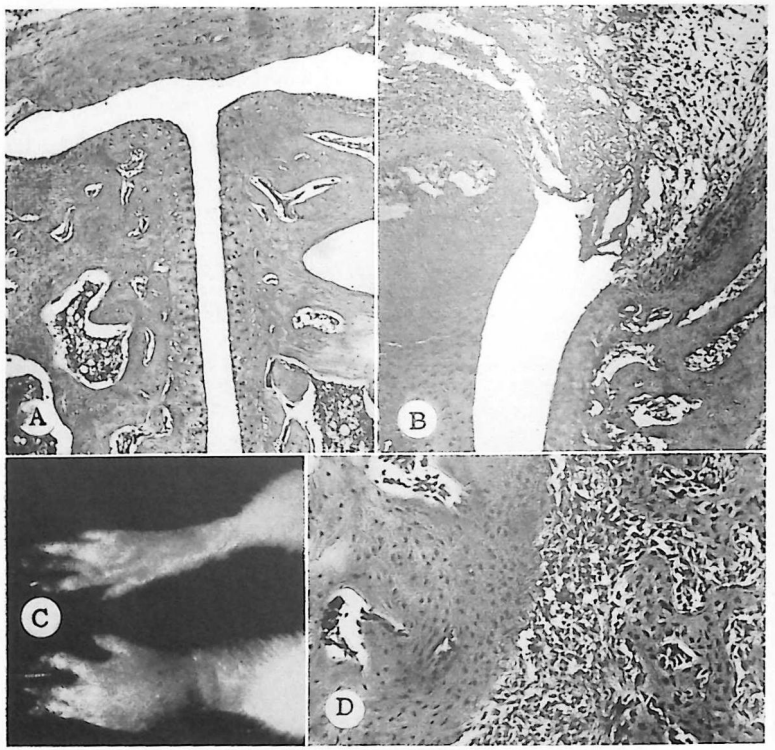
As we shall see later (cf. Joint Diseases of Adaptation), **conditioning factors** play a particularly important rôle in determining whether arthritis will develop upon exposure to non-specific stress and if so, what type of joint lesion will be precipitated. Nevertheless, in all these cases, the non-specific stress factor undoubtedly plays a prominent part. A large variety of infections, intoxications and allergies can cause joint pains with more or less pronounced inflammatory lesions, and many kinds of injuries (emotional, traumatic, etc.) can precipitate an acute episode of arthritis in patients suffering from gout or rheumatism.



Effect of A-R upon "topical irritation arthritis", in the rat. — **A.** Untreated control. All other animals received a local formaldehyde injection underneath the plantar skin. — **B.** Otherwise not treated. — **C.** A-R produced by spinal-cord transection — **D.** A-R procuced by exposure to cold. A variety of other alarming stimuli exerted the same inhibitory effect, presumably due to endogenous ACTH discharge. (After Selye B39702/50)

Conversely, under certain circumstances **stress can exert a curative effect upon a preëxistent arthritis.** Thus if an A-R is produced by any one among a variety of acute stressors (e.g., muscle trauma, spinal-cord transection, bile-duct ligature, starvation, subcutaneous formaldehyde injections), the development of the "formalin arthritis" is most effectively inhibited.

[23] Vagliano B29862/48.
[24] More and McLean B38772/49.
[24b] Lucherini et al. B47798/49.



Hormonal production of arthritis in the rat. — **A.** Normal metatarsal joint of a rat. Control for subsequent figures. — **B.** Acute arthritis produced by DCA. Edematous synovial membrane and exudate in metatarsal joint cavity. — **C.** Arthritis in left hind paw of a rat chronically treated with anterior-pituitary extract. — **D.** Newly formed periarticular bone in the metatarsal region of a rat treated with alkline anterior-pituitary extract. (After Selye B1204/46.)

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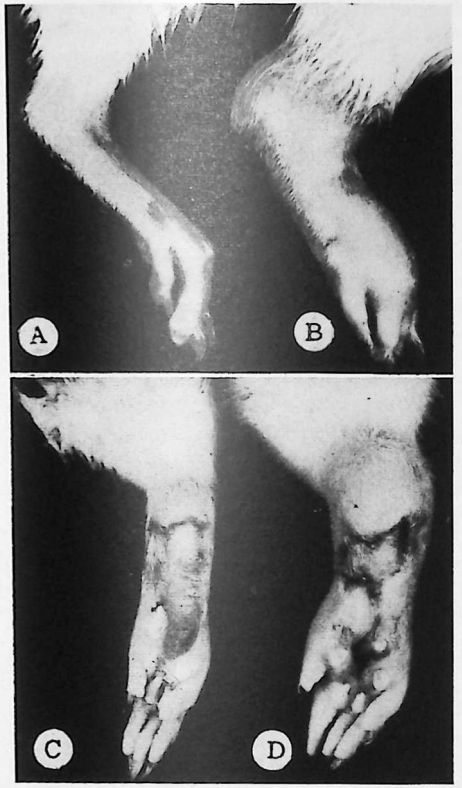
Effect of various corticoids upon "topical irritation arthritis", in the rat. All animals have been adrenalectomized before the experiment in order to eliminate complications by endogenous corticoids, except E which acted as an intact control. The following day treatment began with cortisone (A), acetoxypregnenolone (B) and DCA (C) (subcutaneous injections of 2.5 mg./day in microcrystalline suspension). D and E received no hormones. Nine days after adrenalectomy and initiation of the hormone treatment, all animals were injected under the plantar skin with a suspension of U.S.P. mustard powder. Note that — **A. cortisone** almost completely prevented the inflammatory swelling, while — **B. acetoxypregnenolone** and — **C. DCA** aggravated it. Among the animals not receiving hormone pretreatment, — **D**, the adrenalectomized rat responded more violently than — **E**, the intact control presumably because in the latter the stress of the intervention elicited some gluco-corticoid discharge.

(After Coutu and Selye B46943/50)



Effect of ACTH on "topical irritation arthritis". — **A. ACTH** pretreated, — **B** not pretreated control. Both these animals were given repeated injections of the same amount of formaldehyde into the paw. The controls (B) developed marked indurative chronic arthritic and periarthritic lesions; the ACTH pretreated animals (A) showed only a negligible response. — **C.** and **D.** Plantar view of the specimens shown above. Note that although the direct necrosis-producing effect of formaldehyde was the same in both cases, ACTH pretreatment (left) almost completely prevented the proliferative inflammatory response to the local tissue injury, which is so evident in the control.

(After Selye B39702/49.)



← Legend

This is a "rheumatoid type" of joint lesion elicited in rats by the injection of some irritant, e.g., formaldehyde, into the joint region itself. If exposure to stress occurs when the "formalin arthritis" is already fully developed, the joint lesions rapidly retrogress. These observations were correlated with the clinical effectiveness of stressors (e.g., "non-specific therapy", traumatic injuries, starvation, pregnancy, icterus) and the beneficial effect was attributed to a sudden discharge of ACTH with a resulting increase in gluco-corticoid production.[25] The inhibition by certain stressors (e.g., cold, ultra-violet rays) of the experimental polyarthritis produced, in the rat, by some pleuropneumonia-like organisms,[25a] may also depend upon this mechanism, while the influence of aureomycin [25b] or BAL,[25c] upon this same polyarthritis, presumably depends upon specific pharmacologic effects.

It is possible that after chronic exposure to the same stressor, conditioning factors so alter the response to this particular stimulus that the "LAP-type" of cortical stimulation ensues; this predisposes to arthritis. If now the organism is exposed to a new alarming agent, to which abnormal conditioning has not yet been acquired, a simple ACTH-discharge results; this tends to cure arthritis.

Stimuli Influencing the Response of the Joints During the G-A-S. — The effect of **ACTH** upon various types of arthritis in man will be discussed below (cf. Joint Diseases of Adaptation). Let us merely mention here that impure LAP (which elicits mainly mineralo-corticoid effects) sometimes causes a "rheumatoid type" of arthritis in rats,[26] but this effect is rather inconstant.

Although mere treatment with LAP in itself rarely produces arthritis, it rather consistently aggravates the inflammatory response of joints to local irritation, for instance that caused by formalin. Histologically, this *"formalin arthritis"* resembles an acute rheumatic lesion during the first few days, but later it tends to assume the morphologic characteristics of rheumatoid arthritis. It is especially this latter type of response, which is accompanied by intense fibroplasia and granuloma formation, that is aggravated by LAP in the rat.[27]

Conversely, pure ACTH preparations interfere with the production of "formalin-arthritis" and tend to accelerate its disappearance if the hormone treatment is initiated when the joint lesion has already developed.[28]

A similar *"topical irritation arthritis"* can be produced in the rat by the injection of a 10% suspension of mustard powder into the joint region. Here ACTH exerts even more obvious therapeutic and prophylactic effects.[28a]

In experiments on the rabbit it was found that pure ACTH diminishes the permeability of the synovial membranes to phenolsulphonphthalein "... 0.5 mg. of ACTH per kilogram were almost as effective in decreasing permeability of synovial membranes as the alarm-reaction".[29]

In our experiments concerning the effects of **DCA** overdosage in the rat, we often observed the occurrence of an acute mono- or polyarthritis, which resembled that seen in rheumatic fever. It usually developed in the metatarsal or metacarpal joints, sometime during the 2nd or 3rd week of treatment. These arthritides tended to heal in some joints, reappearing in others and eventually

[25] Selye B39702/49.
[25a] Tripi et al. B44920/49.
[25b] Kuzell et al. B44916/49.
[25c] Gardner et al. B44915/49.
[26] Selye B1204/46.
[27] Selye B39702/49.
[28] Selye B39702/49.
[28a] Coutu and Selye B46942/50, B46943/50.
[29] Seifter et al. B43460/49.

they disappeared completely, although the DCA administration was continuous. In view of the great histologic similarity between these joint lesions and those seen in spontaneous rheumatic fever, we considered the possibility that mineralocorticoids may play a rôle in the pathogenesis of the latter in man. This view appeared to receive further support from the observation that "Aschoff-nodule-like" granulomas in the heart and vascular lesions resembling rheumatic arteritis, developed in these same DCA-treated animals.[30] Unlike many other manifestations of DCA overdosage, arthritis is not definitely more pronounced or frequent in unilaterally nephrectomized than in intacts rats.[31]

Involvement of the joints is much less constant than the other lesions (e.g., cardiovascular and renal changes) caused by excess DCA.[32] This does not necessarily militate against the above interpretation, since in acute rheumatic fever, joint involvement is also inconstant and often absent when the cardiac lesions are still progessive. The fact that several reliable investigators noted acute "rheumatic" joint changes in Addisonian patients treated with high doses of DCA [33] is most suggestive in this connection.

In view of the inconstancy of this particular change, it is not surprizing, however, that in occasional small experimental series, arthritis may be absent in rats receiving DCA.[34] The cause of this inconsistancy in the production of arthritis by DCA has not yet been elucidated, but presumably it depends upon the presence of conditioning factors such as some local irritant.

That the action of mineralo-corticoids upon joints is largely dependent upon local irritation has also been confirmed by experiments in rabbits. Here, diluted staphylococcus filtrate, or hot Ringer solution, was used as a local irritant. The absorption of hemoglobin from normal joints was not influenced by DCA, but pretreatment with this hormone increased the absorption-rate from markedly injured synovial membranes. Curiously the steroid exerted an inverse effect if the joints were only mildly irritated.[35]

In another pertinent series of experiments on rabbits, the permeability of the synovial membranes was measured by the speed of absorption and excretion into the urine of phenolsulphonphthalein. Here the speed of absorption was markedly increased by DCA. Presumably the hormone enhanced the permeability of the synovial membrane.[36]

Apparently, in the production of arthritis — as in the pathogenesis of so many other diseases of adaptation — the ratio between mineralo-corticoids and gluco-corticoids plays a most important rôle. In otherwise untreated **adrenalectomized** rats, arthritis has developed quite frequently, at least in one laboratory [37] and was ascribed to hypocorticoidism. It is known that Addisonian patients often suffer from stiffness of the joints, accompanied by pain, which they tend to describe as "rheumatism" although there rarely develops an actual arthritis.[38] We have not seen arthritis in merely adrenalectomized rats, but we noted in the course of our first experiments concerning the rôle of the adrenal cortex in the production of joint lesions, that, under the influence of DCA,

[30] Selye et al. A72284/44.
[31] Pemberton et al. B25622/47.
[32] Hall B4783/46, Haour B44058/49, Selye 91825/46, B1204/46, 94572/47.
[33] De Gennes et al, B33884/47, De Gennes B27804/47, Laroche B33901/47, B27805/47, Thorn B41761/49.
[34] Harrison 91827/46, B3033/46.
[35] Edlund B37814/49.
[36] Seifter et al. B43460/49.
[37] Chamorro B35471/45.
[38] Thorn B41761/49.

adrenalectomized animals developed arthritis much more easily than intact controls. This led us to assume that some adrenal principle normally antagonizes the arthritis-producing effect of DCA.[39]

The sensitization to DCA by adrenalectomy in the rat is even more obvious if the joints are systematically subjected to histologic investigation. It appears that microscopic signs — such as inflammatory infiltrations in the synovial membranes and the periarticular connective tissue — are quite regularly present in adrenalectomized, but not in intact, DCA-treated rats.[40] Here the increased DCA sensitivity was again ascribed to the absence of adrenal gluco-corticoids.

In agreement with expectations, pure gluco-corticoids such as **cortisone** very effectively inhibit the experimental "formalin arthritis",[41] or "mustard arthritis" [41a] both in the intact and in the adrenalectomized rat. The latter is preferable for the bioassay of anti-arthritic activity, because ablation of the suprarenals removes the source of endogenous corticoids, which otherwise complicate the response of the joint to injury.

Of course in the development of the "rheumatoid type" of arthritis, we must consider not only the accumulation of synovial fluid, but also the formation of edema and granuloma tissue in the synovial villi and in the periarticular tissues. In experiments in which the effect of DCA and cortisone — singly or in combination — was examined in rats with "formalin arthritis", it was found that cortisone not only inhibits the development of this type of lesion in otherwise untreated animals, but even overcomes the aggravation normally induced by DCA. This showed that a high gluco-corticoid:mineralo-corticoid quotient also favors the absorption of edema and granulation tissue from the periarticular structures.[42] As we shall see later, this antiphlogistic effect of cortisone is quite obvious even in structures unrelated to joints (e.g., blood vessels).

On the basis of preliminary experiments, it has been claimed that combined treatment with DCA and ascorbic acid counteracts the development of the "formalin arthritis",[42a] but with the experimental technique used in our Institute, we failed to confirm this.[42b]

Cortisone also diminishes the permeability of the synovial membranes as judged by the phenolsulphonphthalein test. From this it was concluded "that the normal permeability of the synovial membranes is in part controlled by the balance between adrenal steroids of the DOCA (DCA) type and of the compond-E (cortisone) type".[43] However, this test lacks specificity. Some steroids bearing no oxygen at C_{11}, and having little if any effect upon rheumatoid arthritis in man — e.g., **21-acetoxypregnenolone** — act like cortisone in this bioassay procedure.[43a] Yet, acetoxypregnenolone does not inhibit the "topical irritation arthritis" of the rat [43b] and causes no cortisone-like improvement in patients with rheumatoid arthritis (cf. below).

We shall make no attempt to survey the extensive literature on the effects upon joint structures of **other hormones,** since this has been done repeatedly elsewhere.[44] Let us point out, however, that *estrone* tends to decrease the

[39] Selye et al. A72284/44, Hall B4783/46.
[40] Pirozynski and Akert B38484/49.
[41] Selye B39702/49.
[41a] Coutu and Selye B46942/50.
[42] Selye B39702/49, B41241/49.
[42a] Brownlee B45098/50.
[42b] Coutu and Selye B46942/50.
[43] Seifter et al. B43460/49.
[43a] Fitch et al. B46306/50, Seifter et al. B46263/50.
[43b] Coutu and Selye B46943/50.
[44] Selye et al. **A72284/44.** Silberberg and Silberberg **B40243/49.**

permeability of the synovial membranes in rabbits as judged by the phenolsulphonphthalein test; [45] in this respect it somewhat resembles cortisone. In the intact rat, large doses of folliculoids also tend to inhibit (slightly) the development of the "topical irritation arthritis", but this is presumably due to endogenous gluco-corticoid production.[45a]

Testoid compounds have been claimed occasionally to produce arthritis, or at least some joint swelling in man.[46]

It is also of interest that the joint stiffness, which can be induced in guinea-pigs by feeding them on a skim-milk diet is alleviated by some compound present in crude cane molasses. This *"anti-stiffness factor"* is a steroid having the probable formula $C_{28}H_{46}O$.[47]

Joint Diseases of Adaptation

In the following pages we shall discuss various types of arthritis conjointly. We feel that this is justified in the present book because G-A-S mechanisms undoubtedly play a prominent rôle in the development of any kind of arthritis. As we have seen in the preceding pages, even the inflammation of the joint-tissues produced by formaldehyde is largely dependent upon stress sensitivity and particularly the gluco-corticoid:mineralo-corticoid balance. Hence presumably, the course of an arthritis produced by any agent (including local infection or trauma !) would always largely depend upon the efficacy of systemic adaptive mechanisms to cope with local stress. It will be kept in mind, that even in the case of the so-called infectious arthritides, the actual demonstration of micro-örganisms in the joint cavity itself is not always possible. Hence probably many infectious diseases produce joint lesions due to systemic humoral derangements and not to the actual invasion of germs into the joints.

Among the most common forms of joint lesions, it is customary to distinguish the arthritis of rheumatic fever, rheumatoid arthritis (synonyms: atrophic arthritis, chronic infectious arthritis, arthritis deformans) and osteo-arthritis (synonyms: hypertrophic arthritis, degenerative arthritis, osteo-arthrosis). In current textbooks of medicine, considerable space is devoted to a discussion of the differences between these diseases, and especially to the differential diagnosis between the last mentioned two groups. This differentiation is sometimes very difficult and "it must not be forgotten that in the case of a middle-aged individual, rheumatoid arthritis may be superimposed on a degenerative arthritis, and that both processes may attack the same joint".[48]

Since the etiology of all these arthritides is not known, we wonder whether it is really justified to stress so much the differences between them, which are often difficult to detect, rather than the similarities, which are always obvious. In all these, and many other instances, a systemic disease of unknown etiology manifests a specific affinity for joint structures and tends to cause more or less acute non-specific inflammatory or degenerative changes in them. We do not mean to imply by these remarks that all these arthritides are but one disease. However, the manifestations of a disease are merely the sum of the body's specific and non-specific responses to a pathogenic agent. The non-specific responses are by definition always the same. Hence, a difference between one

[45] Seifter et al. B43460/49.
[45a] Selye 35935/ND.
[46] Perrault et al. B25955/48.
[47] Ross et al. B37268/49.
[48] Cecil A63152/30-43.

malady and another can only be due to differences in the evocative pathogenic agent (which in this case cannot be identified) or to different conditioning factors, which may modify the course of the non-specific response (such as age, heredity, diet, previous exposure to stress). We believe that these latter circumstances are the chief factors which determine the type of arthritis that will result from a standard exposure to stress.

Both the histological characteristics and the clinical course of the above mentioned arthritides suggest that one of the major distinctions between the arthritis of rheumatic fever, rheumatoid arthritis and osteo-arthritis is that the first mentioned is the most acute, the last the most chronically developing lesion. Accordingly, the arthritis of rheumatic fever is most common among the youngest, while osteo-arthritis is most frequent in the oldest age group.

It is well known that many other pathogens will cause increasingly less acute inflammatory reactions with advancing age. Even the "formalin arthritis" most closely resembles rheumatic, rheumatoid and osteo-arthritis, in young, middle-aged and senile rats, respectively. In view of these considerations, it may be well not to forget that the underlying mechanism in all these arthritides may be essentially similar, the differences being mainly due to incidental conditioning factors. The production of the polymorph of pulmonary, osseous, cutaneous and miliary types of tuberculosis by the same agent, would be a somewhat comparable case. Only the discovery of distinct pathogenic agents could justify the complete separation of these arthritides and available data rather suggest that any of them may be precipitated by the same stressors.

In the previous section we have already mentioned the **experimental data** which suggest that humoral factors, and particularly adreno-cortical hormones, play an important rôle in the development of various kinds of arthritis. These observations suggested that neither a hyper- nor a hypo- corticoidism is particularly conducive to arthritis, but that inflammatory changes in the joints are most effectively combatted by gluco-corticoids, while mineralo-corticoids have an opposite effect. This appears to be true whatever the nature of the local irritant may be. Hence, a derangement in the gluco-corticoid:mineralo-corticoid balance was considered to be the cardinal factor.

Clinical observations suggested long ago that sub-acute and chronic poly-arthritides are quite common in patients with atypical forms of *Addison's disease*.[49] Some derangement in adrenal function also appears to exist in both male and female patients suffering from ankylosing spondylarthritis, since here *17-KS excretion* is allegedly often increased until the patients reach a state of exhaustion.[50] On the other hand, usually low urinary 17-KS values have been found in rheumatoid arthritis [51] and in rheumatic fever.[52] While any derangement in 17-KS excretion may suggest some adreno-cortical dysfunction, such observations give us no information concerning the gluco-corticoid:mineralo-corticoid balance which is presumably the important factor. Besides, the 17-KS elimination often remains normal in rheumatoid arthritis or spondylitis [52a] and even when a decrease does occur, its significance is difficult to evaluate, since low 17-KS elimination is characteristic of the resistance phase of the G-A-S, no matter how produced.

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[49] Allegra B44837/49, Curschmann A54894/41, 91856/32.
[50] Davison et al. B30925/49.
[51] Fraser et al. A36086/41, Hench et al. B27892/49, Justin-Besançon et al. B46130/49.
[52] Chou and Wang A54250/39.
[52a] Desmarais B46330/49.

The *gluco-corticoid* elimination is often somewhat increased in patients with rheumatoid arthritis, but this is not a constant phenomenon.[52d]

If progesterone is administered intramuscularly, an abnormally high proportion of it is eliminated as *pregnanediol* by rheumatoid arthritics of both sexes. The question was raised whether there is "a relation between this metabolic abnormality and the fundamental pathogenesis of rheumatoid arthritis".[52b] Should this prove to be the case, the observation would support the view that here — as in other "diseases of adaptation" — a deranged steroid hormone production in response to stress is of pathogenic significance.

In women with various types of "arthroses" the urinary elimination of *folliculoids* is low,[52c] but since many other chronic diseases have a similar action, this is not necessarily an indication of a specific steroid-metabolism derangement.

It is perhaps also significant that patients with rheumatoid arthritis often show a flat "diabetic type" of *glucose-tolerance curve*.[53] Since gluco-corticoids can cause a similar disturbance,[54] this derangement could conceivably result from an effort on the part of the patient to combat the arthritis by an increase in gluco-corticoid production, but this remains to be proven.

The *hyperglobulinemia* of active rheumatoid arthritis is allegedly the result of the combined effects of inflammation, tissue destruction and immunization.[54a] Electrophoretic studies show a marked decrease in albumin, a marked increase in fibrinogen and γ-globulin, and a moderate increase in the α_1 and α_2-globulin components is quite characteristic of rheumatoid arthritis, but in rheumatoid spondylitis the protein patterns are strikingly different.[54c]

Because of its metabolic relationships to histamine, the urinary excretion of *histidine* deserves special attention. It is usually subnormal in rheumatoid arthritics, but rises considerably during remissions produced by ACTH. The histidine elimination is also high in pregnancy and particularly in patients who experience a remission from rheumatoid arthritis during the course of gestation.[54b]

The frequent occurrence of arthritis in patients with *Cushing's disease* and *acromegaly* [55] or those suffering from *thyroid disturbances* [56] re-emphasizes the pathogenic importance of an endocrine factor, although purely *"endocrine arthritis"* in rare.[56a]

The possible *relationship between* the *G-A-S* and rheumatoid arthritis has been discussed by many authors from various points of view [57] main emphasis being placed, of course, upon the probable rôle of G-A-S changes in the adrenal cortex.

[52d] Staub et al. B47699/50.
[52b] Sommerville et al. B44426/50.
[52c] Justin-Besançon et al. B46130/49.
[53] Flynn and Irish **93097/46**, Lövgren B41821/45, Polonovski et al. B45426/47.
[54] Selye **94572/49.**
[54a] Wallis **B46704/50.**
[54b] Holbrook et al. B46980/50, Rose et al. B47897/50.
[54c] Paul and Routh B47234/50.
[55] Bassi and Bassi B35709/46, Selye **94572/49.**
[56] Bassi and Bassi B35604/46, Menetrier B37881/47.
[56a] Thiers B46129/49.
[57] Anonymous B43694/49, B36286/49, B39562/49, B43809/49, Bishop B46685/49, Boland B47735/50, Copeman B39547/48, Heilmeyer B47479/50, Hughes B44427/49, Lichtwitz B44069/49, Misgeld B45083/49, Rentchnick B41988/49, Tarantino B46747/49, Theiler et al. B41852/49, Wright B36907/44.

It should also be mentioned in this connection that acute arthritis, not unlike that seen in rheumatic fever, has repeatedly been noted in combination with *cardiac lesions*, especially myocardial infarction.[58] The frequent combination of so-called post-infectious myocarditis, hypertension and arthritis has also been discussed in connection with general adaptive reactions to infectious disease.[59] Since myocardial infarction and myocarditis are common in the experimental hyalinosis produced by mineralo-corticoids, it is also noteworthy that granuloma formation in cardiac [60] or skeletal [61] muscle are comparatively frequent in patients suffering from rheumatoid arthritis. Such granulomas are also characteristic of acute rheumatic fever; these findings again point to some relationship between mineralo-corticoid intoxication, rheumatoid arthritis and the arthritis of acute rheumatic fever.

Among the clinical observations most suggestive of a relationship between the G-A-S and rheumatoid arthritis is that the latter can be *precipitated by a variety of non-specific stressors*, e.g., allergic reactions, focal infections and psychosomatic derangements.[62] All of these are known to be capable of causing derailments of the systemic adaptive responses.

In certain instances, the onset and course of the disease are so obviously correlated with emotional disturbances that the term "psychogenic rheumatism" has been used. Here it is difficult to decide whether the rheumatic lesion, or the psychic disturbance, is the patient's "disease". "What we conventionally call 'disease' is sometimes the 'agent provocateur', sometimes the wound; it is sometimes the overaction of systemic defence measures and sometimes the consequences of mismanagement by relatives, friends and even doctors. . . . All these we have called the 'the disease' . . . What kind of arthritis is it which becomes activated with each quarterly meeting of the board of directors ?".[62a] These problems may find their answer if we interpret rheumatoid arthritis as a disease of adaptation and not one caused by the specific actions of any particular pathogen.

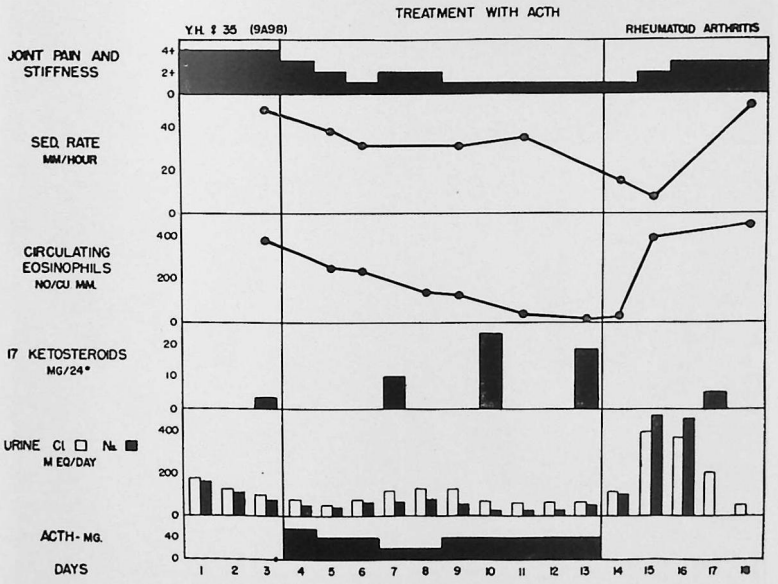
It is perhaps even more suggestive in this connection that exposure of a patient, who already has rheumatoid arthritis, to some new stressor tends to cause a remission in the disease. It will be recalled that the very principle of *non-specific therapy* is to elicit a discharge of ACTH. For this it is necessary to use a stressor to which the organism has not come to react simultaneously with such conditioning responses which would cause an excessive increase in the mineralo-corticoid production. In this event, presumably the ACTH causes a predominantly gluco-corticoid response and restores the abnormal gluco-corticoid:mineralo-corticoid ratio. In this connection it is interesting that according to Hench [63] rheumatoid arthritis is beneficially influenced by a variety of typical systemic stressors such as surgical interventions, starvation, febrile reactions to foreign protein, pregnancy or icterus. He asked himself "but how can each of these procedures specifically affect the entity, rheumatoid

[58] Meyer and Binswanger **88844/42.**
[59] Arnold B41249/49.
[60] Clark and Bauer B43978/48, Gruenwald B42348/48, Oppenheim B45598/46, Rosenberg et al. **B38145/47.**
[61] Anonymous **B36286/49,** Bunim et al. B44502/48, Desmarais et al. B44349/48, De Forest et al. B46028/47, Gibson et al. B39005/46.
[62] Cobb et al. B321/39, Copeman **B39547/48,** Halliday B44599/43, B46202/47, Hench B45356/49, Simonart B43699/46, Hench B45356/49, Hiller B47014/49, Simonart B43699/46, Weiss B3989/47.
[62a] Menninger B44688/48.
[63] B27847/49.

arthritis ?" He concluded that none of these procedures has any "specific merit" and, among other non-specific reactions to injury, he considered the possibility of some endocrine derangement that might ensue upon exposure to stress.[64]

Following this kind of reasoning, shortly afterwards, Hench et al.[65] administered large doses of *cortisone* or *ACTH* to patients with rheumatoid arthritis. They obtained a truly dramatic and almost instantaneous improvement in the condition of the joints. At the same time there was a fall in the previously high erythrocyte sedimentation rate. Upon discontinuation of such therapy, the manifestations usually (but not always) returned or increased promptly.

Several earlier workers have claimed to obtain more or less spectacular benefit from treatment with corticotrophic anterior-lobe extracts [66] or adrenocortical extracts,[67] but of necessity they had to use comparatively small doses of incompletely purified hormone preparations. It is undoubtedly the merit of Hench, Kendall and their group at the Mayo Clinic to have clearly demonstrated the great efficacy of this therapy by the administration of large doses of highly purified hormone products, as soon as these became available.

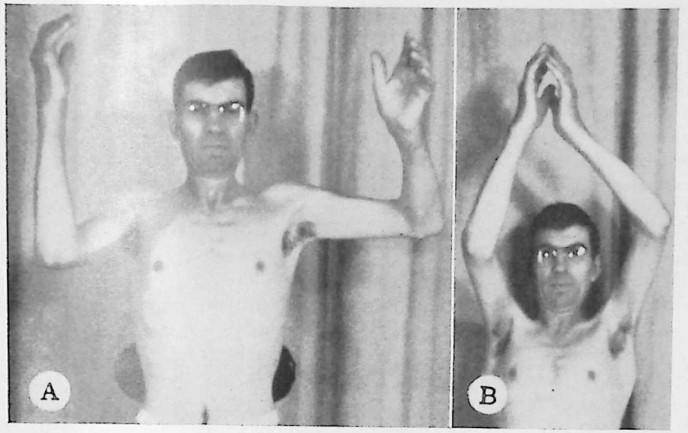


Typical response to ACTH in a patient with acute rheumatoid arthritis. Note the rather gradual fall in sedimentation rate and its prompt rise to abnormal levels following cessation of therapy. The fall in circulating eosinophils, the rise in urinary 17-KS and the very slight, but definite, Na retention — all evidence of adrenocortical activation by ACTH. The marked loss of Na in the urine following cessation of therapy may represent the effect of relative adrenal insufficiency at this point. (After Thorn et al. B39546/49.)

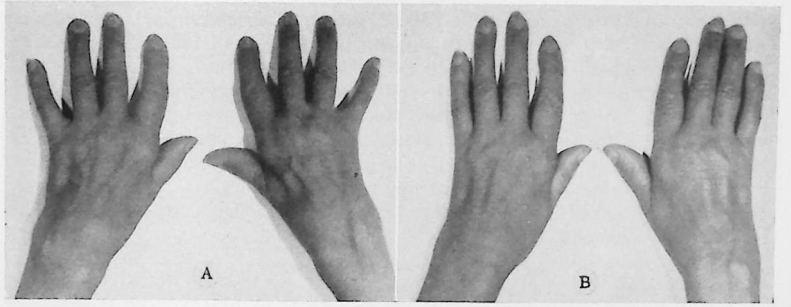
[64] Hench B27847/49.
[65] B41840/49, B27892/49.
[66] Schmidt B41846/49, Greene B43382/49.
[67] Bassi and Bassi B30237/46, Watson A34185/40.



Effect of ACTH in rheumatoid arthritis. — **A.** Before treatment. — **B.** Eight days after commencement of cortisone administration. The patient had received an initial injection of 300 mg. and then 100 mg./day for seven days. Both the swelling and the stiffness of the fingers have regressed considerably. (Courtesy of Dr. E. W. Boland.)



Effect of cortisone in rheumatoid arthritis. —**A.** Untreated patient with subacute rheumatoid arthritis, showing limit of level to which he could raise his arms. This amount of movement caused considerable pain. — **B.** Same patient after four days of treatment with cortisone, showing increased range of movement of shoulders associated with marked reduction of pain and stiffness. (Courtesy of Drs. Hench, Kendall, Slocumb and Polley.)



Effect of ACTH in rheumatoid arthritis. — **A.** Before treatment. — **B.** 12 days after initiation of ACTH administration. Note great diminution in the swelling. (After Mach et al. B45954/50.)

The observations made by the workers of the Mayo Clinic have repeatedly been confirmed on a large number of patients suffering from rheumatoid arthritis. There is no doubt that, almost always both cortisone [68] and ACTH [69]

[68] Anonymous B45084/50,
Boland **B47735/50**,
Boland and Headly B39524/49,
Hollander et al. B47877/50,
Lichtwitz B44069/49, McNee B46150/50,
Misgeld B45083/49.

[69] Anomymous B36285/49,
Boland **B47735/50**,
Brochner-Mortensen et al. B43390/49,
Clark et al. B46978/50,
Coke B44441/49,
Elkinton et al. B45107/49, B46985/50,
Gil B46731/50, Kinsell B46305/49,
Hollander et al. B47877/50,
Lichtwitz B44069/49,
Mach et al. B45954/50,
Markson B44450/49, McNee B46150/50,
Misgeld B45083/49,
Ragan et al. B43463/49,
Spies and Stone B44446/49, B43903/49, B45101/50,
Spies et al. B45105/49,
Thorn et al. B39546/49.

are eminently effective if adequate doses (about 100mg./day of either preparation) are administered. With *cortical extracts*, even if given in large quantities, the results are less conclusive,[70] presumably because it is difficult to administer enough.

In agreement with expectation, *DCA* is ineffective, and indeed tends to aggravate the joint lesions in rheumatoid arthritis.[71] According to one preliminary communication, DCA given in combination with *ascorbic acid* has approximately the same effects as ACTH or cortisone,[72] but this claim has not been confirmed by subsequent investigators, whose results were quite variable and contradictory.[73] Ascorbic acid alone may have some effect.[73a]

Since *adrenaline* is particularly effective in causing an ACTH discharge through the A-R mechanism, this hormone has been administered to patients with rheumatoid arthritis. Some benefit could be observed, although the endogenous ACTH discharge, that can be obtained with innocuous doses of adrenaline, proved much less effective than the exogenous administration of ACTH or cortisone.[74] Essentially similar results have been obtained with *insuline*,[74a] presumably through the same mechanism.

A number of other steroids have been used more or less empirically. Beneficial effects have allegedly been obtained in rheumatoid (and occasionally even in osteo-) arthritis with various *folliculoids*,[75] *progesterone*,[76] Δ^5-*pregnenolone*,[77] *testosterone*,[78] and *combinations* of testosterone, estradiol and Δ^5-pregnenolone.[79] It has also been claimed that the hydrarthrosis or arthritis which is occasionally produced by testosterone overdosage,[80] can be improved by folliculoids.[81] All these observations will have to be confirmed on a larger clinical material since up to now only preliminary reports are available, and the results — if positive at all — are certainly not comparable to the spectacular remissions obtained by ACTH and cortisone. The same reservations must also be made concerning *21-acetoxypregnenolone*, which has recently been recommended for the treatment of rheumatoid arthritis.[81a] As stated above, none of these steroids, except cortisone, proved to inhibit the "topical irritation arthritis" in the rat. Incidentally in one patient, whose rheumatoid arthritis improved spectacular after ACTH, subsquent treatment with large doses of testosterone was quite ineffective.[81b]

[70] Shirlaw B41845/49, Thorn et al. B39546/49.
[71] Clark B47862/50. Rausten B47667/50, Rausten B47667/50, Spies and Stone B43903/49.
[72] Lewin and Wassen B43383/49.
[73] Anonymous B43384/49, B45084/50, Blackburn and Burke B47666/50, Douthwaite B46304/49, Fox B44408/49, Gitman B44444/49, Hartfall and Harris B44411/49, Hart and Starer B44412/49, Kellgren B44410/49, Le Vay and Loxton B44409/49, B47664/50, Loxton and Le Vay B44413/49, Spies et al. B44414/49, Zondek B47314/50.
[73a] Massell et al. B47740/50.
[74] Godlowski B46434/49, Thorn and Bayles B44425/49, Thorn et al. B39546/49.
[74a] Godlowski B46434/49.
[75] Coste and Hochfeld B43243/47, Coste et al. B45358/48, Gaida B45357/49, Hochfeld B46131/49, Layani B38270/48, Layani et al. B36554/48, Mahoudeau et al. B36236/48, Weil and Sichère B45900/48, B45901/48. B44770/48.
[76] Reich B40230/49, Weil and Sichère B45900/48.
[77] Davison and Koetz B41839/49, Freeman et al. B47650/50, Heilmeyer B47479/50.
[78] Ishmael et al. B41223/49, Lederer B36828/48, B43496/49, Weil and Sichère B45900/48, B44770/48, B45901/48.
[79] Ishmael et al. B41223/49.
[80] Perrault et al. B25955/48.
[81] Laroche and Hochfeld B41679/48.
[81a] Fitch et al. B46306/50, Seifter et al. B46263/50.
[81b] Brochner-Mortensen et al. B43390/49.

A recent survey of several other, more or less closely related compounds (Δ^4-*pregene-17-*(α), *20*(β), *21-triol-3-one diacetate, pregnane-3, 12, 20-trione, 17-methyl-*Δ^5-*androstene-3*(β), *17*(α)*-diol, 17*(α) *hydroxyprogesterone, 17*(α)*-hydroxy-11-desoxycorticosterone-21-acetate, desoxocortisone, ergostanyl acetate*), revealed that none of these had any effect upon rheumatoid arthritis or the eosinophil count in man.[81c]

Among non-hormonal agents which may have a benificial effect in rheumatoid arthritis, *salicylates* have received considerable attention. Some workers ascribed their therapeutic efficacy merely to the production of an A-R.[82] In this sense they would act essentially as any other non-specific therapeutic agent. Because of their undoubtedly specific effect in rheumatic fever, this requires confirmation.

Glucuronic acid treatment has been recommended, in rheumatoid arthritis and allied conditions, mainly because in such mesenchymal diseases there appears to be some evidence of a glucuronic-acid deficiency.[82a] Although beneficial results have been noted in some cases, final judgment must await confirmation on a larger clinical material.

Since *anti-histaminics* can cause remissions in allergic diseases, and in this resemble gluco-corticoids, it has been suggested — on purely theoretical grounds — to examine the possible value of the former in the treatment of some diseases of adaptation, for instance, in rheumatoid arthritis.[82b] However, clinical observations revealed that anti-histaminics actually aggravate the joint lesions in rheumatoid arthritis. In patients simultaneously afflicted by rheumatic (rheumatoid arthritis, rheumatic fever) and allergic (asthma) diseases, there appears to be "an alternation between the symptoms of rheumatism and bronchial asthma," as if the two conditions were mutually antagonistic.[82c] Yet, recent experiments suggest that in the rat many manifestations of DCA overdosage (e.g., nephrosclerosis, hypertension) are effectively counteracted by anti-histaminics.[82d] Hence, perhaps further experiments along these lines may still yield interesting results, at least in some of the "diseases of adaptation", which are simulated by mineralo-corticoid overdosage.

Certain *thiosemicarbazone-derivatives* ("Tb I", "Conteben") have allegedly given most satisfactory results in rheumatoid arthritis. The diminution of the joint manifestations was accompanied by a very pronounced decrease in the E.S.R. and eosinopenia. The relationship of this therapy with the G-A-S mechanism has been discussed in detail and the evidence favoring an inhibition of mineralo-corticoid production or an increase of gluco-corticoid secretion has been reviewed. These observations, as well as certain derangements in the steroid metabolism of patients with rheumatoid arthritis were interpreted as additional evidence that here we are dealing dith a disease of adaptation.[82e]

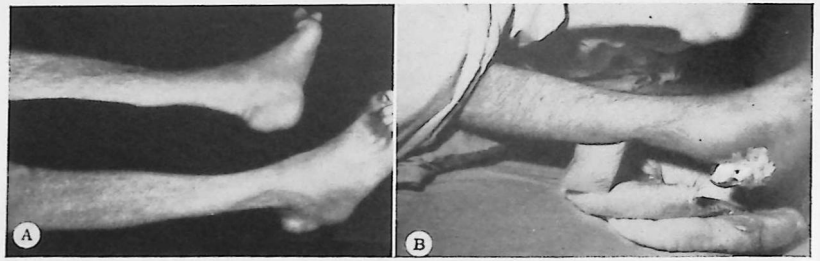
Preliminary experiments suggest that *postpartum plasma*,[82f] *niacin*,[83] *adenylic nucleotides* [83a] and *ATP* [84] also hold some promise in the treatment of rheumatoid arthritis, but none of these agents have as yet given such spectacular therapeutic results as are obtained with ACTH and cortisone.

[81c] Spies and Stone B43903/49, Terry and London B47064/50.
[82] Forman et al. B37491/48.
[82a] Hodas et al. B44577/49, Peterman B44576/47.
[82b] Selye B39702/49.
[82c] Järvinen B46478/50.
[82d] Guillemin and Selve B47398/ND.
[82e] Heilmeyer B47479/50.
[82f] Granirer B46946/50.
[83] Kaufman B36351/49.
[83a] Ruskin B47755/49.
[84] Carlström and Lövgren B41824/43, Lövgren B41822/44.



Acute gouty arthritis precipitated by withdrawal of ACTH. Note swelling of second digit and cellulitis of back of the hand which appeared 48 hours after the administration of ACTH. The patient was successfully treated for the acute attack by a second course of ACTH.

(Courtesy of Dr. L. Hellman, Medical Division, Montefiore Hospital.)



Effect of ACTH and cortisone in gout. — **A.** Note well developed tophi during an attack, before treatment. — **B.** Liquefaction and breakdown of the tophus following a few tays of treatment with large doses of ACTH and cortisone.

(Courtesy of the staff of the hospital for Special Surgery, New York City research under the direction of Drs. Freyberg and Trager.)

In the juvenile form of rheumatoid arthritis, known as **Still's disease,** ACTH is also very effective.[84a]

In this section we have not spoken about **gouty arthritis** since this condition has already been discussed in the section on "Metabolic Diseases of Adaptation". Let us merely re-emphasize a few cardinal facts here. ACTH increases the uric-acid concentration of the blood and urine, but, in gouty arthritis, the clinical improvement after ACTH therapy is much greater than that obtained

[84a] Stillman and Bayles B46981/50.

with other agents causing a comparable uric-acid excretion (e.g., acetylsalicylic acid).[85] It will also be recalled that, upon interruption of ACTH therapy in predisposed patients, an acute attack of gouty arthritis can be actually precipitated by some "withdrawal phenomenon".[86]

TEETH

The influence of the G-A-S on dental development has not yet been systematically examined. One rather pertinent investigation was concerned with the importance of systemic factors upon the development of alveolar bone. It was concluded "that in systemic health and disease, alveolar bone reflects the prevailing status of the entire skeletal system in terms of the relative predominance of bone formative or bone resorptive changes".[87]

It is common knowledge, of course, that various systemic diseases, intoxications, malnutrition and other types of stress delay and derange dentition in children. Yet it is noteworthy that even in advanced hunger osteopathy the teeth are usually not affected,[88] and that dental caries are allegedly even less than normally common in malnourished patients.[89]

[85] Boland **B47735/50.** Thorn et al. B39546/49.
[86] Hellman B32329/49. Thorn et al. B39546/49.
[87] Glickman B30994/49.
[88] Keys B37797/48. **B46730/50.**
[89] Mann et al. B38639/47.

BLOOD COUNT

(See also: iron and hemoglobin metabolism, erythrocyte sedimentation rate, blood-coagulation, erythrocyte resistance, blood-sludging.)

Virchow [90] was probably the first to point out clearly that the old concept of "pyemia" corresponded to a leucocytosis, while Israel [90a] recognized the fact that this was not a disease in itself but the consequence of other diseases. Towards the end of the last century the non-specific nature of most types of leucocytoses had become almost generally accepted and its participation in defense phenomena was suggested by such names as "Kampf Leucocytose", especially in the German literature. On the other hand, it was also observed that sometimes an equally non-specific diminution of the white-cell count occurred under the influence of disease or non-specific protein therapy; this was referred to as leucolysis ("Leucolyse").[91]

Systematic experiments on animals soon revealed that the white-cell count is normally quite different in various vascular territories of the body and that these differences may become even more pronounced under the influence of diverse injuries. Thus, one early investigator noted that in the splenic vein of a rabbit, there were 3,400 leucocytes per cc. of blood, while, at the same time, the splenic artery contained 28,000. Presumably an increase or decrease in circulating leucocytes is not necessarily indicative of an altered production or destruction of these cells. It may also result from an abnormal distribution, perhaps due to local "chemotaxis", causing retention of white cells in certain organs, from which they can later be discharged into the general circulation when needed.[92]

Subsequently, with the gradual improvement of hematologic technics, increasingly more emphasis was placed upon the differential white-cell count. It was found that even within the same vascular territory, the different types of leucocytes do not necessarily show parallel variations. It has also been recognized that some abnormalities of the blood-count are highly specific for certain diseases (e.g., leukemias, anemias, agranulocytoses, erythrocytoses), while others are relatively non-specific (e.g., the neutrophil leucocytosis of infections, the eosinophilia of the allergic diseases). Thus the differential blood-count became an important diagnostic tool in modern medicine.[93]

Systemic stress. — In 1936, when the concept of the G-A-S began to crystallize, it became evident that some changes in the blood-count are entirely non-specific and represent manifestations **characteristic** only of the G-A-S itself. Observations on the mouse and rat revealed that such diverse alarming stimuli as adrenaline, formaldehyde, cold, trauma or forced muscular exercise cause essentially similar changes in the white-cell count. This led us to "conclude that the total white-cell count increases, mainly as a result of *neutrophilic leucocytosis* during the alarm reaction. At the same time, there is *relative lymphopenia*. Following exposure to very severe alarming stimuli, a period of leucopenia precedes this characteristic reaction. Leucopenia was observed throughout the whole experiment in those cases in which the animal was unable to resist the alarming stimulus so that death ensued".[94]

[90] B27276/871.
[90a] B27274/889.
[91] Löwit B27275/892.
[92] Schulz **A32636/893.**
[93] French and Douthwaite **99226/45,** Palmer **95299/46.**

Blood-count	*Normal*	*Alarmed*
Total white-cell count	13,000	25,000
% Polymorphs	35	76
% Lymphocytes	62	24
% Eosinophils	3	0

Effect of A-R upon the white cell count in the rat. Synoptic symmary of various experiments. (After Selye 94572/49.)

In view of the rather extensive recent literature concerning this subject (cf. below), it is especially emphasized that all these alarming stimuli caused a considerable absolute increase in the total white-cell count, which was entirely due to polymorphonuclear leucocytosis. The accompanying lymphopenia was almost invariably relative; only occasionally did we find a small diminution in the absolute number of the lymphocytes (cf. table). The mildness of this absolute lymphopenia was somewhat surprizing to us since histologic studies showed that, at the same time, the lymphocytes in the germinal centers of the lymph-nodes, as well as the thymocytes, underwent practically complete disintegration. From this it is evident that the circulating lymphocytes are much more resistant to destruction by alarming stimuli than those in lymphatic organs, especially in the thymus and the germinal centers.

Our experiments on rats exposed to cold, forced muscular exercise, or formaldehyde injections revealed furthermore that "in contradistinction to the neutrophils, the *eosinophils* diminish almost to the point of complete disappearance from the circulation, but reappear later in larger numbers when the neutrophils return to normal. The *reticulocytes* show a simultaneous, rather considerable rise".[95] Numerous subsequent observations showed the intensity and constancy of the eosinopenia and reticulocytosis during the A-R phase of the G-A-S.[96] All these findings were only of theoretic interest, however, until it was shown that in man, this eosinopenia is a highly sensitive and constant sign of the A-R, probably mediated through the discharge of ACTH and glucocorticoids. It is due to these clinical observations that the eosinopenic response has been developed into a diagnostic procedure capable of testing selectively the responsiveness of the hypophysis (exposure to stress), adrenal cortex (injection of ACTH) and the peripheral targets (injection of gluco-corticoids).[97] The various techniques recommended for the counting of eosinophils have been reviewed elsewhere.[97a]

The *red-cell count* rises during the shock phase of the A-R but tends to return to or below normal during the resistance phase, presumably due to initial hemoconcentration followed by blood dilution.[98]

It should be emphasized that all these hematologic changes were pronounced only during the A-R phase and tended to disappear as the animals approached the stage of resistance.[99] Unfortunately, no systematic investigations have yet been carried through to the later periods of the stages of resistance and exhaustion.

[94] Harlow and Selye A8400/37.
[95] Dalton et al. A18306/39.
[96] Dalton and Selye A31950/39, Ehrich B46789/50, Harlow B4781/37.
[97] Thorn B41761/49.
[97a] Randolph and Rollins B46951/50.
[98] Dalton and Selye A17985/38.
[99] Selye 73232/38, Harlow B4781/37.

Traumatic shock proved to be particularly effective in causing polymorphonuclear neutrophil leucocytosis with relative lymphopenia during the A-R in the mouse and rat.[100] Essentially similar changes have been observed in the cat and rabbit,[101] the dog [102] and man.[103]

Eosinopenia following various surgical operations has been noted in the dog [104] and in man.[105] Since ACTH and corticoids likewise cause eosinopenia, recent investigators believe that "the occurrence of eosinopenia following operations may be construed as further evidence of the rôle of the adrenal cortex in the alarm-reaction in man".[106] The often total absence of eosinophils in women during labor and delivery has also been attributed to the adrenocortical stimulation which accompanies the A-R elicited by stress.[107]

The red-cell count shows less consistent variations because it depends largely upon the degree of hemorrhage which accompanies the trauma. The hemoconcentration — due to the A-R itself — tends to cause a rise, the accompanying hemorrhage, a fall in hematocrit values.[108] There also tends to be a widespread trapping of erythrocytes in the minute vessels of all the organs in the body; this naturally likewise influences hematocrit values.[109]

It has long been known that severe **hemorrhage** also causes neutrophilia. The so-called "crusta phlogistica" (the white-cell layer in the blood clot) increases following repeated blood letting; a fact frequently noted by the ancient physicians.[110] Numerous subsequent animal experiments confirmed the existence of a "post-hemorrhagic leucocytosis" and revealed that it is principally due to an increase in polymorphonuclear neutrophils. It has been claimed by earlier investigators that the serum of severely bled animals acquires leucopoietic properties, perhaps due to leucotactic protein degradation products, but this has not been confirmed.[111] Of course, at the same time, the circulating red-cell volume and the hematocrit values are diminished.[112]

In man, following an acute hemorrhage the leucocytosis may be considerable (up to about 30,000/cc.); there is a relative increase in polymorphonuclear neutrophils and often some immature forms appear. Immediately after a severe hemorrhage the red-cell count may remain normal, due to compensation by the discharge of erythrocytes from depots (e.g., the spleen) into the blood. Later, however, blood dilution occurs and the color index falls, because red-cell replacement occurs more rapidly than hemoglobin formation.[113]

Observations on patients with sudden profuse hemorrhage into the peritoneal cavity (e.g., ruptured ectopic gestation, bleeding from a ruptured ovarian follicle), may also cause marked neutrophilia with a shift to the left.[114] This again suggests the non-specificity of this response.

In view of the considerable pertinent literature, it is somewhat surprizing that one group of investigators (apparently quite unaware of any previous

[100] Harlow and Selye A8400/37, Munro and Noble 98562/47, 97324/47.
[101] Allen 76347/38. Cruickshank B46358/42.
[102] Sonobe A8283/37.
[103] Cruickshank B46358/42, Lambret and Driessens A2914/37.
[104] Krumbhaar B27408/17, Lawrence and Maddock B27409/30.
[105] Roche et al. B46957/50, Thorn B41761/49.
[106] Laragh and Almy B28605/48.
[107] Davis and Hulit B38344/49.
[108] French and Douthwaite **99226/45**, Palmer **95299/46.**
[109] Gibson et al. B26950/47.
[110] Schulz **A32636/893.**
[111] Feenders **37979/36**, Schulz **A32636/893.**
[112] Gibson et al. B26950/47.
[113] French and Douthwaite **99226/45**, Palmer **95299/46.**
[114] Kaufman and von Saal 81789/40.

publication on post-hemorrhagic leucocytosis) claimed that in rabbits, removal of one quarter of the blood volume produces no increase in the total leucocyte count. Hence it was concluded that leucocytosis cannot be regarded as a characteristic manifestation of the A-R. This statement is all the more astonishing since their own figures indicate a rise from 8,450 to 12,000 leucocytes/cc. during the 24 hours following the hemorrhage.[115]

In mice hemorrhage also elicits the marked eosinopenia characteristic of the A-R.[116]

Following experimental **burns** in the rabbit, there is an immediate increase in the erythrocyte and hemoglobin content of the blood which accompanies the hemoconcentration due to plasma loss. At the same time, the total white-cell count increases even more markedly than the red-cell count. 12 to 24 hours after a severe burn, however, the leucocyte count falls to extremely low levels with almost complete disappearance of the polymorphonuclear neutrophils, while the red-cell count diminishes.[117] This leucopenia is rather reminiscent of that which we observed in particularly severe alarm-reactions, caused by a variety of other agents to which the animals could not resist (cf. above). It likewise occurs in man, following severe burns.[117a]

In confirmation of clinical observations, it has also been shown in the dog that severe burns can damage the erythrocytes so that there is poikilocytosis and microcytosis, with discharge of free hemoglobin into the plasma. Many of the red cells contain granules similar to the so-called "Heinz bodies". This effect is apparently due to a direct action of heat upon the erythrocytes since it occurs even in blood heated in vitro.[118]

Similar blood destruction, after burns, has also been reported in various other animal species as well as in man.[119] At the same time, the white-cell count is greatly increased and remains high, especially if infection supervenes.[120]

Following severe burns in man, secondary anemia usually begins to be manifest after the 5th day. It may be caused by reabsorption of fluid from the tissues, primary or secondary red-cell destruction due to increased erythrocyte fragility, and sometimes to inhibition of hemopoiesis due to sepsis or malnutrition.[121] Trapping of erythrocytes in the capillaries may also play a rôle.[122]

There is no doubt that in the anemia of burns, a specific, direct, toxic action of heat upon the erythrocytes is of importance. Nevertheless, a recent clinical study led to the conclusion that "a predominant rôle must be ascribed to the absence of erythrocyte regeneration and the hypothesis that the alarm reaction intervenes as an agent causing erythrocyte destruction".[123]

Exposure to **cold** causes a predominantly neutrophil polynuclear leucocytosis in the peripheral blood, for instance in the guinea-pig and rabbit. This was assumed to be largely due to a change in white-cell distribution, since heart blood taken at the same time showed leucopenia.[124] It has been observed in guinea-pigs that the neutrophilia of cold is usually accompanied by lymphopenia and eosinopenia.[125]

[115] Boyd et al. A14717/38.
[116] Speirs and Meyer B43545/49.
[117] Lambret et al. A8119/37.
[117a] Sacher B45845/48.
[118] Barac and Nizet B24096/46.
[119] Hilgenfeldt **38008/36.**
[120] Harkins **91182/44.**
[121] Harkins 91182/44, Moore et al. B35220/46.
[122] Gibson et al. B26950/47.
[123] Monsaingeon and Hurpé B35217/48.
[124] Rovighi and Secchi A420/14.
[125] Josey and Lawrence A32635/32.

Subsequent investigations in the mouse and rat showed that the intensity of these hematologic changes runs parallel with other manifestations of the A-R produced by cold and hence the response was regarded as part of the G-A-S.[126]

In man, exposure to cold has also been demonstrated to cause lymphopenia,[127] eosinopenia [128] and a rise in hematocrit — the latter due to hemoconcentration — if the resulting stress is sufficiently severe to produce other manifestations of the A-R (e.g., increased erythrocyte sedimentation rate, diuresis).[129]

Heat (produced by radiotherm or hypertherm) occasionally causes an initial lymphocytosis, but as fever develops, this is followed by lymphopenia and neutrophilia, both in the rabbit and in man. This was regarded as a "non-specific reaction" representing a "mobilization of the defense forces of the body".[130] Essentially similar hematologic changes were observed in man during exposure to humid heat [131] and especially after an actual heat stroke,[132], as well as in rats exposed to heat.[132a]

Ionizing radiations and especially x-rays exert a rather specific effect upon the blood-count, causing rapid disintegration of both lymphocytes and polymorphonuclears. However, they also elicit non-specific G-A-S manifestations, and hence the hematologic picture resulting from exposure to x-rays is a combination of specific and non-specific actions. Numerous observations, on various animal species and man, reveal that during the few hours following irradiation, there is marked leucopenia with a diminution of both lymphocytes and polymorphonuclears, but on the following day, a polymorphonuclear leucocytosis usually ensues; this is, in turn, followed by a more prolonged leucopenia. The transitory leucocytosis may perhaps be interpreted as part of the A-R produced by this stressor, which, at its height, overcompensates for the specific white-cell destroying action of the rays.[133] The simultaneous occurrence, at a certain stage of lymphopenia with polymorphonuclear neutrophilia,[134] as well as of organ changes typical of the G-A-S [135] led to the suggestion that at least part of the hematologic syndrome after x-irradiation may be due to a superimposed A-R.[135a]

Experiments in which two cats were united by cross circulation, one being x-irradiated, the other shielded, gave no evidence of any humoral transmission of factors which would affect the blood-count.[136] However, perhaps here the duration of the transfusion was not long enough for the corticoids to manifest their effects.

After total body irradiation, there tends to be a transient neutrophilia in various animal species.[137] Erythropoiesis is also markedly depressed, presumably because of damage to the hemopoietic elements of the bone-marrow.[138] Even this response may be largely non-specific as it is duplicated in the rat by acute starvation.[139]

[126] Dalton et al. A18306/39, Elmadjian and Pincus B366/45, Harlow B4781/37, Harlow and Selye A8400/37.
[127] Finesinger et al. B4476/46.
[128] Bader et al. B33091/48.
[129] Eliot et al. B32737/49.
[130] Doan A14836/38.
[131] Pincus and Elmadjian B1243/46.
[132] Malamud et al. **B18019/46.**
[132a] Latta and Nelson B38667/48.
[133] Reding 39925/35.
[134] Dougherty and White 95612/46, Prosser et al. B26618/47.
[135] Painter et al. 98568/47.
[135a] Lecomte and Fisher B46838/49.
[136] Lawrence et al. B37515/48.
[137] Bloom and Jacobson B37514/48.
[138] Salomon et al. B32890/49.
[139] Salomon et al. B32890/49.

Essentially similar hematologic changes have occurred in mice receiving injection of U^{235},[140] as well as in goats,[141] swine [142] and man,[143] exposed (from a great distance) to the atomic bomb. Among the employees of the Los Alamos Scientific Laboratory (Division of Atomic Bomb Project), neutropenia often occurred even when the absolute number of lymphocytes remained normal.[144]

Because of the extraordinary sensitivity of leucocytes to ionizing radiations, it is difficult to distinguish here between specific and non-specific effects. Ionizing radiations are especially effective alarming stimuli and, at the same time, particularly conducive to leucocyte destruction; both these features are characteristic of especially intense stress situations to which adaptation is difficult or impossible. Whether the non-selective destruction of all white-cell types by ionizing radiations should be regarded as related to the A-R is nevertheless very doubtful. It is perhaps more justified to consider the transient polymorphonuclear neutrophilia as part of the G-A-S, especially since it is absent if irradiation is too severe to be withstood and most evident when countershock phenomena are particularly obvious.[145]

Upon **ultraviolet irradiation** a transient leucopenia during the first few hours is soon followed by a marked polymorphonuclear neutrophilia with lymphopenia. Here again, excessive exposure tends to cause only severe leucopenia in which all white-cell types participate. This response, which is highly reminiscent of that caused by other stressors, has been found to occur both in the rabbit and in man.[146]

In patients receiving **electro-convulsive therapy** there is a transitory lymphocytosis with relative neutropenia during the first few minutes,[147] but later this gives way to lymphopenia and eosinopenia, accompanied by a transitory neutrophilia. The latter response was ascribed to activation of the adrenal cortex, since similar results were obtained with injections of purified ACTH.[148]

The transitory neutrophilia caused by electro-shock therapy is duplicated by insulin-shock, air-insufflation of the cerebral ventricles and other stressors. This again was taken to signify that such responses are mediated through the same mechanism.[149]

Following both "grand mal" and "petit mal" reactions to electro-shock therapy in male psychotics, marked lymphopenia ensued in about three hours, although, this was preceded by distinct lymphocytosis during the first 15 minutes after the convulsions.[150] The resemblance of this response to that produced by the stress of other alarming agents has been emphasized.[151]

Nervous and emotional stimuli which are notoriously effective in producing other manifestations of the G-A-S, also proved highly active in eliciting the corresponding hematologic changes. In the cat, the so-called "heat puncture", in which fever is produced by *lesions in the hypothalamus,* was found to cause

[140] Tobias et al. B4455/48.
[141] Cronkite B24042/48, Tullis and Warren B41776/47.
[142] Tullis B41901/49, B27010/48, Tullis and Warren B41776/47.
[143] Cronkite B24051/48, De Coursey B38048/48, Liebow et al. B41902/49.
[144] Dickie and Hempelmann B38111/47.
[145] Ellinger 68685/35, Prosser et al. 98573/47, Reding 39925/35.
[146] Wada 1245/29.
[147] Delmas-Marsalet B26881/46.
[148] Altschule et al. B36865/49, Cleghorn et al. B19125/48.
[149] Delay et al. B34966/47.
[150] Carse and Slater B26273/46, B27273/46, Mikkelsen and Hutchens B19838/48.
[151] Mikkelsen and Hutchens B19838/48.

polymorphonuclear leucocytosis with lymphopenia and eosinopenia.[152] In man, following the injection of irritants into the cerebro-spinal fluid, erythrocytosis, reticulocytosis, neutrophilia and lymphopenia occur. This was attributed to a chemical stimulation of the hemopoietic centers.[153]

Systematic investigations in rabbits indicate that "stimulation of the posterior region of the tuber cinereum or mammillary body resulted in lymphopenia, which was similar in time-relations and magnitude to that following an emotional stress stimulus". Stimulation of other regions of the hypothalamus or hypophysis did not elicit the response.[153a]

It has been claimed that *emotional* excitement tends to cause leucocytosis in the cat and leucopenia in the rabbit,[154] but the cause of this alleged species difference is not known. In rabbits, sympathetic stimulation produces lymphocytosis, parasympathetic stimulation and polymorphonuclear leucocytosis.[155] Certain differences in reactivity have therefore been attributed to varying degrees of sympathico-tonus and parasympathico-tonus, but these "explanations" are rather vague.

It has repeatedly been emphasized that these hematologic changes occur so rapidly that they could hardly be ascribed to actual formation or destruction of cells; probably they are due to a redistribution of the leucocytes in the various vascular territories. This interpretation has received support from actual determinations in various blood vessels.[156]

The first systematic studies which attempted to correlate the hematologic response to a nervous injury with the G-A-S, showed that after *spinal cord transection* in the rat there is polymorphonuclear neutrophilia and hemoconcentration with a rise in the red-cell count. This coincides with other manifestations of the A-R (e.g., enlarged brown adrenals, gastric ulcers, pyknosis and karyorrhexis of thymocytes). It was pointed out, however, that in this particular case, the resulting hypothermia is probably of great importance, since maintenance of the normal body temperature (by placing the animals in a warm chamber) prevented all these manifestations. Nevertheless, the changes in blood picture could be ascribed to the resulting A-R since similar manifestations were produced by formaldehyde injections, and here, maintenance of the body temperature exerted no protective effect.[157]

In mice in which emotional stress was produced by *tying the animals to a wire grid*, there developed a pronounced lymphopenia which again was ascribed to the A-R.[158]

In rats subjected to a similar emotional stress (by tying the hind limbs with gauze and fastening them to a board) lymphopenia was manifest within two hours. Prefrontal leukotomy did not influence this lymphopenia but "the lymphocytic count in the control animals rapidly and progressively returned to normal pre-stress levels, and in these animals the absolute polymorphonuclear-cell count showed a marked rise after stress. In the leukotomized animals, the lymphocyte count did not return to normal as rapidly as in the controls nor did the increase in polymorphonuclear cells occur in these animals".[159]

[152] Borchardt 22895/28, 23991/29, Rosenow A32698/29, 23462/28.
[153] Furbetta and Giunti B38185/48, B38186/48.
[153a] Harris and de Groot B47142/50.
[154] Nice and Katz **A51/36.**
[155] Camp **B312/27.**
[156] Camp **B312/27,** Nice and Katz **A51/36.**
[157] Dalton 79110/40-41.
[158] Elmadjian and Pincus B366/45.
[159] Greene et al. B33049/49.

In man, stressful psychomotor performance causes a fall in the lymphocyte count. Here the Hoagland-Werthesen *pursuit meter* was used. This is an apparatus consisting of an airplane stick and rudder pedal controls that operate a pointing, rectangular light-beam. Fatigue is measured by the efficiency with which the operator manages to keep the beam on an irregularly moving object. It was concluded that "the lower the drop in lymphocytes, the greater the decline in efficiency of performance as scored on our pursuit meter and measured by decline in the "fatigue ratio".[160]

Further observations with this pursuit meter confirmed the drop in lymphocytes in normal persons and revealed that it tends to run inversely parallel with the 17-KS output. Conversely, in *psychotics* the lymphocyte count rises with the stress and this is accompanied by irregular variations in 17-KS excretion. It was pointed out that "if this can be established as generally typical of certain psychotic patients, we have available a tool for the quantitative investigation of a deranged, adaptive, physiological function".[161]

Upon exposure to heat and high humidity, normal persons likewise responded with a drop in blood lymphocytes, while psychotics almost invariably exhibited an increased blood-lymphocyte count. The authors state that: "with the short time stress employed here, it is entirely likely that we are dealing with the first stage of the adaptation syndrome, which involves adreno-cortical hypersecretion as the result of the pituitary stimulation following stress. The inability of the patients to exhibit an adreno-cortical response may be due to a block to secretory activity in the adrenal cortex itself or to a failure of typical pituitary secretion".[162] In discussing these results Pincus[163] points out that: "the psychotics whom we studied were men who had broken down under the particular stresses of their lives. Is the poor functioning of the physiological stress response mechanism etiologic to the mental breakdown ?"

Subsequent investigations showed that various *other psychologic stressors* cause a fall in blood lymphocytes in most normal individuals.[164] This response, accompanied by eosinopenia and increased uric-acid excretion, was also elicited by standard stress situations in patients with *anxiety neuroses.* It was emphasized that all these changes are similar to those produced in normal or neurotic individuals by relatively small doses of purified ACTH.[165] In women suffering from "hysteria" the lymphocyte count is often normal, judged by the lymphopenia caused by "stress interviews", allegedly "there was evidence that the discussion of disturbing topics produced a mild alarm-reaction" in normal and psychoneurotic patients.[166] Lymphopenia during "stress interviews" has also been noted in a series of "psychoneurotic patients", whose condition was not otherwise specified.[167] (Cf. also: "Neuropsychiatric Diseases of Adaptation".)

All these data support the view that lymphopenia — at least the relative lymphopenia accompanied by eosinopenia and polymorphonuclear neutrophilia — is truly characteristic of the A-R produced by "emotional stress".

It is difficult to reconcile this with the phenomenon of *emotional lymphocytosis* which had often been seen by earlier investigators in the rat[168] as well as in man.[169] It should be kept in mind however, that many factors affect the blood-

[160] Hoagland et al. A95861/46.
[161] Hoagland et al. B1244/46.
[162] Hoagland B4975/47, Pincus and Elmadjian B1243/46.
[163] 98426/47.
[164] Graham et al. B4439/48.
[165] Altschule et al. B36865/49, Cleghorn et al. B19125/48.
[166] Shands and Finesinger B31901/48.
[167] Finesinger et al. B4476/46.
[168] Farris B27405/38.
[169] Farris B27404/38.

count during the G-A-S. For instance, both adrenaline and the corticoids, liberated at this time, can cause blood-corpuscle discharge from the spleen. The corticoids apparently also cause lymphocyte destruction. It is obvious therefore that the final effect of stress will again largely depend upon conditioning factors (e.g., lymphocyte stores, dietary factors conditioning ACTH secretion) which vary greatly in different individuals, even within the same species, according to age, sex, heredity, degree of stress, previous exposures, etc.

It is a well known fact that **muscular exercise** exerts an important influence upon the blood picture. In man, a so-called "myogenic leucocytosis" is seen a few minutes after muscular exertion;[170] this is usually accompanied by a slight increase in the red-cell count.[171] Differential blood-counts on athletes revealed that an increase in large lymphocytes is mainly responsible for this "myogenic leucocytosis" and that the response is much more pronounced in untrained than in trained individuals.[172] Parallel with the lymphocytosis, the neutrophils tend to diminish, although, with excessive exertion, neutrophilia with left deviation may occur. In some men a sudden, often pronounced, increase of the eosinophils (up to 10 per cent) has been noted, but this is generally followed by an equally rapid drop.[173] The cause of these irregular responses could not be established, but experience shows that most men respond with eosinopenia after muscular exercise.[174]

Extensive systematic investigations in animals and man led to the conclusion that "myogenic leucocytosis" is characterized by: (1) a rapidly increasing leucocytosis which continues to rise long after the muscular work; (2) in the beginning, a relative and absolute lymphocytosis, which in the case of excessive exertion, turns into a severe lymphopenia; (3) later, relative and absolute neutropenia, which is followed by pronounced neutrophilia and left deviation of the blood-count. This is occasionally accompanied by eosinopenia and basopenia.[175]

The more intense the muscular exertion the more likely is it to cause lymphopenia. But dietary conditioning factors are also important in determining the direction of the deviation from the norm as shown by observations in the rat [176] (cf. Blood count ← Diet, pp. 419, 432). The transient initial lymphocytosis [177] and erythrocytosis [178] was particularly striking in the rat and dog after muscular stress. It can perhaps be ascribed to sudden discharge from depots, for instance, the spleen (cf. below).

Our studies concerning the influence of the G-A-S upon the blood-count in the rat and mouse suggest that the so-called "myogenic leucocytosis" is merely part of an A-R. The same explanation presumably also holds of the accompanying lymphocytopenia and eosinopenia, although we do not yet have any definite explanation for the sometimes irregular rises in the lymphocyte count. Unlike other alarming stimuli, forced exercise often caused a fall in the red-cell counts of our rats. This may be due to blood dilution; perhaps because, while running, the animals lose blood from incidental wounds to their legs.[179]

[170] Grawitz A32630/10.
[171] Rakestraw A7856/21, Vinaricky B38598/47, B38661/48.
[172] Ernst and Herxheimer A32633/24.
[173] Schultz **A32631/29.**
[174] Bader et al. B33091/48, Stein B33476/48, Stein et al. B37251/49.
[175] Arnhold A14970/37, Egoroff A32632/24, Farris 78039/40, Jokl **79702/31,** Michailesco and Alexiu A15436/38.
[176] Dumm et al. B37736/49.
[177] Stone and Hechter B19207/48.
[178] Lang A8502/37, A15435/38.
[179] Dalton and Selye A17985/38, A31950/39, Dalton et al. A18306/39, Harlow and Selye A8400/37.

The so-called "war **lymphocytosis**" also deserves to be mentioned in this connection. As the name implies, it has been regarded as a characteristic response in times of war. Its etiology led to considerable speculation. Some German authors regarded it as "typical of the Germanic races",[180] while Russian investigators referred to it as a "social deviation" of the blood-picture,[181] attributable to nervous exertion, nutritional deficiency or excessive muscular work among the underprivileged.

Anoxia is notoriously effective in producing a rise in the red-cell count with a corresponding increase in blood hemoglobin, so that the color index remains unchanged. Especially in the initial stages, there is a considerable increase in circulating reticulocytes. The pertinent literature clearly indicates that this response is due to a stimulation of erythropoiesis in the hemopoietic tissues as part of a specific response to oxygen want.[182]

More recent experiments on rats led to the conclusion that "relatively high hematocrit levels may be maintained by short exposures to 18,000 or 25,000 ft. at 2- or 3-day intervals, but that such acclimatization is lost completely by exposure at greater intervals".[183]

Data concerning changes in the white-cell count are more controversial.[184] Experiments on rats and guinea-pigs led to the conclusion that reduction of atmospheric pressure causes temporary leucocytosis (presumably due to the emptying of reservoirs) followed by leucopenia (allegedly due to depression of hemopoiesis in bone-marrow and lymph-nodes). Failure to recognize the biphasic nature of this response may explain the inconsistency of the results reported by earlier investigators.[185]

In men exposed to the psychic stress of pursuit meter operation under anoxic conditions, the lymphocytopenia of stress is particularly pronounced.[186]

Conversely, exposure to **increased atmospheric pressure** depresses erythropoiesis in man.[187] This is presumably also a specific response although the accompanying neutrophilia, followed by neutropenia, may have been due to the G-A-S.

It is obviously not within the scope of this monograph to discuss the enormous literature concerning the hematologic effects of various spontaneous **diseases** of man.[188] In connection with changes presumably due to non-specific stress, it is well to remember, however, that various chronic infections, toxemias and advanced neoplastic diseases tend to cause an *anemia* which is often sufficiently severe to be the presenting symptom. The color index in such cases tends to be low and the anemia is generally ascribed to "toxic inhibition of the marrow function". Fulminating infections may also cause hemolytic or macrocytic anemias.[188a]

The mechanism of the anemia associated with chronic infections and intoxications has recently been the object of extensive systematic studies. This type of anemia is usually normocytic and normochromic, but may be slightly micro-

[180] Bockelmann and Nassau B27403/18, Klieneberger B27401/17, Lämpe and Saupe B27402/19.
[181] Egoroff A32632/24.
[182] van Liere **B26199/42.**
[183] Altland B32703/49.
[184] De Gætani **A18403/38,** van Liere **B26199/42.** Matsunobu and Yogi A16484/38.
[185] Meyer et al. 56692/35.
[186] Pincus 98426/47.
[187] Farber B38155/48.
[188] French and Douthwaite **99226/45.** Palmer 95299/46.
[188a] Vaughan B44244/48.

cytic and hypochromic. There is no accompanying reticulocytosis. The bone-marrow is hyperplastic with an increase in the myeloid-erythroid ratio. The plasma iron concentration is decreased, while blood-copper and protoporphyrin are increased. The theory was offered "that the anemia of infection is due to failure to form heme as the result of lack of iron to incorporate into the proto-porphyrin molecule".[189] Radio-iron studies showed that some iron is capable of entering the erythrocytes as hemoglobin even in the anemia of chronic infection. However, since intense iron therapy is ineffective, it was concluded that lack of iron in itself cannot be the limiting factor here.[190] Administration of copper was also ineffective.[191]

It is very probable that the "anemia infantum pseudoleukæmica" (von Jaksch's disease) is a related condition. Here splenomegaly, enlargement of the liver and lymph-nodes is combined with severe anemia, while primitive erythrocytes and leucocytes appear in the blood. This should be regarded as a syndrome rather than a disease. "It is probable that it represents the response of the extremely labile hemopoietic tissues of the infant to one of a variety of different conditions. Thus it may be found in association with rickets, tuberculosis, syphilis, gastro-intestinal disturbances and undernutrition".[192]

As regards the pathogenesis of these hematologic changes, it is interesting that the *erythrocytosis* frequently noted in the first stages of malignant diphtheria has been regarded as due to hemoconcentration resulting from an acute, relative, adreno-cortical insufficiency.[193]

Polymorphonuclear neutrophilia with left deviation and *relative lymphopenia* is most pronounced in acute infections, especially when pus formation is intense (e.g., peritonitis, appendicitis, cholecystitis, salpingitis, osteomyelitis, otitis, pyelitis, pyelonephrosis, pyemia). It is comparatively independent of the etiologic organism. Quite frequently polymorphonuclear neutrophilia may be the deciding factor in recommending an operation in a doubtful case of appendicitis. However, the very fact that similar neutrophilia may be associated with an acute attack of gout, acute yellow atrophy of the liver, uremia or diabetic coma suggests its non-specific nature.[194]

Experimental observations in animals showed that the changes in the white-cell count produced by infections are largely due to redistribution of the white-cells in the different vascular territories.[195] Be this as it may, the typical white-cell picture of the A-R has been reproduced experimentally. In the cat for instance, pneumococcus infection resulted in polymorphonuclear neutrophilia with left deviation, lymphopenia and eosinopenia.[196]

Significantly, various acute febrile conditions in man have long been known to cause *eosinopenia*.[197] Recently this change has been regarded as part of an A-R caused by adreno-cortical stimulation incident to sudden stress. Thus for instance in acute porphyria the eosinopenia is accompanied by metabolic (hyponatremia, hypochloremia, increased excretion of uric acid) and adrenal changes which can be duplicated by ACTH or corticoids.[197a]

[189] Cartwright et al. 93254/46.
[190] Greenberg et al. 96955/47, Vaughan B44244/48.
[191] Cartwright et al. 93254/46, Wintrobe et al. 96954/47.
[192] French and Douthwaite 99226/45.
[193] Nitschke and Krätschell B20000/38.
[194] French and Douthwaite **99226/45**, Palmer **95299/46.**
[195] Borchardt 23991/29, Hoff A14716/38.
[196] Borchardt 23991/29.
[197] Zappert B27406/893.
[197a] Prunty B37297/49.

Some infections on the other hand, are more conducive to *lymphocytosis* (e.g., whooping cough, chronic tuberculosis without secondary infection), while a slight lymphocytosis is normal in childhood. In typhoid fever and malaria we often note marked leucopenia with relative lymphocytosis.[198]

A survey of the literature concerning hematologic changes produced by focal infections led to the conclusion that these develop in four stages, depending upon the state of defense of the organism: (1) the phase of combat (characterized by neutrophilia), (2) the phase of defense (with monocytosis), (3) the phase of healing (with lymphocytosis and eosinophilia) or (4) the phase of exhaustion (with leucopenia). The latter allegedly represents the final stage of all the chronic focal infections.[199]

Parasitic infections, for instance trichinosis, notoriously tend to cause pronounced *eosinophilia*. This is in marked contrast to the eosinopenia characteristic of the A-R and of treatment with corticoids or ACTH (cf. below). In this sense, it cannot be considered as a non-specific change, yet, the specificity of the response is only relative, as a great variety of parasitic organisms (as well as inanimate allergens) can elicit it[200] (cf. "allergic conditions", below).

It is obviously very difficult to evaluate the part played by non-specific stress in the manifold-hematologic responses produced by infections and other diseases. Numerous pathogenic agents exert evidently specific effects upon the blood-count. These can be superimposed upon the non-specific G-A-S manifestations. Furthermore, the effect of systemic stress itself will vary, depending upon the intensity of the damage and the length of exposure. However, since all stressors demonstrably affect the blood-count, it will obviously be indispensable, henceforth, to distinguish between specific and non-specific hematologic effects. Systematic investigations from this point of view have not yet been undertaken in the case of spontaneous diseases. Therefore the only assumption which appears to be warranted at present is that the polymorphonuclear neutrophilia with left deviation, accompanied by relative lymphopenia and eosinopenia — as seen especially in acute infections and intoxications — are probably part of the resulting A-R. Further work will be necessary to establish the mechanism through which micro-organisms causing widespread, purulent, inflammatory lesions are particularly effective in conditioning the organism to respond in this manner to stress.

In various **allergic conditions** eosinophilia is rather characteristic and sometimes attains an extraordinary degree. However, marked fluctuations occur; extreme shifts in the eosinophil and total white-cell count were particularly obvious in animals during experimental shock produced by various proteins, anaphylaxis, histamine and other drugs.[201] In acute allergic attacks in man, as well as in severe anaphylactic shock in animals, eosinopenia tends to develop and this has been compared to that which we described as being characteristic of the A-R.[202]

Several investigators expressed the opinion that the absence of eosinophil cells in the blood during immunization therapy is to be regarded as an unfavorable sign indicating diminished reactivity on the part of the organism. A survey

[198] French and Douthwaite **99226/45**, Palmer **95299/46.**
[199] Goia **B25571/46.**
[200] French and Douthwaite 99226/45, Palmer 95299/46, Urbach and Gottlieb **B2133/46.**
[201] de Weerdt A9841/38, Rocha e Silva B28507/47, Sonobe A8283/37.
[202] Urbach and Gottlieb B2133/46.

of the pertinent literature led to the conclusion that: "...it is now generally believed that the eosinophil cells participate in the defense process of the human body, especially in conditions of hypersensitiveness".[203]

Pronounced eosinophilia (up to 20 per cent) has been produced in mice by feeding them muscle from rats infected with Trichina spiralis.[204] This is also seen after actual infection with this organism.[205] It is well to keep in mind that diametrically opposed reactions may be produced by the same agent under different experimental circumstances. This is particularly true of changes in which the end result depends upon the relative intensity of consumption and production. Thus, as we have said in other connections, an A-R produced by traumatic injury causes hyperglycemia in the intact, but hypoglycemia in the adrenalectomized animal; exposure to chronic stresses of various kinds causes loss of adrenal-lipids during the A-R, but increased lipid storage during the resistant stage. The possibility should not be neglected, therefore, that the eosinopenia of the A-R may be related to the eosinophilia of parasitic infestations and allergic conditions.

The functional significance of this eosinophilia is not known, but interestingly an anaphylactogenic protein could be detected in eosinophils and not in other leucocytes.[206]

In connection with the effect of stressors on other leucocytes, it is noteworthy that in ragweed-sensitive patients, lysis of leucocytes is often obtained in vitro upon addition of ragweed extract to the blood.[207]

In our earliest experiments concerning the G-A-S we often used drugs (e.g., formaldehyde, adrenaline) to produce an A-R and found that polymorphonuclear neutrophilia with lymphopenia and eosinopenia are *characteristic* hematologic manifestations of this stage.[208] The underlying mechanism is probably the same in the neutrophilia produced by various so-called non-specific therapeutic agents such as foreign proteins, milk or blood injections and parenteral administration of colloidal metals.[209] If the patient does not respond well to such non-specific therapy, the leucocytosis may be absent or actually replaced by leucopenia.

The so-called "leucocyte-reaction" of Gouin[210] is apparently based on this response. It consists of an increased total white-cell count produced by various non-specific drugs in patients who respond favorably to them. Absence or reversal of the leucocytosis under these conditions is regarded as an unfavorable sign. This reaction has been recommended for the rapid screening of many non-specific remedies to determine which one would be most likely to be beneficial in a particular case.

In the rat, the hematologic changes elicited by acute *alloxan* intoxication are similar to those caused by various stressors. They are accompanied by other A-R changes and have been ascribed to the G-A-S.[210]

[203] Urbach and Gottlieb B2133/46.
[204] Stein B37271/49.
[205] Larsh and Nichols B39070/49.
[206] Godlowski B37391/48.
[207] Squier and Lee B38653/47.
[208] Dalton and Selye A17985/38, A31950/39, Dalton et al. A18306/39, Ehrich B46789/50, Harlow and Selye A8400/37.
[209] Feenders 37979/36, Hiraocka 38773/36, Muto **38774/36.**
[210] **93238/46.**
[210a] Arvy and Gabe B44853/49.

Various *bacterial toxins and vaccines* cause an increase in the total white-cell count in experimental animals.[211] If the resulting damage is very severe, however, leucopenia ensues.[212] In man and rats, typhoid vaccine causes lymphopenia with polymorphonuclear neutrophilia[213] and eosinopenia.[213a]

If bacterial toxins cause severe shock, hemoconcentration may ensue and the red-cell count consequently increases, unless widespread trapping of erythrocytes in capillaries,[214] or accompanying hemorrhages cause acute anemia. The more chronic so-called anemia of infection that has been produced in the dog by injection of staphyloccoci (cf. above) could not be reproduced by staphylococcal toxin, or by typhoid vaccine.[215]

From a clinical point of view it is especially interesting that bacterial pyrogens, such as are used in the therapy of hypertension, produce hematologic changes in the rabbit, which are identical with those seen during the A-R or after ACTH administration. At the same time, typical A-R changes are noted in the adrenal cortex and other organs.[215a] These observations are in agreement with the assumption that bacterial pyrogens exert their beneficial effect largely through the production of an A-R.

Colchicine causes a transient neutrophilia followed by a prolonged lymphopenia in the rabbit.[216] This response has not yet been correlated with the well known A-R-producing action of this drug. However, in man, colchicine intoxication elicits such hematologic alterations simultaneously with characteristic A-R changes in other organs.[216a]

The fact that intraperitoneal injection of very hypertenic *glucose* solutions causes hematologic G-A-S changes[217] is readily understandable. The lymphocytopenia after such injections has been considered to be part of the resulting A-R.[218] It is more difficult to explain, however, why an acute lymphopenia — similar to that seen in the A-R — is produced in the rat by oral administration of a 50% glucose solution.[219] In man, oral administration of 100-200 gm. of glucose also results in a pronounced decrease of circulating lymphocytes.[220] This response was found to be exaggerated in patients suffering from diabetes or psychoneuroses.[221] Evidently glucose promotes corticoid discharge more markedly than could be expected on the basis of its extremely mild stressor effect. Perhaps its ability to sensitize the adrenals to ACTH is responsible for this (Cf. Adrenal ← ACTH, p. 334). Yet, this response has also been ascribed to the "non-specific stress factor".[221a]

The intravenous administration of comparatively dilute *hemoglobin* solutions in the dog elicits a transitory leucopenia with relative lymphocytosis, followed by leucocytosis and absolute neutrophilia.[222] This was considered to be part of a "hemoclastic crisis" similar to that produced by intravenous administration of other "macromolecular substances".[223]

[211] Doan A14836/38, Hoff and Linhardt 23011/38, Lithander 97243/45, Paschkis and Martos A14911/38, Rosenow B33449/31.
[212] Olitzki et al. 84474/42.
[213] Lewis and Page B25995/48.
[213a] Ehrich B46789/50.
[214] Gibson et al. B26950/47.
[215] Cartwright et al. 93255/46.
[215a] Windle et al. B47197/50.
[216] Balduini and Bertolotti B38118/48.
[216a] Layani et al. B38533/47.
[217] Mirkis 39955/36.
[218] Dohan and Lukens B19202/48.
[219] Elmadjian et al. 95224/46.
[220] Marks et al. B19152/48.
[221] Jailer et al. B30916/48, Marks et al. B19152/48.
[221a] Jordan et al. B47058/50.
[222] Hueper 91802/44.
[223] Hueper 91719/42, 91723/43.

Insulin, given in shock-producing doses to mental patients, caused largely polymorphonuclear neutrophilia.[224] There usually is a peak elevation at about the fourth hour. This is accompanied by transitory lymphocytosis during the second hour, followed by extreme lymphopenia by the sixth hour. The eosinophils and basophiles tend to disappear at the time of the maximum leucocytosis. There also is a slight rise in the red-cell count and hematocrit values.[225] All these changes are rather similar to those produced by other stressors.

Various *"macromolecular substances"* (colloids, lipid suspensions, india ink, etc.) cause monocytosis in the rabbit as part of their effect upon the R.E.S. In animals pretreated with india-ink, tagged monocytes are discharged into the blood (even a month after ink injection) by intravenous administration of foreign protein.[225a] This response may well be related to the well-known activation of the R.E.S. by the A-R.

The effect of colloids and foreign proteins on other blood elements has been discussed above in connection with the "characteristic" G-A-S response.

Considerable importance has been attached in the literature to the fact that *nucleic acid*, administered intravenously, causes very pronounced leucocytosis in various animal species.[226] Disintegration of nuclei as a result of the caryoclastic crisis liberates much nucleic acid during the A-R and this may play a rôle in the resulting white-cell change. The particularly intense neutrophilia of extensive suppurations may in part find its explanation in this action of nuclear disintegration products, since here, cell destruction (with liberation of their nucleic acids) is especially pronounced.

Intense granulocytopenia has been caused by *sulfa* drugs[227] given in the treatment of infections, and by *thiourea derivatives*[228] administered for thyrotoxicosis. The mechanism of this response is still unknown, but it is noteworthy that granulocytopenia, no matter how produced, is associated with a considerable decrease in resistance, especially to infections. It is curious furthermore that the sulfa derivatives, which proved to be so effective in the treatment of many infections, should possess a pronounced white-cell-destroying property if given in toxic doses. This granulocytopenia is actually the antithesis of the polymorphonuclear neutrophilia seen in the A-R. However as we said in connection with the eosinophilia of the allergies, diametrically opposed responses can be produced by the same agent under different conditions, especially if the end result depends upon the proportion between production and utilization of a cell type. It will be recalled that very severe stressors, to which resistance is impossible, also tend to cause leucopenia. The relationship between the A-R and the drug agranulocytoses would certainly deserve more attention than it has so far received.

The often reported production of allergies and periarteritis nodosa by sulfa drugs is reminiscent of spontaneous "diseases of adaptation", but the possible pathogenic interrelations between these conditions are obscure.

It is well known that various toxic *tissue extracts* can produce a non-specific polymorphonuclear neutrophilia, often accompanied by reticulocytosis. It has been particularly emphasized that the reticulocytosis produced by some impure

[224] Delay et al. B34966/47.
[225] Baird and Dixon B29636/48.
[225a] Büngeler A32692/27.
[226] Paschkis and Martos **A14911/38.**
[227] Lederer and Rosenblatt **83667/42**
[228] Selye 94572/49.

organ extracts, recommended for the treatment of pernicious anemia, is merely due to this non-specific effect and not to the anti-anemic principle.[229]

Turpentine, injected subcutaneously or intramuscularly, produces abscesses and the resulting chronic inflammation eventually causes a replica of an "anemia of chronic infection".[230] This type of anemia (as that of spontaneous chronic infections) is presumably due to a depression of hemopoiesis during late phases of the G-A-S, especially the stage of exhaustion. It should not be confused with the hematologic responses seen in the A-R.

In man, *urethane* causes a particularly pronounced lymphopenia and neutropenia, often preceded by slight neutrophilia and lymphocytosis.[231] This effect resembles that of x-rays and arsenic. It is so pronounced that the drug is recommended in the treatment of chronic leukemias, indeed, even here, overdosage may cause agranulocytosis.[232] In one case of myeloid leukemia, the neutrophils returned to normal under the influence of urethane, but fatal alymphocytosis ensued.[232a]

The literature concerning the palliative treatment of experimental and spontaneous leukemias with urethane has been discussed in the light of a possible relationship to adreno-cortical function. It was pointed out that urethane causes an enlargement of the adrenals such as is seen during the G-A-S. However, since adrenalectomy does not prevent the effect of this drug upon the white-cell count, it has been suggested that the adrenal enlargment "might be an alarm-reaction to urethane secondarily, but directly the result of the liberation of proteolytic products by the compound".[233]

It is interesting that the marked eosinophilia of mice, fed muscles from rats infected with Trichina spiralis, can also be counteracted by urethane.[234]

Various *vesicants* (such as nitrogen or sulfur mustards) induce severe leucopenia both in animals and in man. Unlike urethane, these drugs allegedly cause a particularly pronounced reduction of polymorphonuclear leucocytes and other myeloid elements, with a slight fall in red-cells and almost no change in lymphocytes.[235] Others claim, however, that both sulfur and nitrogen mustards cause lymphopenia and neutropenia often accompanied by eosinopenia.[236] These discrepancies may perhaps be explained by differences in the experimental conditions and particularly in the severity of the intoxication. It has been suggested that the white-cells may be leaving the body through the gastrointestinal tract which, after intense intoxication with vesicants, shows ulcerative lesions similar to those produced by other alarming stimuli.[237]

Nitrogen mustards have also given satisfactory results in polycythemia vera rubra, due to their effect upon erythrocytes,[238] but nothing is known concerning the possible rôle of stress in this response.

Many types of **dietary deficiencies** exert a pronounced effect upon the blood-count. It is very probable that the non-specific stress of malnutrition

[229] Scheerer A658/37.
[230] Cartwright et al. 93254/46, Greenberg et al. 96956/47.
[231] Moeschlin B38205/47, B37548/47. B37547/47.
[232] Aubertin **B37546/47.** Löwinger **B38056/47.** Moeschlin B37547/47. Undritz **B29866/47.**
[232a] Undritz B29866/47.
[233] Dury and Robin B19209/48.
[234] Stein B33029/49.
[235] Bacq et al. B23246/47.
[236] Karnofsky et al. B37880/48, Kindred 99940/47.
[237] Kindred 99940/47.
[238] Bortz and Haden B38723/48, Eldon B38724/48.

plays an important rôle in the pathogenesis of various "nutritional anemias". It would not be within the scope of this volume, however, to analyze the extensive pertinent literature.[239] Suffice it merely to mention a few observations which are particularly suitable for the illustration of relationships between the stress of malnutrition and the hematologic responses during the G-A-S.

In the guinea-pig, *fasting* causes polymorphonuclear neutrophilia, lymphopenia and eosinopenia. It was emphasized that this response is essentially similar to that caused by exposure to cold.[240] In man chronic starvation may lead to the development of a "nutritional anemia", but this is not always the case even if the cachexia becomes severe.[240a]

In rats kept on *protein-deficient* diets, neutrophilia was likewise found to be accompanied by lymphopenia; at the same time the red-cell count fell.[241] An often macrocytic anemia was also one of the leading signs of the malnutrition accompanied by hunger edema among inmates of concentration camps during the second World War.[242] The mechanism of the anemia of starvation is incompletely understood, but it has been shown in rats that acute starvation depresses erythropoiesis not unlike total-body x-irradiation does.[243]

Granulocytopenia and anemia also develops in rats on *riboflavin* [244] or *pantothenic acid* [245] deficiency. At least in the latter case, this is accompanied by widespread involution of the thymico-lymphatic tissues, loss of lipids from the adrenal-cortex and other manifestations of the G-A-S. Certain vitamin deficiencies no doubt affect the blood-count by virtue of their specific actions, but it is highly probable that in all these instances, the resultant systemic stress influences the picture and in some cases the G-A-S response may even be the principal pathogenic factor.

In connection with all of these observations it is well to remember that the total white-cell count shows **diurnal variations.** In man, there are two maxima in the early morning and early afternoon and two minima in the late morning and during the night, respectively.[246] Both men and women also exhibit diurnal changes in the number of circulating lymphocytes. These closely parallel the 17-KS excretion rhythm. The count is at its lowest point in the morning, followed by a rise through the day and into the night. The possibility has been considered that the morning depression may be incident to the stress of awakening and taking up daily activities. As in the stress tests, psychotic patients showed rather irregular diurnal variations.[247]

During **pregnancy** — and especially during delivery or eclamptic seizures — there is marked eosinopenia in women. This has been ascribed to increased corticoid production, but it remains to be seen to what extent the placenta itself might also contribute to the elaboration of corticoids.[248]

Stimuli Influencing the Hematologic Response to Systemic Stress. — **Hypophysectomy** causes anemia in various experimental animals.[249] In the rat, for instance, there is a 30% decrease in the leucocyte count, with a correspond-

[239] French and Douthwaite **99226/45,** Palmer **95299/46.**
[240] Josey and Lawrence A32635/32.
[240a] Keys et al. **B46730/50,** Klotzbücher B45392/48, Wellers and Waitz B46013/47.
[241] Brown B32987/49.
[242] Gsell B27611/48, Keys **B37797/48,** Uehlinger B24304/47, **B27612/48,** Walters et al. B37536/47, B38083/47.
[243] Salomon et al. B32890/49.
[244] Endicott et al. B37601/47.
[245] Ashburn et al. B37602/47.
[246] French and Douthwaite **99226/45,** Palmer 95299/46.
[247] Elmadjian and Pincus B1242/46, Pincus 98426/47.
[248] Davis and Hulit B38344/49.
[249] Selye **94572/47.**

ing fall in hematocrit and hemoglobin, a slight decrease in erythrocyte-volume and -hemoglobin. All this is presumably due to partial atrophy of the bone-marrow. *Thyroxine* and/or *testoid* treatment was found to have beneficial effects upon this anemia, the best results being obtained by simultaneous treatment with both these hormones in rats given a protein-rich diet.[250]

ACTH continues to exert its normal eosinopenic effect after hypophysectomy in the mouse [251] and rat.[251a]

The decrease in lymphocytes [252] and eosinophils [253] seen in rats after *adrenaline* administration is allegedly not prevented by hypophysectomy; it was concluded that these effects can therefore not be mediated solely by the hypophyseo-adrenal axis. In mice adrenaline also caused some eosinopenia even after hypophysectomy but less than in intact animals.[254] While some hematologic actions of adrenaline are obviously independent of the pituitary and adrenal-cortex (e.g., those secondary to splenic contraction), it is highly probable that in toxic doses the hormone also acts by stimulating ACTH and corticoid production. Additional experiments will be necessary, however, to elucidate the relative importance of these two mechanisms in the production of hematologic changes by adrenaline. Systematic, carefully controlled, observations in the rat show that (contrary to earlier statements) adrenaline does not cause eosinopenia after hypophysectomy.[254a]

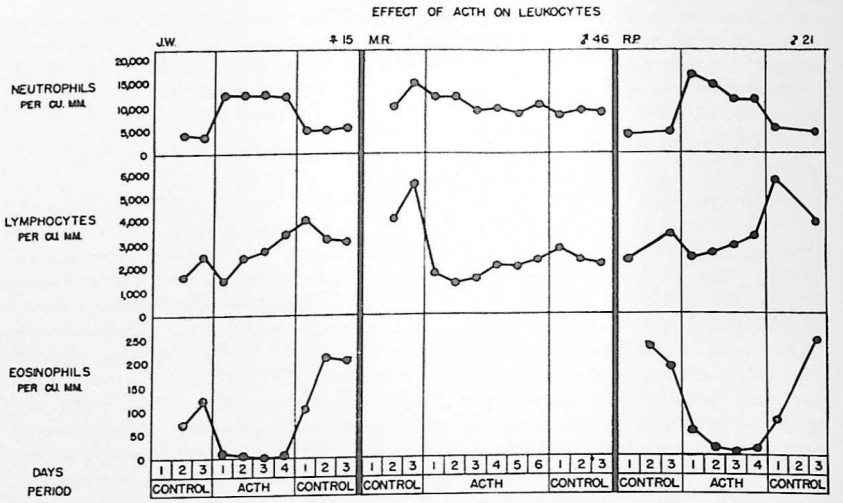
Hemorrhage causes much less marked eosinopenia in hypophysectomized than in intact mice, but since the effect is not completely abolished it cannot be exclusively mediated through an ACTH discharge.[255]

Severe *x-irradiation* produces profound lymphopenia even in hypophysectomized rats, presumably due to the direct lympholytic action of these rays.[256]

In man, purified **ACTH** causes marked eosinopenia, accompanied by a less spectacular and less consistent lymphopenia and neutrophilia within a few hours.[257] A similar response to ACTH was observed in the dog [258] and rat.[25] - The hematocrit values tend to drop for a few hours in man treated with single large doses of ACTH (40-400 mg.)[259] though chronic treatment may cause polycythemia. Similarly a brief period of leucopenia tends to precede the leukocytosis after a single dose of ACTH in man. The neutrophilia is accompanied by a "shift to the left".[259a]

On the other hand, none of these hematologic changes were observed in *Addisonians,* hence it was concluded that this effect of ACTH is mediated by the adrenal-cortex.[260]

[250] Crafts B32990/49, B39041/49.
[251] Speirs and Meyer B43545/49.
[251a] Recant et al. B47003/50.
[252] Hungerford B31654/49.
[253] Recant et al. B17739/48.
[254] Speirs and Meyer B43545/49.
[254a] Recant et al. **B47003/50.**
[255] Speirs and Meyer B43545/49.
[256] Dougherty and White 95612/46.
[257] Forsham et al. B17987/48, Herbert and de Vries B33146/49, Luft et al. B45270/49, Randolph and Rollins B46951/50, Recant et al. **B47003/50,** Sayers et al. B37710/49, Sprague et al. B46430/50, Stein et al. B33476/48, Tronchetti and Rossi B45524/49.
[258] Haynes et al. B32764/49.
[258a] Recant et al. B47003/50, Tronchetti and Rossi B45524/49.
[259] Herbert and de Vries B33146/49.
[259a] Randolph and Rollins **B46951/50.**
[260] Forsham et al. B17987/48, Hills et al. B33083/48, Recant et al. B47003/50, Roche et al. B35923/49, B46957/50, Thorn et al. B31972/48.



Typical hematologic changes following injection of ACTH in man.
(After Forsham et al. B17987/48.)

In animals, *adrenalectomy* prevents the normal hematologic response to ACTH, and particularly the eosinopenia, since this depends upon the discharge of gluco-corticoids.[260a]

In another series of observations, polymorphonuclear neutrophilia with relative lymphopenia was seen both in normal and in *hypopituitary individuals*, although in the latter, the polymorphonuclear leucocytosis was subnormal. Eosinophil counts were not reported.[261] In some patients with pituitary tumors the eosinopenic response to ACTH is deficient,[261a] perhaps because the adrenal cortex is too atrophic to react normally to corticotrophic stimulation.[261b]

As judged by the few pertinent data now available, ACTH decreases the normally high blood-eosinophil count in *Löffler's syndrome*, but not in *tropical eosinophilia*.[262]

In patients suffering from *myasthenia gravis* large doses of ACTH caused a pronounced fall in circulating lymphocytes and eosinophils.[263]

In *lymphatic leukemia* such treatment also causes eosinopenia but no change in circulating lymphocytes.[264] This is especially noteworthy since adreno-cortical extracts are said to produce lymphopenia and regression of the abnormal lymphoid tissue in mice with spontaneous lymphatic leukemia. Hence it was suggested "that mouse lymphoid leukemia differs significantly from the human variety".[265]

The eosinopenic response to ACTH, in patients with various types of *cancer*, is usually normal.[265a]

[260a] Recant et al. B47003/50.
[261] Greer and Brown B28267/48.
[261a] McIntosh et al. B46952/50.
[261b] Recant et al. B47003/50.
[262] Rose B41837/49, B44963/49, Herbert et al. B46433/50.
[263] Hellman B32768/49.
[264] Hellman B32769/49.
[265] Hellman B32769/49.
[265a] Bonner et al. B46956/50.

In patients with complicated *post-operative* convalescence a normal eosinopenic response to ACTH (or adrenaline) is indicative of a "restoration of the adrenal cortical reserve".[266]

In men exposed to *cold* or *heat*, ACTH produced a normal hematologic response, thus indicating no depletion of the "cortical reserve" of reactivity, but perhaps for this the stress was not sufficiently intense.[267]

The lymphopenic effect of ACTH is diminished in the *pantothenic acid*-deficient rat, presumably because the adrenal cortex is less responsive.[268]

The **age** of the patient also influences the response to ACTH. During the first two or three days of life, the eosinopenic effect — and several other actions — of ACTH are less pronounced than a few days later.[268a] This would indicate that the adrenal cortex is not fully responsive to stimulation until it reached a certain degree of maturity. On the other hand, aged patients respond to ACTH by approximately the same degree of eosinopenia as young adults. This is all the more noteworthy since the eosinopenia, caused by adrenaline injections, is less pronounced in the aged than in the young. Presumably the responsiveness of the adrenal does not decline, but the ability to produce endogenous ACTH, in response to stress, is diminished with advancing age.[268b]

Constitutional and hereditary factors are apparently also of import. In certain rats, which are refractory to alarming stimuli, treatment with corticotrophic pituitary extracts allegedly fails to influence the blood-count, unless cortical extract is simultaneously administered.[268c]

The existence of a special **"hemopoietic anterior-lobe hormone"** is dubious.[269] However, since thyroid hormone and testoids stimulate erythropoiesis (cf. below), it is obvious that **thyrotrophin** and **gonadotrophin** will indirectly exert similar effects. It has been claimed that gonadotrophic urinary extracts can cause reticulocytosis in women and that perhaps the reticulocytosis of pregnancy is due to an excess of such hormone.[270] This requires confirmation because many other changes in hormone metabolism could be involved during pregnancy.

Impure anterior-pituitary preparations, such as *LAP*, which tend to produce myeloid infiltration in various organs (cf. Hemopoietic System, p. 452), likewise cause reticulocytosis.[270]

Posterior-pituitary extracts also stimulate reticulocyte formation,[271] but it is doubtful whether this is a specific effect or merely part of the resulting systemic stress, and the loss of blood from gastric ulcers. Vasopressin-containing extracts are especially prone to produce an A-R with intense bleeding from the stomach.[272]

In any case, the lymphopenia and eosinopenia characteristic of ACTH is not due to contamination with posterior-lobe hormones. Toxic doses of posterior-pituitary extracts did produce hematologic responses similar to those obtained with ACTH, but here the effect was ascribed to the ensuing A-R.[273]

[266] Roche et al. B35923/49, B46957/50.
[267] Stein et al. B33476/48.
[268] Dumm et al. B37736/49.
[268a] Venning B46953/50.
[268b] Solomon and Shock B46955/50.
[268c] Nigeon-Dureil and Ratsimamanga B46555/49.
[269] Selye **94572/49.**
[270] Scheerer A658/37.
[270a] Carey B46475/50, Selye and Stone B29705/50.
[271] Dodds and Noble 54523/35, 55669/34, Scheerer A658/37.
[272] Selye et al. 58020/36.
[273] Forsham et al. B17987/48.

Adrenalectomy has no marked and consistent effect upon the blood-count of otherwise untreated animals, although it tends to cause some anemia and lymphocytosis.[274] The interpretation of pertinent data is complicated by the fact that this operation causes particularly severe systemic stress, the damaging effect of the surgical trauma being superimposed here upon the hypocorticoidism. To eliminate this complication, systematic investigations were carried out in rats maintained on an adequate corticoid replacement therapy for some time after adrenalectomy. "The red blood cell count showed a rapid increase during the first 2 or 3 days after discontinuation of cortin treatment, and remained well above normal until death. The large lymphocytes, the small lymphocytes, and the neutrophiles, after small irregular variations, increased markedly in number during the 24 hour period preceding death. Reticulocyte counts made on the blood of these rats agree with our previous finding that after adrenalectomy a great increase in reticulocytes occurs, followed by a drop to nearly normal numbers before death." [275]

To what extent *adrenaline* influences the blood-count after adrenalectomy has been the subject of considerable controversy. It has long been known that in the normal animal adrenaline causes marked polymorphonuclear neutrophilia accompanied by eosinopenia and lymphopenia. On the basis of observations in the cat, it had been claimed that all these responses are inhibited by adrenalectomy.[276] Experiments in the dog showed that adrenaline causes pronounced lymphopenia and polymorphonuclear neutrophilia both in intact and in splenectomized animals, while after adrenalectomy there was a transitory lymphocytosis. If the suprarenal vein of such an adrenalectomized and adrenaline-treated dog was connected with the jugular vein of an intact dog, the number of lymphocytes in the latter decreased for a period of two hours. This lymphopenia was ascribed to hyperactivity of the adrenal cortex.[277] In the rat, the relative neutrophilia and marked lymphopenia caused by adrenaline under normal conditions is absent after adrenalectomy.[278]

Subsequent investigators confirmed that adrenalectomy prevents lymphopenia following adrenaline injection in the rat and showed that no such inhibition is observed after mere removal of the adrenal medulla. Since hypophysectomy also failed to present this effect (cf. above), it was concluded "that at least one effect of epinephrine is to act directly on the adrenal cortex, releasing substances which lower the level of circulating mononuclear leucocytes".[279] According to preliminary observations it was thought that the eosinopenic effect of adrenaline is present even in completely adrenalectomized rats,[280] but this was not confirmed,[280a] indeed, adrenalectomy prevents both the lymphopenia and the eosinopenia normally elicited by adrenaline in the mouse and rat.[281] Perhaps these inconsistencies will find their explanation when the rôle played by conditioning factors (e.g., diet, heredity, previous exposure to stress) are taken into account. In any event, small doses of cortical extract greatly augment the eosinopenic action of adrenaline, apparently due to a peripheral synergism.[281a]

[274] Selye **94572/47**, Valentine et al. **B33082/48.**
[275] Dalton and Masson A31850/40, Masson and Dalton 77178/40.
[276] Borchardt 23991/29.
[277] Malméjac et al. 93394/46.
[278] Gellhorn and Frank B28597/48.
[279] Hungerford B31654/49.
[280] Recant et al. B17739/48.
[280a] Recant et al. B47003/50.
[281] Dury and Bacchus B32734/49, Speirs and Meyer B43545/49.
[281a] Recant et al. B47003/50.

In adrenalectomized mice eosinopenia was also produced by gluco-*corticoids* (e.g., cortisone and to a lesser extent dehydro-corticosterone), but DCA was almost, estrone and testosterone entirely inert.[284] In rats, cortisone, Kendall's "cpd. F" and cortical extracts caused eosinopenia even after ablation of the suprarenals, while DCA was inactive.[284a]

In *Addisonians*, 17-hydroxy-corticosterone causes an increase in circulating neutrophils with lymphopenia and eosinopenia, even in the case of severe adrenal insufficiency, but DCA has no such effect.[282] Cortisone also causes eosinopenia in Addisonians.[283]

In Addison's disease under basal conditions, there is a tendency towards lymphocytosis with neutropenia and a normocytic-normochromic anemia. Under stress, the blood-picture remains fixed and fails to show the usual leucocytosis and lymphopenia of the A-R.[285]

Surgical *trauma*, which regularly causes marked eosinopenia in normal man fails to elicit this response in Addisonians.[286]

The lymphopenia and neutrophilia normally elicited by *hemorrhage*, in the mouse or rat, is not only prevented by adrenalectomy,[287] but even by mere adreno-demedullation.[288] This suggests that the discharge of adrenaline during the A-R plays some rôle in the genesis of the characteristic hematologic changes.

Small doses of *x-rays*, just sufficient to elicit a sharp drop in blood-lymphocytes in intact mice, are ineffective in this respect after adrenalectomy. Since, on the other hand, large doses of x-rays cause lymphopenia both in the presence and in the absence of the adrenals, it was concluded that in the latter case, the effect is not mediated by corticoids.[289]

The lymphopenia elicited by exposure to *cold* in the mouse, is not manifest after adrenalectomy.[290]

Nervous stimuli, such as the so-called "heat puncture" of the hypothalamic nuclei, cause polymorphonuclear neutrophilia with lymphopenia and eosinopenia in the normal cat, but this response (and especially the neutrophilia) is inhibited by adrenalectomy.[291] In mice exposed to nervous stress (being tied to a wire grid), the normally pronounced lymphopenia can be prevented by bilateral adrenalectomy.[292] However, in merely adreno-demedullated rats, excitement (caused by electro-shock) also fails to produce the normal lymphopenic response. It was therefore concluded that elimination of adrenaline secretion suffices to suppress this effect.[293]

The erythrocytosis following *muscular exercise* is allegedly manifest in the intact dog and rat, but missing after adrenalectomy.[294]

The infectious leucocytosis elicited in normal cats by *pneumococcus* injections is not present after adrenalectomy.[295]

Typhoid vaccine causes severe lymphopenia in adrenalectomized rats, whether or not they had been previously treated with cortical extract. In

[284] Speirs and Meyer B43545/49.
[284a] Recant et al. B47003/50.
[282] Baez-Villasenor et al. B33084/48, Hills et al. B33083/48, Recant et al. B47003/50.
[283] Forsham et al. B35919/49.
[285] Baez-Villasenor et al. B33084/48.
[286] Roche et al. B35923/49.
[287] Speirs and Meyer B43545/49.
[288] Gellhorn and Frank B36927/49.
[289] Dougherty and White 95612/46.
[290] Elmadjian and Pincus B366/45.
[291] Borchardt 22895/28, 23991/29.
[292] Elmadjian and Pincus B366/45, Pincus B37780/49.
[293] Gellhorn and Frank B36927/49.
[294] Lang A15435/38, A8502/37.
[295] Borchardt 23991/29.

contrast, the polymorphonuclear neutrophils increase somewhat more markedly in rats treated with cortical extract or Kendall's "cpd. A" than in untreated adrenalectomized animals.[296]

Infection with a strain of *Trichinella spiralis*, which caused only slight eosinophilia in normal rats and mice, was entirely devoid of this action after adrenalectomy. Replacement therapy with cortical extracts restored the eosinophilic response to infection, but since the effect was mild no conclusion could be drawn.[297]

The lymphopenia caused by *anoxia* in the dog is not only inhibited by adrenalectomy, but even by mere splanchnicotomy. Hence, here again adrenaline-liberation appears to be of major importance.[298]

The reticulocytosis and polycythemia produced by exposure to low barometric pressures in the rat is not prevented by adrenalectomy. "It is concluded that although adrenalectomy in the rat results in alterations in the red-cell production and/or destructive mechanisms, the adrenal is not essential for the response of the erythropoietic stress imposed by lowered barometric pressures.[298a]

Various drugs which elicit lymphopenia and polymorphonuclear leucocytosis in intact animals, are ineffective in this respect after adrenalectomy. This has been shown in particular for *glucose*,[299] *choline* and *pilocarpine*.[300]

The neutrophilia and lymphocytosis, usually seen after adrenalectomy in the rat, is diminished by large doses of *calcium pantothenate*.[301] The mechanism of this inhibition is unknown.

The leucopenia and absolute lymphopenia produced by *urethane* were of similar magnitude in normal and in adrenalectomized rats. Hence "the adrenal glands were not involved in these changes in the blood-picture".[302]

In view of all these observations, it is perhaps not unreasonable to assume that systemic stress can influence the blood-count to some extent even in the absence of the adrenals. Yet adrenal hormones (presumably both adrenaline and gluco-corticoids) greatly modify this response, especially when — as in the A-R — excessive quantities of these compounds are present in the blood.

While there is considerable disagreement concerning the effect of adrenaline in adrenalectomized or hypophysectomized animals (cf. above), data regarding its effect in the intact organism are more consistent. It has been shown by experiments on the mouse and rat that adrenaline produces the same kind of polymorphonuclear neutrophilia, eosinopenia and relative lymphopenia as other alarming stimuli.[303] This has been confirmed in man.[304] Since these responses are very rapid, they have been ascribed to a redistribution of white cells rather than to mere formation or destruction.[305] However, after moderate doses, the erythrocyte count shows no very obvious variations, radio-phosphorus-labelled erythrocytes are not discharged into the circulation [306] and simultaneous blood-counts in various vascular territories likewise fail to reveal any such

[296] Lewis and Page B25995/48, B37772/49.
[297] Larsh and Nichols B39070/49.
[298] Malméjac and Gross B38652/47.
[298a] Gordon and Piliero B47133/50.
[299] Elmadjian et al. 95224/46, Pincus B37780/49.
[300] Borchardt 23991/29.
[301] Dumm et al. B35959/49.
[302] Dury and Robin B19209/48.
[303] Dury and Bacchus B32734/49, Harlow and Selye A8400/37.
[304] Hortling and Pekkarinen B39100/49, Recant et al. B47003/50.
[305] Camp B312/27.
[306] Nylin B25025/46.

redistribution of blood-cells [307] in adrenaline-treated men. Yet, certain in vitro experiments (see below) suggest that a discharge of splenic lymphocytes also participates in this picture.

Several other sympathomimetic drugs, and stimulation of the sympathetic nervous system itself, exert similar actions upon the blood-count, hence this action was considered to result from adrenergic stimulation. Parasympathomimetic drugs allegedly cause lymphocytosis with leucopenia, that is, the reverse response.[308] It should be kept in mind, however, that if the reaction is non-specific, the intensity and duration of the stress can influence the response, irrespective of any specific action.

Simultaneous treatment with *cortical extract* diminishes or abolishes the lymphopenia and polymorphonuclear neutrophilia normally produced by adrenaline in the rat.[309] It was concluded that: "the primary factor involved in the action of adrenaline on the lymphocytes seems to be the lowering of the concentration of adreno-cortical hormones in the tissues". However, in the same publication it is stated that: "it is suggested in agreement with Sayers and Sayers that adrenaline increases the consumption of adreno-cortical hormones in the tissues and that the lowering of their concentration in the blood leads to increased secretion of adrenocorticotrophic hormone which in turn increases secretion of adreno-cortical hormones, the latter induce lymphopenia".[310] These two statements appear mutually contradictory. It is now generally agreed that injection of corticoids causes lymphopenia and polymorphonuclear leucocytosis in otherwise untreated animals (cf. below). Hence it appears more probable to us, that the antagonism between corticoids and adrenaline is merely due to the prevention of many toxic adrenaline effects by the former. The eosinopenic action of adrenaline is increased by gluco-corticoids.[319a]

In man "significant eosinopenia has been observed following injection of epinephrine and of insulin. This change was exaggerated in patients with essential *hypertension* and diminished or absent in patients with *adrenal or pituitary insufficiency*. Marked eosinopenia has been found after surgical operations". Here insulin and trauma may have acted upon the eosinophils through the discharge of adrenaline during the ensuing A-R.[311] The lymphopenic effect of adrenaline has also been confirmed in patients suffering from *myasthenia gravis*.[312]

The eosinopenic action of adrenaline is not prevented by complete transection of the *nervous* (and vascular) connections between pituitary and hypothalamus in the rat. Hence, the hormone does not appear to stimulate ACTH discharge as a result of a direct action upon the hypothalamus which would be transmitted to the pituitary through the stalk.[312a]

It has been thought that during the A-R, the liberation of adrenergic hormones is indispensable for the stimulation of ACTH production (cf. "Adrenals"). Formaldehyde, as a typical stressor agent, produces eosinopenia in animals.[312b] Yet "epinephrine does not appear to be the obligatory activating agent for ACTH production in stress, since significant eosinopenia is still obtained in completely sympathectomized dogs by injection of formaldehyde.[312c]

[307] Hortling and Pekkarinen B39100/49.
[308] Camp B312/27.
[309] Gellhorn and Frank B28597/48, Selye et al. A30865/40.
[310] Gellhorn and Frank B28597/48.
[310a] Recant et al. B47003/50.
[311] Laragh and Almy B28605/48.
[312] Hellman B32768/49.
[312a] Recant et al. B47003/50.
[312b] Dalton and Selye A31350/39, Dalton et al. A18306/39.
[312c] Recant et al. B47003/50.

In *allergic* patients with marked eosinophilia, adrenaline (and insulin which causes adrenaline discharge) decreases the eosinophil-count.[313] In mice in which eosinophilia had been previously produced by feeding muscle tissue from rats infected with *Trichina spiralis*, adrenaline also decreases the eosinophil count, but only in the presence of the adrenals.[314]

In various *infectious diseases* the adrenaline neutrophilia tends to be somewhat more than normally pronounced.[315]

Adrenaline given in small doses which in themselves caused no change in the white-cell picture was found to produce in *urethanized* animals "a polymorphonuclear leucocytosis along with a previously existing urethane-induced lymphopenia. It is apparent that urethane's effect on the white blood cells is not restricted to the lymphocytes and that urethane is somehow related to the adrenal cortex mechanism".[316]

Cortical extracts cause polymorphonuclear neutrophilia, with shift to the left, lymphopenia and eosinopenia in man.[317] Gluco-corticoids such as cortisone[318] or Kendall's "cpd F."[319] are definitely active in this respect, while DCA[319a] and many of its non-gluco-corticoid derivatives[319b] are inert. The claim that cortisone fails to cause eosinopenia in rheumatoid arthritics[319c] requires confirmation.

Chronic treatment with cortisone tends to cause a polycythemia rubra[320] reminiscent of that seen in Cushing's disease.

Cortical extracts also produce lymphopenia, eosinopenia and neutrophilia in various animal species[321] and cortisone has been shown to cause similar changes in the mouse[321a] and rat.[321b]

In clinical *lymphatic leukemia*, the lymphocytosis could not be markedly influenced by cortical extracts.[322] However, potent cortical extracts diminish the eosinophilia induced in mice by feeding them muscle from *trichinous* rats.[323]

In the *isolated spleen* of the rabbit, perfused under constant pressure, addition of adreno-cortical extract to the perfusion fluid causes an immediate discharge of splenic lymphocytes. Subsequently however, there is a tendency for lymphocytes to disappear from the perfusion fluid. This secondary lymphopenia has been ascribed to accelerated lymphocyte-breakdown in the spleen. Glucose, adrenaline, DCA and estradiol dipropionate in the doses tested, failed to duplicate this lymphocyte discharge from the spleen which was produced by cortical extracts. The addition of cortical extracts to *perfused thymus, liver or lung* does not produce discharge of lymphocytes from these tissues.[324]

There is considerable disagreement concerning the hormonal mechanism responsible for the polymorphonuclear neutrophilic leucocytosis, the eosinopenia and the lymphopenia characteristic of the A-R. However, the data published

[313] Godlowski B34538/48.
[314] Stein B33029/49, B37271/49.
[315] Hortling B27318/48.
[316] Dury and Robin B19209/48.
[317] Hellman B32769/49.
[318] Perera et al. B33431/49, B36595/49, Recant et al. B47003/50.
[319] Fourman et al. B39685/49, Recant et al. B47003/50.
[319a] Recant et al. B47003/50.
[319b] Spies and Stone B43903/49.
[319c] Sprague et al. B46430/50.
[320] Hench et al. B27892/49.
[321] D'Angelo B32727/49, Recant et al. **B47003/50**, Shapiro and Schechtman **B27704/49.**
[321a] Antopol B47052/50.
[321b] Selye 35935/ND.
[322] Hellman B32769/49.
[323] Stein B33029/49, B37271/49.
[324] Hechter B19206/48.

up to date are best compatible with the interpretation that in the final analysis all these changes are dependent mainly upon gluco-corticoids. Various types of stress and adrenaline imitate this response presumably due to activation of the pituitary-adrenal-cortex mechanism. Since adrenaline is particularly effective in this respect, it is quite possible that, during stress, an adrenergic discharge from the medulla and from sympathetic nerve endings may largely contribute to the genesis of the characteristic blood-picture (cf. Theoretic Interpretation, pp. 437-439).

Since the spleen is an important reservoir of formed blood-cells, considerable attention has been given to the effect of **splenectomy** upon the hematologic response to various agents.[325] Under most experimental conditions the spleen plays no important rôle in the variations of the white-cell count produced by systemic stress. Thus extensive experiments on the rabbit led to the conclusion that "the spleen plays no part in the production of a drug leucocytosis".[326]

The increase in the total white-cell count elicited in the rabbit by *sodium arsenite*,[327] *salvarsan*,[328] intravenous injection of *hypertonic NaCl* or *glucose* solutions,[329] *albumose*,[330] *coli bacilli*,[331] or *hemorrhage*,[332] develops normally after splenectomy in the rabbit.

The anemia, leucopenia and thrombocytopenia, which normally occurs following *x-irradiation*, is greatly diminished (and survival is prolonged) in mice whose spleens are shielded by lead.[333] However, this is apparently due only to the fact that the spleen compensates for the deranged myelopoietic ability of the bone-tissue.

Allegedly, the eosinopenia caused by *adrenaline* in the rat is prevented by splenectomy while the neutrophilia is actually increased.[334] However, in the mouse, splenectomy did not interfere with the production of eosinopenia by adrenaline[335] so that the spleen is hardly indispensible for this response. Indeed, subsequent experiments showed that even in the splenectomized rat, adrenaline produces eosinopenia, although the typical lymphopenic and neutrophil response is abolished. "The eosinophil therefore seemed most unequivocally, of the leucocytes studied, responsive to adrenal cortical activity alone".[335a] The latter conclusion is justified, since — as we have said before — the effect of adrenaline upon the eosinophils is mediated by the adrenal cortex.

On the other hand, the erythrocytosis usually produced by adrenaline or *muscular exercise* in the dog and rat is prevented by splenectomy and even by mere denervation of the spleen or the administration of ergotamine.[336] Perhaps under the experimental conditions here employed, splenic contraction played an important rôle in determining the hematologic response.

It is somewhat puzzling that with the same stressor agent one experimentor appears to obtain lymphopenia and another lymphocytosis. Recent experiments on the effect of corticoids upon the spleen may help to explain this apparent paradox. It has been found that a cortical extract which induces

[325] Perla and Marmorston-Gottesman 32161/35.
[326] Camp B312/27.
[327] Hiraoka 38773/36.
[328] Anan A50/36.
[329] Anan A9333/37.
[330] Anan A9334/37.
[331] Faludi A14718/38.
[332] Feenders 37979/36.
[333] Jacobson B33422/49, Jacobson et al. B34769/49.
[334] Dury and Bacchus B32734/49.
[335] Speirs and Meyer B43545/49.
[335a] Dury B46217/50.
[336] Láng A8502/37, A15435/38.

lymphopenia in otherwise untreated adrenalectomized rats or mice, causes lymphocytosis in adrenalectomized animals exposed to "swim-stress" (fatigue by swimming). Conversely, the absolute lymphocytosis produced by "swim-stress" in intact rats is significantly decreased either by adrenalectomy or by splenectomy. It was assumed that corticoids participate in these reactions by inducing a splenic lymphocyte discharge. DCA fails to produce lymphocytosis in swimming adrenalectomized rats, while cortical extract (rich in gluco-corticoids) treatment is highly effective in this respect. "It is apparent that the lymphopenic activity of adreno-cortical hormones would tend to counteract the effect of the splenic reaction upon the circulating lymphocyte level and that the resulting effect would depend upon the magnitude, latent period and duration of these opposing reactions".[337] It is perhaps also conceivable that the end result would depend upon the proportion between the degree of stress and the amount of corticoids present. The lymphocytosis-producing and lymphopenic effect of gluco-corticoids may be conditional upon the simultaneous action of other metabolic changes produced by stress.

Blockade of the reticulo-endothelial system does not influence the leucopenia induced by coli bacilli in the rabbit.[338] Hence, the phagocytic power of the macrophage system is dispensable for this response. The lymphopenia elicited by glucose is not influenced by **thymectomy** in the rat.[339] Presumably this lymphatic organ is not essential for the disappearance of circulating lymphocytes, although it undergoes such marked changes during the A-R.

A possible participation of the liver in the hematologic response to stress was suggested by Japanese investigators who claimed that the leucocytosis produced by a variety of non-specific damaging agents does not occur in animals bearing an **Eck-fistula.**[340]

Thyroidectomy also fails to prevent non-specific drug-leucocytosis.[341]

We have already mentioned the fact that **nervous stimuli** are particularly active "stressors" conducive to rapid changes in the white-cell count. We have spoken of the possible rôle played in this connection by a hypothetical "leucocyte center" in the hypothalamic region.[342] The nervous regulation of hematologic responses has been extensively reviewed elsewhere.[343] Lymphocytosis has been ascribed to parasympathetic, polymorphonuclear neutrophilia to sympathetic stimulation.[344] It has also been claimed that after high transection of the spinal cord, non-specific drug-leucocytosis fails to occur,[345] and many observations suggest that brain-stem anesthetics prevent such hematologic responses.[346]

On the other hand, there is considerable evidence to show that nervous mediation is not an indispensable prerequisite for ACTH discharge during the G-A-S. This has been discussed, in connection with various other manifestations of ACTH secretion, in other sections of this book. As regards the hematologic results of gluco-corticoid secretion, it is pertinent to mention here, however, that transection of the stalk does not prevent the typical alteration of

[337] Stone and Hechter B19207/48.
[338] Faludi A14718/38.
[339] Sass-Kortsak and Vogt B36775/48.
[340] Anan A50/36, 38775/36, 38776/36, 38777/36, Muto 38774/36.
[341] Anan A9333/37, A9334/37, A50/36, 38777/36.
[342] Rosenow 23462/28.
[343] Hortling B27318/48.
[344] Camp B312/27.
[345] Anan 38776/36, 38777/36, A50/36, A9333/37, A9334/37, Hiraoka 38773/36, Hoff and Linhardt 23011/38.
[346] Paschkis and Martos **A14911/38.**

the bloodcount following the administration of adrenaline and insulin or after trauma.[346a] Furthermore, the eosinopenia elicited by alarming doses of formaldehyde is not prevented by complete sympathectomy in the dog.[346b] Destruction of some hypothalamic nuclei, on the other hand, appears to block this response, although it is not yet quite clear which nuclei are involved here.[346c]

In view of the extensive literature concerning the nervous regulation of the blood-count,[347] it is important to note that if, in a pair of *parabiotic* rabbits, one animal develops leucocytosis following air insufflation of the brain ventricles, the same leucocytosis will develop a few minutes later in the other twin. This has been considered as definite proof that regulation of the white blood count is due to humoral substances (the so-called "leukopoietines").[348] (Cf. also: Parabiosis, p. 432.)

Liver extracts containing the anti-pernicious-anemia factor, tend to cause reticulocytosis, especially in pernicious anemia,[349] but in certain species (e.g., guinea-pig) even among healthy individuals. This is obviously a specific property of the anti-pernicious-anemia principle. It has been emphasized, however, that the response must be viewed critically before a specific action of a liver extract can be deduced from tests on healthy animals, since "the number of circulating reticulocytes in the guinea-pig increases after a variety of physiological disturbances".[350] Reticulocytosis is certainly also a characteristic response to non-specific stressors during the A-R (cf. above).

The rôle of the liver in the regulation of hematologic responses to non-specific stress, is further indicated by observations in rats in which granulocytopenia was produced by protein-deficient diets. Here the administration of an anti-anemic hepatic extract inhibited the fall in neutrophils.[351]

Folliculoid hormones cause marked, often fatal, anemia in certain animal species, but in man they are comparatively ineffective in this respect.[352] In the mouse, in which the erythrocyte number is likewise not much altered by folliculoids, these hormones cause marked lymphopenia and a transient rise, followed by a persistent decrease in neutrophiles. Pretreatment with folliculoids does not influence the leucopenic response of mice to *x-irradiation,* but appears to protect them against the red-cell destruction caused by the rays.[353] It is not known whether these effects are dependent upon the stressor effect of the folliculoids.

In the rat, folliculoids do not change the erythrocyte-count significantly, but if given conjointly with *LAP* (which in itself is also ineffective in this respect) they cause a severe anemia and icterus.[353a]

That various **drugs** influence the blood-count due to their stressor effect, has already been mentioned in the preceding pages. Let us merely emphasize here that some chemical substances can alter the normal G-A-S response by virtue of certain specific properties. Thus, a variety of *radioactive elements* (e.g., thorium-X, radio-phosphorus), *benzol, urethane,* natural and artificial

[346a] Hume and Wittenstein B46961/50, Recant et al. B47003/50, Harris B47462/ND.
[346b] Recant B47003/50.
[346c] Hume B33420/49, Harris and de Groot B47142/50.
[347] Hoff **B27407/34.**
[348] Beer A17285/38.
[349] Palmer **95299/46.**
[350] Hummel A7881/37.
[351] Daft B38098/47.
[352] Selye **94572/49.**
[353] Patt et al. B32806/49, Straube et al. B33113/48.
[353a] De Grandpré and Selye B47463/ND.

folliculoids and *mustards*, possess especially marked leucocyte destroying actions. They counteract the leucocytosis characteristic of certain stages of the G-A-S and are even useful in the treatment of leukemias.[354]

Cobalt not only prevents the non-specific "anemia of infection" in the rat, but actually reverses it so that polycythemia ensues.[355] In this respect it is manifestly a conditioning factor.

In relation with the possible adrenergic component involved in the production of hematologic responses during the G-A-S, it is of special interest that *dibenamine* increases the lymphopenic effect of tourniquet shock in the rat.[356] This shows that elimination of a dibenamine-sensitive nervous factor cannot prevent this characteristic A-R response.

The stressor effect of inadequate diets has likewise been discussed in the preceding pages. However, it may be well to mention certain data illustrating how nutritional factors can affect the normal hematologic response to stress. Thus the granulocytopenia, caused by protein deficiency in the rat, can be compensated by the administration of *pteroylglutamic acid* or a mixture of the *essential amino-acids*. It appears that here a lack of pteroylglutamic acid is involved in the pathogenesis of the granulocytopenia and that the rat can synthetize this food factor from the essential amino-acids.[357]

Pantothenic acid also appears to participate in the hematologic response to stress. Rats respond with a subnormal lymphopenia in the "swim test" if they are kept on diets deficient in this vitamin. Since pantothenic acid exerts important effects upon the adrenals "these results are interpreted as a reflection of the changes in the adrenal cortex induced by pantothenic acid deficiency".[358]

When two animals are joined in **parabiosis**, and one of them is x-irradiated while the second is protected, both develop transitory leucocytosis followed by leucopenia. Indeed, even if the parabiotic union is severed 20 minutes after irradiation of one twin, typical blood-changes still ensue in both animals. From this it has been concluded that the hematologic changes caused by x-irradiation are mediated through a humoral factor, but the identity of this agent — particularly its possible relationship to the adrenals — has not been investigated.[359] The hematologic changes induced by neurogenic stimuli (cf. above) are likewise transmitted from one parabiont to its twin.[360]

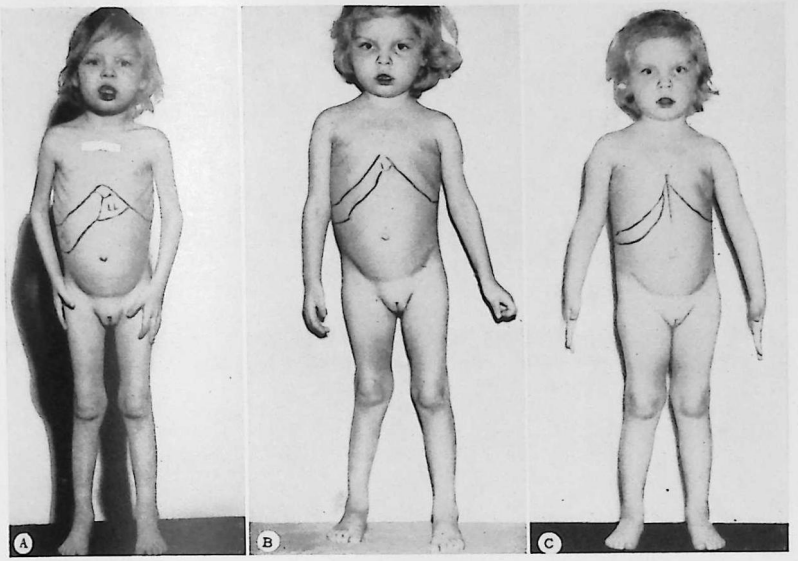
The rôle played by **heredity** has been emphasized on the basis of experiments on certain rats, which are allegedly refractory to alarming stimuli. In these, stressor agents (e.g., swimming), or even anterior-pituitary extracts, apparently fail to influence the blood-count, while corticoids are effective.[361]

Blood Diseases of Adaptation

So little is known about the rôle of systemic stress in the pathogenesis of blood dyscrasias that it will suffice merely to point out a few conditions in which derailments of the G-A-S appear to participate. This is done mainly in order to encourage further research along these lines.

Anemias. — Certain anemias, especially those accompanied by hypoferremia, are obviously related in some manner to systemic stress. In the preceding

[354] Aubertin **B37546/47.**
[355] Wintrobe et al. B37960/47.
[356] Wiedeman and Lewis B37752/49.
[357] Daft B38098/47.
[358] Dumm et al. B37736/49.
[359] Kolpakov and Khodos B46039/49.
[360] Beer A17285/38.
[361] Nigeon-Dureuil and Ratsimamanga B46555/49.



Acute granulocytic leukemia. — **A.** After 2 days of ACTH (50 mg./day). — **B.** One week after stopping ACTH. — **C.** One month after stopping ACTH.
(After O. H. Pearson. N.Y. Acad. Med. 1950, in press.)

pages we mentioned the so-called *anemias of infection, intoxication, malignancy, malnutrition* and the *"anemia infantum pseudoleukæmica"*. In all these, the manifestations of the anemia are very similar although the eliciting agent differs. Presumably conditioning factors (heredity, age, diet, previous exposure to stress) are most important in determining whether a non-specific anemia will develop upon exposure to stress. If anemia ensues such factors can undoubtedly also modify its manifestations, but the fundamental mechanism appears to be essentially the same.

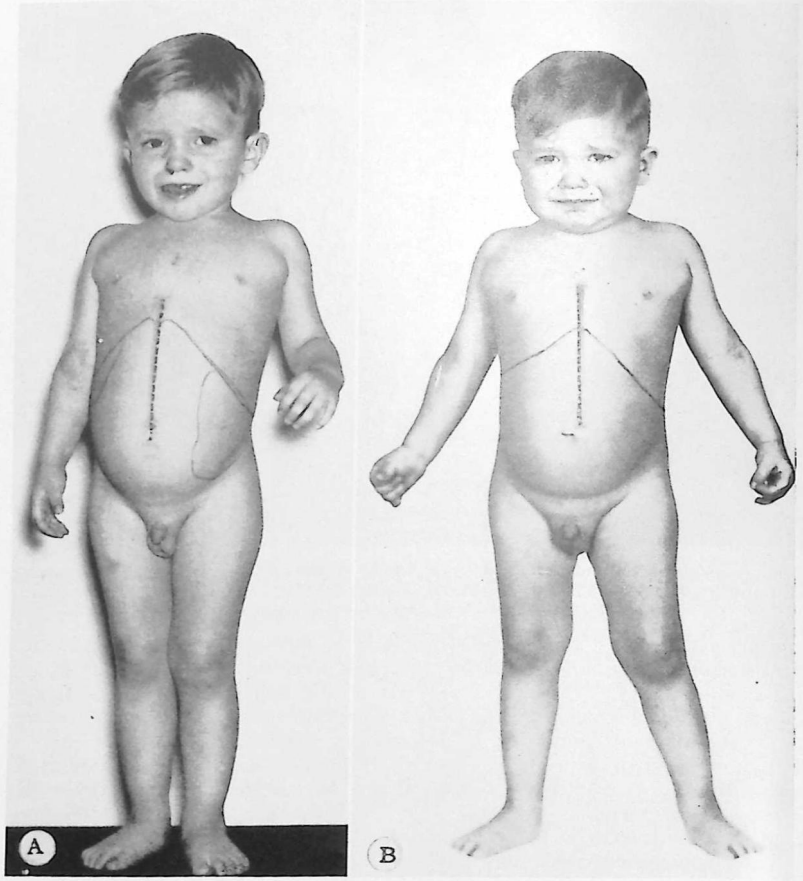
In some anemias *psychic factors* appear to be of pathogenic importance.[1a]

The common occurrence of *anemia in Addison's disease* suggests that lack of corticoids seriously impedes blood formation, especially since in this case corticoid therapy restores the blood-count towards normal.[1] In the sense of our definition, this would be a "primary disease of adaptation" due to a defect in an organ of systemic adaptation.

Interestingly, certain *hemolytic anemias* may undergo marked remissions during ACTH treatment.[1b]

Polycythemias. — In *Cushing's syndrome* (be it due to a basophil adenoma of the anterior-lobe with secondary adreno-cortical hyperplasia, or to a primary growth of the adrenal-cortex itself), there tends to develop a polycythemia which in many respects is the counter part of the anemia of Addison's disease.[2] Since prolonged overdosage with ACTH or cortisone produces a similar polycy-

[1a] Halliday **B46202/48.**
[1] Selye **94572/49.**
[1b] Thorn. B47468/ND.
[2] Forssell B34069/46, Selye **94572/49.**



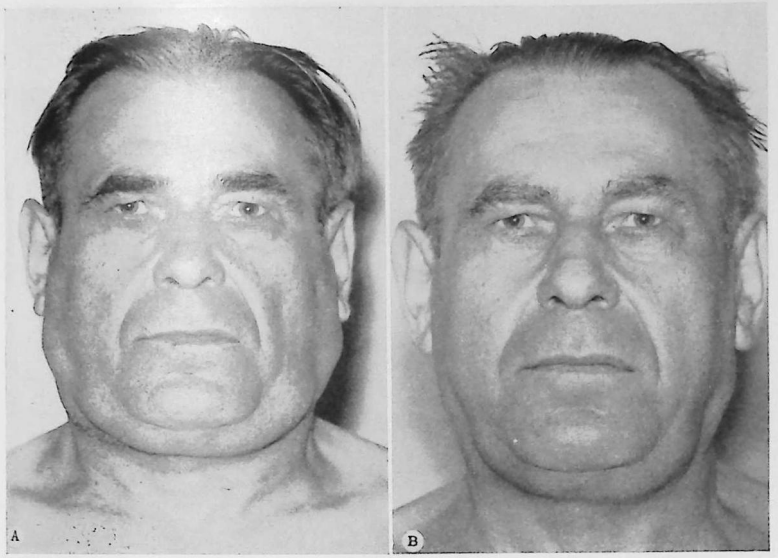
Acute lymphocytic leukemia, resistant to antifolic therapy. — **A.** Before treatment. — **B.** After 21 days of ACTH (50 mg./day). Note that shrinkage of liver and spleen had occurred after one week of ACTH administration. (Courtesy of Dr. O. H. Pearson.)

themia even in normal individuals,[3] it is reasonable to assume that an excess of gluco-corticoids is responsible for this hematologic change. It remains to be seen to what extent such an excess is involved in the pathogenesis of *polycythemia vera rubra*.

The polycythemia of the shock-phase of the A-R is unrelated to these diseases since it has definitely been shown to result merely from hemoconcentration.

Leukemias. — We have already seen that the white-cell count is markedly influenced by the G-A-S. Later in this book, we shall present data indicating

[3] Hench et al. B27892/49.



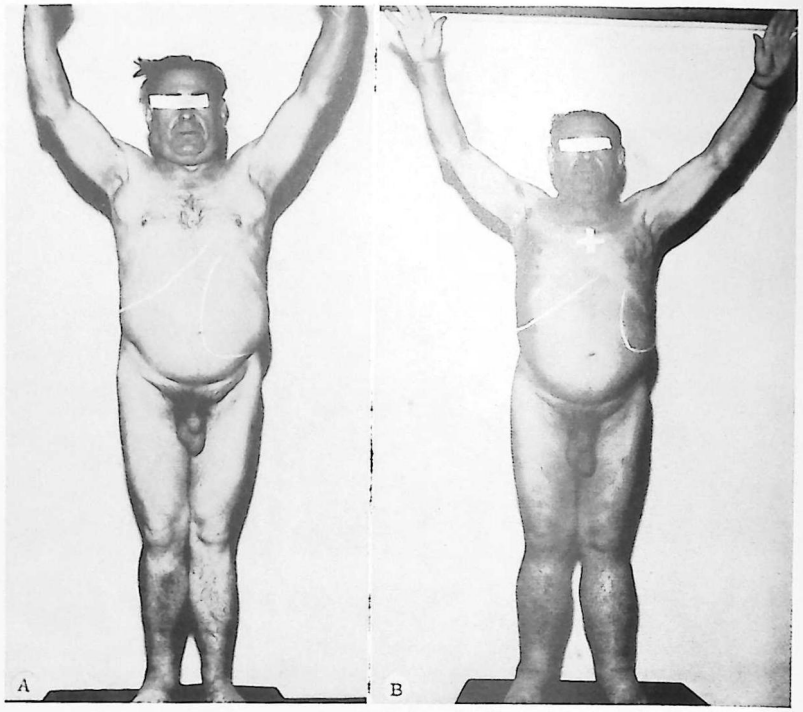
Chronic lymphatic leukemia. — **A.** Before treatment. — **B.** After 24 days of ACTH, 100 mg./day. (After Pearson et al. B46975/50.)

that the same is true of the hemopoietic and lymphopoietic organs. Clinical hypocorticoidism is often associated with lymphocytosis as well as an excessive development of the lymphatic organs; hyperthyroidism can also exert rather similar effects.[4] Since both the corticoids and the thyroid hormone participate in the G-A-S mechanism, it is suggestive to assume that they may also play a part in the genesis of certain leukemias. This view is further supported by the many observations (cf. above) which show that lymphopenia and neutrophilia are produced by ACTH and by various gluco-corticoids.

Susceptibility to transplantable leukemia is greatly increased by **adrenalectomy** in mice [4a] and rats.[4b] Conversely, **transplantation of additional adrenals** into rats decreases their sensitivity to this type of leukemia.[4c]

In man, acute lymphatic leukemias may show prolonged remissions upon treatment with **cortical extracts,**[4d] but this is not always the case.[4e] Particularly promising results have been obtained in the acute, lymphatic leukemias of children with **ACTH,**[4f] but it remains to be seen whether such remissions can be maintained. In one case of eosinophilic leukemia, recently brought to our attention, ACTH was spectacularly effective. Granulocytic leukemias may also respond favourably.[4ff]

[4] Selye **94572/49.**
[4a] Law **B44871/47.**
[4b] Murphy and Sturm **B47029/50**
[4c] Murphy and Sturm B47029/50
[4d] Michael and Richardson B44447/49.
[4e] Hellman B32769/49.
[4f] Astwood et al. B47853/50, Eliel et al. B47865/50, Farber et al. B46976/59, Pearson et al. B46975/50, B46309/50.
[4ff] Pearson and Eliel B47894/50.



Chronic lymphatic leukemia. — **A.** Before. — **B.** After ACTH therapy.
(Same patient as shown in previous picture.)

In most of the leukemias of man, there are no manifest indications of hypo-corticoidism. However the same is true of rheumatoid arthritis. It may well be that in both these conditions the derangement is not the direct result of hypo- or hyper-corticoidism, but that its development is merely enhanced by derangements in the gluco-corticoid:mineralo-corticoid balance. In these diseases a derailment of the G-A-S mechanism, and particularly a malfunction of the adrenal-cortex, is probably not the main pathogenic factor, it merely creates a predisposition for a disease whose principal pathogen (heredity? microörganisms?) is still unknown.

Occasionally folliculoids also caused remissions in clinical lymphatic leukemia.[4g] This may well be due to their marked direct lympholytic action.

Agranulocytosis. — We have already called attention to the fact that during a very intense A-R marked leucopenia tends to ensue, especially if the organism is unable to resist the stress (cf. above). Agranulocytosis can occur in clinical medicine under the influence of a variety of apparently quite unrelated stressors, such as drugs, allergens, physical agents. It appears to result from an excessive utilization of the granulocytes during stress whenever the compensatory production of new leucocytes lags behind their consumption for defensive purposes. It has therefore been emphasized that agranulocytosis is not a disease entity in itself; it has no characteristic symptomatology other than the usual septic complications which are due to the body's inability to defend itself against infections.[5] There is no doubt that ACTH and gluco-corticoids can raise the granulocyte count, but their participation in the pathogenesis of agranulocytosis has not yet been adequately examined. However, at least in one case, **cortisone** caused an immediate remission.[5a]

[4g] Albeaux-Fernet and Danel B44825/49.

Theories Concerning the Participation of the Blood-count in the G-A-S

Regulation by specific metabolites. — Several investigators expressed the view that certain specific metabolites, liberated during the shock-phase, stimulate leucocyte formation. Presumably, such blood-borne agents may also play a rôle in other hematologic responses during the G-A-S.[6] Allegedly blood taken during the shock-phase possesses the property of increasing the leucocyte count in normal animals.[7]

Although none of these blood-count regulating substances has as yet been isolated in pure form, some of them have been designated with such terms as *"neutrophilins"*,[8] *"leucotaxin"*,[9] *"leucopoietins"*,[10] *"leukerethin"*,[11] etc.

It is noteworthy, however, that in the hands of some investigators, blood taken from animals at the peak of the leucopoietic reaction causes no leucopoiesis when injected into other individuals.[12]

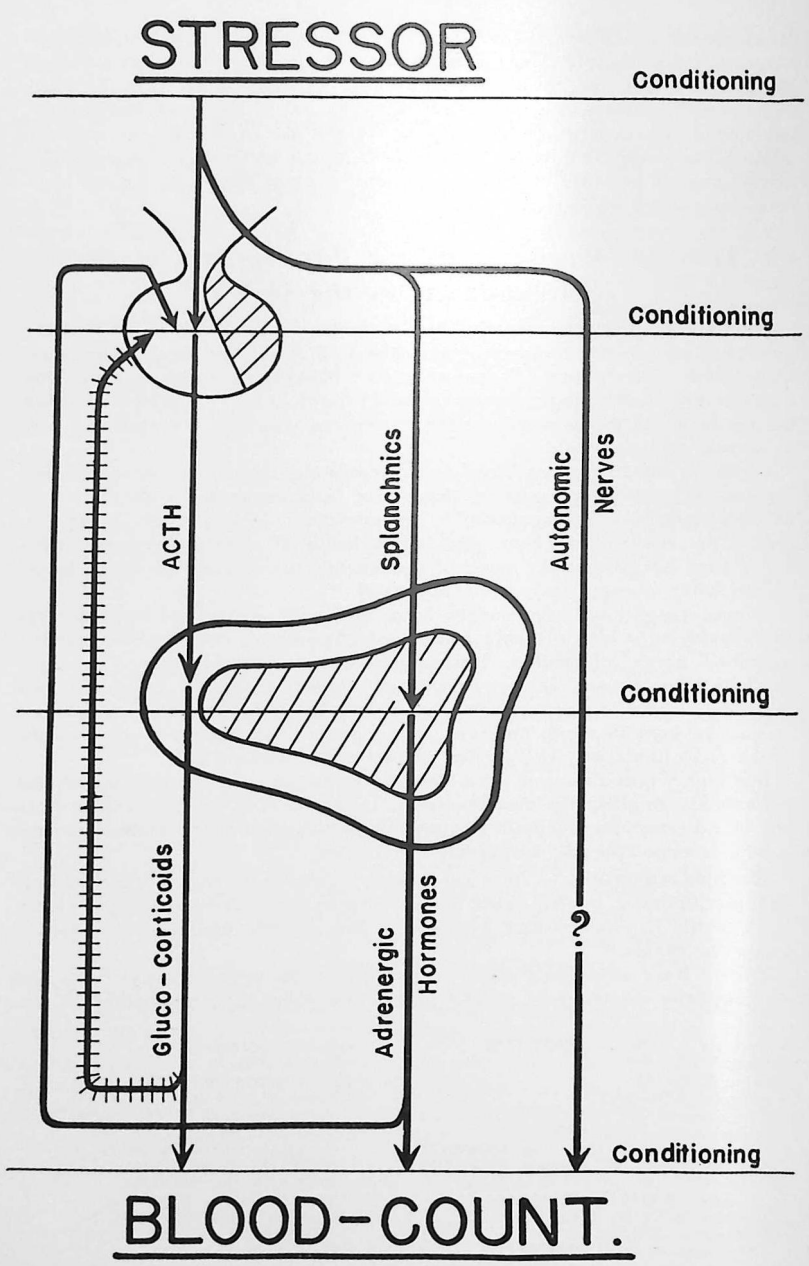
In recent pertinent experiments, leucocytes were obtained in large numbers by introducing a considerable amount of physiologic NaCl solution into the peritoneal cavity of rabbits. Intravenous administration of cells so collected, or of an ether extract of them, produced marked leucopenia. It was assumed that this is due to some special *leucopenic factor* contained in leucocytes.[13] It must be kept in mind, however, that a phase of leucopenia is characteristic of the A-R, hence any toxic tissue extract would produce it.

It is highly probable that some blood-borne factors (and certainly the adrenal hormones) can affect the blood-count during the G-A-S, but much further work will be necessary to elucidate the possible participation of the above-mentioned special leucopoietic and leucopenic metabolites.

Nervous regulation. — Surgical lesions, located in the region of the thalamic and hypothalamic nuclei, cause leucocytosis in various animal species. Hence much work has been done concerning the possible existence of a special **leucocyte center.**[14]

Efforts have also been made to coördinate the nervous theory with that assuming the existence of special blood-count influencing metabolites. It was

[5] Furbetta and Buttaro B38117/48.
[5a] Scott B47469/ND.
[6] Selye **B1204/46.**
[7] Büngeler A32692/27, Büngeler and Schwartz A32693/27, Büngeler and Wald A32694/28, Cannon 83773/42, Deflandre **A32696/25.** Menkin A57481/43, Naegeli **A26002/23.**
[8] Anan 38776/36, 38777/36, A50/36, 38775/36, A9333/37, A9334/37, Hiraoka 38773/36, Muto 38774/36.
[9] Cullumbine B38022/47, Cullumbine et al. B38021/47, Menkin **A57481/43.**
[10] Beer A17285/38.
[11] Abderhalden B38666/48.
[12] Feenders 37979/36.
[13] Weisberger et al. B33446/49, B34780/49.
[14] Borchardt 22895/28, Hayashida B43958/35, B43959/35, B43960/36, B43961/35, B43962/36, B43963/36, Hoff 54106/34, Nasu B43964/36, B43965/36, Rosenow 23462/28, A32697/29, A32698/29, Sagurei et al. B22508/33, Urra et al. A32699/34.



assumed that leucocytosis during stress is produced through stimuli exciting the leucocyte center, which in turn acts by causing liberation of leucopoietic substances.[15] It must be admitted, however, that — apart from the observation that certain brain lesions can cause leucocytosis — much of this literature is highly speculative.

Of course the hypothalamic centers may affect the blood-count through the discharge of ACTH and corticoids but this will be discussed below.

The effect of **adrenergic substances** (cf. above) upon the blood-count is well established. Since their production is largely under nervous control there is no doubt that at least this part of the blood-count regulating mechanism depends upon neurogenic stimuli, but we shall discuss this aspect of the problem under the next heading.

The Hypophysis-Adrenal System. — Before attempting to interpret the hematologic responses to non-specific stress on the basis of the G-A-S concept, it should be clearly stated that available information is insufficient to propose a theory which could explain all the known facts. Nevertheless, it may be of heuristic value to examine how far the observed data fit into the general concept of the non-specific defense reaction to stress.

For the actual observations upon which this interpretation is based, the reader is referred to the preceding pages.

As we have stated before, it is not known **how a stressor affects the hypothalamic centers and the anterior-lobe.** It is undoubtedly true, however, that exposure to stress leads to an autonomic response with stimulation of the splanchnic nerves and a subsequent discharge of **adrenergic substances** (adrenaline, nor-adrenaline). These can influence the blood-count, even in the absence of the pituitary and adrenal, presumably due to their effect upon the hemopoietic organs, and the distribution of blood cells between the reservoirs and the circulating blood. Less is known about the direct effect of *autonomic nerves other than the splanchnics,* probably they can also influence the blood-count through essentially similar means.

It is quite certain, on the other hand, that any stressor will discharge **ACTH** from the anterior-lobe. This leads to increased production of **gluco-corticoids** which exert important effects upon the blood-count, in particular: lymphopenia, eosinopenia and neutrophilia. These actions presumably depend not only upon a redistribution of blood elements, but also upon the actual destruction of some lymphocytes and perhaps also of eosinophils.

The gluco-corticoids so produced tend to diminish ACTH production through the "compensatory atrophy" phenomenon, but this inhibition is obviously not so great as to prevent a rise in the blood-corticoid level during stress.

We also know that adrenaline, discharged under the influence of the splanchnic stimulation, can act back upon the anterior-lobe and add to the ACTH-discharging effect of the original stressor itself.

Of course not all stressors produce the same hematologic response in all individuals. This is presumably due to the well-known effect of **conditioning** factors which are so instrumental in enabling the, essentially stereotypical, G-A-S response to produce a polymorph symptomatology.

There is good reason to believe that the above-mentioned mechanism can be conditioned at least at four levels, namely, at the pre-pituitary, pituitary, adrenal and post-adrenal levels.

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[15] Beer A17285/38.

We have already mentioned in previous sections that a variety of factors can aggravate or mitigate the effect of a given stressor at the *pre-pituitary level*. Let us add here that certain stimuli — particularly nervous irritation — tends to activate more markedly the vegetative centers and the autonomic nerves than the ACTH-corticoid mechanism. Hence adrenergic substances and corticoids are not necessarily always produced in set proportions. The hematologic effects of adrenergic substances are not identical with those of the corticoids. Therefore certain differences in the hematologic response to stress may depend upon the relative proportion of adrenergic and corticoid substances produced during the G-A-S.

The ACTH discharge from the *pituitary* depends upon the often discussed conditioning factors (e.g., age, heredity, diet, availability of ACTH stores, previous exposure to stress, the blood-concentration of adrenaline and corticoids).

The response of the *adrenal* itself is in turn dependent upon factors conditioning the discharge of corticoids. These are essentially the same as those effective at the pituitary level, but the blood-sodium and blood-glucose concentration also appear to act directly upon the adrenal-cortex and modify its response to ACTH (cf. Adrenal ← ACTH, p. 346). Nothing is known as yet about factors which may modify the response of the adrenal-medulla to splanchnic stimulation during stress. Autonomic blocking agents could obviously do so, but we have no reason to believe that such compounds arise endogenously during stress.

Finally, conditioning can occur at the *post-adrenal level*. The availability of the various blood cells in the reservoirs (spleen, lymphatic organs, bone-marrow) and the above-mentioned peripheral antagonism between gluco-corticoids and adrenaline (e.g., the former cause lymphopenia, the latter lymphocytosis), are but a few examples of this type of effect.

It has not yet been shown that during the G-A-S, hematologic changes may also occur due to variations in the formation of anti-pernicious anemia factor or other principles which are independent of the pituitary-adrenal system, although this possibility should be kept in mind. Specific peripheral effects (not mediated through the hypothalamus-hypophysis-adrenal system) of certain stressors (e.g., x-rays, radioactive elements, urethane, nitrogen mustards) can undoubtedly modify the typical hematologic response during the G-A-S.

Summary of Observations Concerning the Participation of the Blood-Count in the G-A-S

The most **characteristic features** of the hematologic response during the A-R appear to be neutrophilia, lymphopenia and eosinopenia. If the stress is very severe and hemoconcentration ensues, the hematocrit values and the erythrocyte count rise above normal.

Much less is known about the changes typical of the later phases of the G-A-S. Some lymphocytosis often follows upon the initial lymphopenia although the neutrophilia tends to continue, especially if the stressor causes inflammatory changes or fever. The eosinophils show less characteristic changes unless the stressor is an allergen; in that event, marked eosinophilia ensues. Both the eosinophilia and the neutrophilia, in these latter instances, must be regarded as specific effects superimposed upon the G-A-S pattern.

As yet little is known concerning the **blood diseases of adaptation.** Certain anemias, especially those accompanied by hypoferremia, appear to be related to the G-A-S. They are currently known under such names as the anemias of infection, intoxication, malignancy, malnutrition, etc. The anemia of Addison's disease suggests that lack of corticoids may interfere with red-cell formation. The accompanying lymphocytosis intimates that excess production of lymphocytes may result from hypocorticoidism.

Conversely, in cases of hypercorticoidism (e.g., Cushing's disease) there is eosinopenia, lymphopenia and some neutrophilia. These changes can be duplicated by the administration of ACTH, but only in the presence of functional adrenals. Hence these actions are presumably mediated through the suprarenal cortex. This view receives further confirmation from the observation that gluco-corticoids also produce similar hematologic responses, even in Addisonian patients or adrenalectomized animals.

Hypercorticoidism due to disease, the administration of ACTH or gluco-corticoid treatment, also increases the erythrocyte count, hence it is probable that certain types of polycythemia may be caused by an increase in the production of gluco-corticoids.

Little is known concerning the possible rôle of the G-A-S derailments in the pathogenesis of the leukemias. However, ACTH and gluco-corticoids are effective in certain cases. In these diseases, a derailment of the G-A-S mechanism, and particularly a malfunction of the adrenal-cortex, is probably not the main pathogenic factor. It merely creates a predisposition for the disease.

The **theoretic** interpretation of pertinent data must be concerned with the possible utility of the hematologic changes during defense and the mechanism through which they are regulated.

It is probable that the neutrophilia is useful because the polynuclear leucocytes help defense through phagocytosis. The leucopenia and eosinopenia may be due to increased utilization of these cell types which presumably contain substances useful for humoral (serologic) defense. The erythrocytosis might represent an excessive defense measure planned to furnish adequate oxygen carriers for the increased metabolic needs during emergencies; it would also help to protect against loss of blood which so often occurs during stress situations.

As regards the mechanism through which hematologic changes are elicited during exposure to stress, adrenergic and gluco-corticoid hormones appear to be of the greatest importance. Through unknown pathways stress acts upon the hypothalamic centers of the vegetative nervous system. From here autonomic impulses are carried to the adrenal medulla through the splanchnics. The adrenergic substances thus discharged, have a marked direct effect upon the blood-count (lymphocytosis and after very large doses, hemoconcentration). They can also further stimulate ACTH production. Yet the anterior-lobe discharges ACTH during the G-A-S even if adrenergic effects are blocked; hence, stress must also be able to stimulate ACTH production through other means.

ACTH discharges gluco-corticoids. The latter likewise exert a direct effect upon the blood-count (promptly producing neutrophilia, lymphopenia and eosinopenia and after prolonged treatment, polycythemia).

The resulting hematologic response to stress will largely depend upon the proportion of adrenergic and gluco-corticoid hormones discharged, as well as upon the responsiveness of the whole blood-cell system. Both the production

of adrenal hormones (adrenergic and corticoid) and the responsiveness of the peripheral target organs (circulating or stored blood-cells, hemopoietic and blood-destroying tissues) depend very considerably upon conditioning factors such as heredity, nutrition, specific actions of the stressor, etc. It is mainly due to such differences in conditioning that, through the same mechanism, exposure to stress can produce varying hematologic changes under different circumstances.

ERYTHROCYTE RESISTANCE

Up to the present, no special studies have been published concerning possible changes in blood-corpuscle resistance which might be **characteristic** of the G-A-S.

The fragility of erythrocytes placed in hypotonic solutions of saline has been studied in a series of **spontaneous diseases**, but according to current opinion, the only condition in which this test is of diagnostic importance is familial acholuric jaundice, where it is often greatly increased. In various types of **anemias** there is usually a tendency for a diminished erythrocyte fragility.[1] Furthermore, a number of compounds of the **"vitamin P"** group which increase capillary-resistance simultaneously diminish red-cell fragility.[2]

It is perhaps worth mentioning, in connection with the possible effect of stress, that after heavy overdosage with **insulin** and during **anoxia** erythrocyte fragility is allegedly increased in dogs.[3] In man exposed to high altitude anoxia, red-cell fragility is often also increased.[4] However, even very intense **muscular exercise** appears to have no consistent influence upon red-cell fragility, as indicated by observations on athletes.[5] Numerous observations on patients suffering from various types of **surgical and medical shock** likewise revealed no change in blood-corpuscle resistance which could be definitely ascribed to non-specific stress.[6]

It is particularly interesting, in relation to the concept of the diseases of adaptation, that experimental renal hypertension in the dog results in an increased erythrocyte fragility.[7]

[1] French and Douthwaite **99226/45.**
[2] Parrot and Gabe B23309/47.
[3] Booth B19638/41.
[4] van Liere **B26199/42.**
[5] Jokl 79702/31.
[6] Palmer **95299/46.**
[7] Ellis et al. B47127/50.

ERYTHROCYTE-SEDIMENTATION RATE (E. S. R.)

The erythrocyte-sedimentation rate (E.S.R.) depends on a variety of conditions, but perhaps principally on the protein, and especially the fibrinogen, content of the plasma. In any case, experience shows that usually, the E.S.R. is most markedly increased when the blood-fibrinogen content is high.[1]

Special studies concerning changes in E.S.R. which are **characteristic** of the G-A-S, have not yet been published. However, available data strongly indicate — indeed one might say definitely prove — that acute, non-specific, systemic stress accelerates the E.S.R. It has long been known to clinicians that "there is an increased sedimentation-rate whenever there is tissue breakdown: with infective, toxic or neoplastic processes and to some extent after operations and fractures of bone".[2]

[1] Ham and Curtis B24137/38.
[2] French and Douthwaite **99226/45.**

From a diagnostic point of view, the chief value of the E.S.R. lies in indicating the rate of progress of **chronic diseases** such as rheumatoid arthritis, phthisis, nephritis, rheumatic fever, etc. Whenever such conditions take a sudden turn for the worse, the E.S.R. increases, allegedly as a result of increased tissue breakdown. It is for this reason that the most experienced students of the E.S.R. considered it a valuable indicator of the "activity" [3] or "evolutional potential" ("potential evolutif") of chronic diseases.[4]

The E.S.R. also increases **in acute diseases,** but even in lobar pneumonia, where the malady starts very abruptly, it takes several days to reach its maximum. Because of this latency period, the E.S.R. is less valuable in the diagnosis of acute diseases.[5]

The E.S.R. has also been of considerable assistance in assessing the efficacy of therapy in patients suffering from chronic diseases (e.g., tuberculosis, rheumatic fever, arthritis), "since it frequently is the last non-specific laboratory test to return to normal in these infections, it has been a sensitive index of disease activity".[6]

On the other hand, a decrease in the E.S.R. below normal has only rarely been observed in spontaneous diseases, and was thought to be devoid of diagnostic significance.[7] Interestingly some hypernephromas greatly diminish the E.S.R.[8]

During the A-R stage of the G-A-S, tissue breakdown is intense and it is therefore not surprising that observations in animals and man reveal a marked rise in the E.S.R. after exposure to such alarming stimuli as surgical **trauma,**[9] **x-rays,**[10] **burns,**[11] intravenous injection of **hemoglobin** and other **macromolecular substances,**[12] exposure to **cold,**[13] forced **muscular work.**[13a]

All these observations show that, at least during the A-R stage, the E.S.R. rises. Observations on patients with chronic diseases suggest that during the stage of resistance the values return toward normal, while in the stage of exhaustion there is apparently a secondary increase.

Among the **stimuli influencing the E.S.R. during the G-A-S,** the corticoids are important. It has been shown in patients suffering from rheumatoid arthritis, that both ACTH and cortisone can considerably decrease the previously increased E.S.R. This change occurs simultaneously with a marked improvement in the clinical condition.[14]

Our animal experiments revealed, furthermore, that the corticoids do not only affect an abnormal E.S.R. but that mineralo-corticoids (such as DCA) accelerate, while gluco-corticoids (such as cortisone) considerably diminish the E.S.R. of normal rats. ACTH — which causes a predominantly gluco-corticoid type of response — acts essentially as the gluco-corticoids themselves.[15]

From these observations it has been concluded that there is an antagonism between mineralo- and gluco-corticoids as regards the E.S.R., similar to that which exists between these two types of cortical hormones, as judged by their effects upon many other target organs.

[3] Ham and Curtis **B24137/38.**
[4] Barbier and Piquet **99336/46.**
[5] French and Douthwaite **99226/45.**
[6] Ham and Curtis B24137/38.
[7] Barbier and Piquet 99336/46.
[8] Alovson B34403/46.
[9] Paolantonio and D'Eramo B37991/47.
[10] Painter et al. 98568/47.
[11] Harkins 91182/44,
Hilgenfeldt **38008/36,** Sacher B45845/48.
[12] Hueper 91802/44.
[13] Eliot et al. B32737/49.
[13a] Wellers and Waitz B46013/47.
[14] Hench et al. B27892/49.
[15] Selye and Carey B44002/49, B46476/50.

BLOOD SLUDGING

Extensive capillaroscopic observations have shown that, both in man and in experimental animals, under the influence of traumatic injuries, burns, infections, intoxications and many spontaneous diseases, the blood cells in the capillaries tend to agglutinate into irregular clumps (not "rouleaux" formation); this changes the blood from its normal relatively fluid state, to a circulating sludge. The resulting hard masses resist passage through the capillaries, consequently, capillary blood-flow is slowed down, causing "endothelial anoxia of the stagnant type". Eventually, the post-capillary venules begin to leak, so that the hemoconcentration increases and finally, thrombosis may ensue. All these changes occur most readily near the site of direct injury (e.g., trauma, burn), but if damage is severe, they may affect most of the capillary territories in the body. In man this phenomenon of blood sludging can be readily studied on the bulbar conjunctiva.[1]

It is very probable that sludging of blood is a major factor in the development of shock, for instance after thermal **burns,**[2] and perhaps even in the formation of **post-operative** thromboses and embolisms.[3] Blood sludges have also been shown to cause plugging of renal glomeruli; hence, they may be the cause of post-operative and post-traumatic kidney injuries.[4]

There is no close relationship between the coagulability of the blood and the phenomenon of blood sludging, as judged by observations on **anaphylactic and peptone shock.** It has long been known that during these latter conditions, a thin membrane of fibrin tends to be deposited on the inner surface of capillaries, to which clumps of formed blood-elements adhere.[5] Yet, at least in the case of anaphylactic shock, some relationship between the derangement in capillary circulation and blood clotting does appear to exist, since numerous investigators claimed to have prevented anaphylactic shock by administering heparin between the sensitizing and the eliciting dose of the antigen.[6]

Anti-coagulants (e.g., heparin and dicumarol) "may cause some diminution in the tenacity of the adherence of the blood cells to one another, but sludge formation as such is not prevented".[7] On the other hand, observations on severely burned patients show that transfusions — of *saline, glucose, plasma* or *whole blood* — tend to break up the agglutinated masses of blood sludges, while they exert their beneficial effect upon the patient's general condition.[8]

Adrenaline administration and *sympathetic stimulation* proved highly effective in causing blood-sludging in the cat; hence it was concluded that this must also occur whenever stress (e.g., nervous stimuli) elicits an adrenergic discharge.[8a]

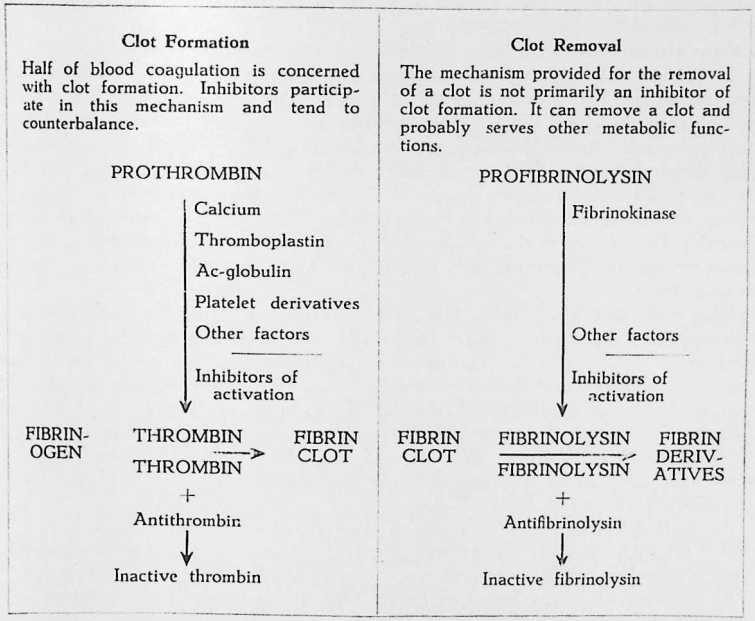
Something like **blood-sludging may also affect the leucocytes** more or less selectively. Pertinent observations were made on the behaviour of leucocytes as seen in the blood vessels that had grown in transparent chambers inserted into the ears of rabbits. Intravenous injection of various toxic substances caused the leucocytes to become sticky and to adhere to the vascular endothelium or to each other. Simultaneously, there was profound, systemic leucopenia presumably because white-cells were temporarily kept out of the circulation.[9] Such changes are obviously non-specific and may well be related to

[1] Knisely B26037/48, Knisely and Bloch B4611/45, Knisely et al. B4613/45, B4612/45, B4614/46, B3454/47, Warner B18347/48.
[2] Brooks et al. B18256/48.
[3] Laufman et al. B26402/48.
[4] Warner B33081/49.
[5] Grégoire **B24136/46.** Nolf and Adant **B26394/46.**
[6] Grégoire **B24136/46.**
[7] Laufman et al. B26402/48.
[8] Brooks et al. B18256/48.
[8a] Fowler B44785/49.
[9] Essex and Grana B39031/49.

the G-A-S, although their participation in systemic defense has not yet been elucidated. In any event, a leucopenia produced by stress — and even changes in the differential blood-count during the G-A-S — may partly depend upon the more or less selective removal of certain white-cell types from the circulation, due to their temporary adherence to blood-vessel walls.

BLEEDING-TIME, BLOOD-CLOTTING, PLATELETS

Blood clotting depends both upon the formation and upon the removal of clotted material. Contemporary opinion concerning the underlying mechanism may be summarized thus; [1a]



A diagrammatic representation of blood-clotting
(After Seegers B46906/50)

Systemic stress. — It appears to be **characteristic** of the A-R that the bleeding-time is shortened [1] and the blood-clotting time diminished, although the platelet count shows only irregular variations.[2] These changes tend to vanish during the stage of resistance, but the data presently available are insufficient to assess the changes characteristic of the latter stages of the G-A-S.

In connection with **traumatic injuries,** the problem of post-operative thrombosis has received special attention.[3] It has been suggested that the tendency

[1] Rozsa and Karady B44551/50, Ungar B4934/47.
[1a] Seegers B46906/50.
[2] Dalton et al. A18306/39.
[3] Lenggenhager B31239/48. Troell B26680/47, B26678/31.

to form thromboses and embolisms, even in vascular territories distant from the original lesion, is due to a decrease in the blood-clotting time,[4] and clot-retraction time.[4a]

The platelet count allegedly rises after exposure to any agent causing excessive tissue destruction, such as x-irradiation, non-specific protein therapy and trauma, but in the latter instance, a preliminary fall precedes the rise. This was ascribed to a greater tendency of platelets to agglutinate into clumps following trauma than after other stimuli causing tissue destruction.[5] Following exposure to a variety of stressors, including traumas, platelet agglutination runs approximately parallel with the E.S.R.[6] This also suggests that the change is non-specific.

In rats in which shock was produced by trauma, the blood-clotting time was diminished and the chief change noted in the clotting system was the more rapid activation of prothrombin.[7]

Hemorrhage is particularly effective in accelerating clot formation,[8] but it is very probable that here the response is largely due to a specific defense mechanism against loss of blood.[9] Curiously, in severe hemorrhagic shock the prothrombin-time becomes progressively prolonged (while the plasma-fibrinogen decreases). Perhaps we are dealing with a biphasic response in that blood-clotting is accelerated under the influence of mild stress, but diminished in the case of severe damage. The underlying mechanism is not clear. Acute vitamin-K deficiency has been considered on the assumption that during "shock" there is an increased demand for this vitamin. Another explanation could be that the prothrombin is destroyed by the proteolytic enzymes formed during shock.[10]

Following extensive **burns,** thromboses and embolisms of vessels are quite common, but consistent changes in the blood-coagulation time have not been observed. Apparently, depending upon conditions, the blood-clotting time may be normal, increased or decreased. This again suggests that the effect of stress on the coagulability of the blood depends upon many conditioning factors. Of course, owing to the direct action of heat or of secondary infections at the site of injury, local thromboses often occur in burned patients; these may secondarily lead to embolisms and thromboses elsewhere, but this is not directly related to the G-A-S.[11]

In man suffering from **heat**-stroke, and after artificially induced fever, a fall in the platelet-count was noted by several investigators.[12] The prothrombin-time is also frequently prolonged upon exposure of patients to extreme heat.[13] The bleeding-time was found to be slightly or moderately increased in most patients suffering from heat-stroke and, in very severe instances, there may also be a considerable delay in clotting-time.[14]

Exposure to **cold** was accompanied by a decrease in blood-clotting time in rats, while other typical manifestations of the A-R developed.[15]

[4] Geissendörfer 34093/35.
[4a] Hirschboeck B45779/48.
[5] König **A32639/32.**
[6] de Letona B37959/47.
[7] Irish et al. 93396/46.
[8] Bernard 38305/872, Cannon B14905/39, Nitzescu and Runceanu A32665/27.
[9] Ferguson **B19247/48.**
[10] Davidson and Tagnon B19261/48, Lucia and Aggeler B27867/41.
[11] Hilgenfeldt **38008/36.**
[12] Malamud et al. B18019/46, Wilson and Doan B27868/39, Wright et al. B27869/46.
[13] Malamud et al. B18019/46, Wilson and Doan B27868/39, Wright et al. B27869/46.
[14] Malamud et al. B18019/46.
[15] Dalton et al. A18306/39.

Exposure to **ionizing radiations,** and especially to x-rays, rather consistently delay blood-clotting in experimental animals and man.[16] Since other types of stress cause variable modifications in the blood-clotting time, the action of ionizing radiations seems to be comparatively specific. Yet, allegedly, the A-R mechanism also plays a rôle here.[16a]

The underlying mechanism is incompletely understood. It has been pointed out, however, that there is no close relationship between the *platelet-count* and the delay in blood-clotting,[17] although an at least transitory diminution of the platelet-count occurs quite regularly.[18] Some authors nevertheless assumed that thrombocytopenia is the cause of impaired coagulability[19] but this view was not accepted by others.[20]

A generalized hemorrhagic tendency is one of the most striking features of the syndrome which follows acute total-body irradiation (x-rays, atomic bomb) in the mid-lethal range.[21] This hemorrhagic disease is usually accompanied by thrombocytopenia, both bleeding- and clotting-time are prolonged and clot-retraction is impaired. Indeed, if the clotting-time is sufficiently prolonged, the blood of an irradiated dog allegedly delays the clotting of normal blood, "thus demonstrating the presence of an active anticoagulant not normally present in blood". It was assumed that this substance may be *heparin* or some similar compound.[22] Yet the evidence concerning increased production of heparin-like substances during exposure to ionizing radiations has likewise not been unanimously accepted (cf. p. 243). Many observers maintain that the hemorrhagic tendency under such conditions is not necessarily accompanied by incoagulability of the blood but may be largely due to capillary damage (cf. Capillaries).

Administration of vitamin K, ascorbic-acid, calcium salts and fresh whole-blood transfusions did not prevent hemorrhage after total-body irradiation.[23]

Shock due to **electrical injury** causes an initial slight decrease followed by an increase in blood-clotting time.[24]

Nervous stimuli, especially emotional excitement[24a] or splanchnic stimulation,[24b] greatly accelerate blood-clotting. This is probably due to an effect of adrenaline (discharged during nervous stress) upon the liver, since either adrenal inactivation or hepatectomy prevent the response. Furthermore, exogenously administered adrenaline causes a similar decrease in blood-clotting time (cf. below) as long as the liver is intact. "Rapid coagulation may reasonably be considered, therefore, as another instance of an adaptive reaction serviceable to the organism in the injury which may accompany pain or which may follow the struggle that fear or rage may occasion".[25]

The decrease in blood-coagulation time often observed following intense **muscular exercise** is usually accompanied by a transitory increase in the platelet-count; yet, following short periods of exhaustive exercise, the platelet

[16] Dixon B23895/48, Jacobson et al. B43939/48, Otuka A16368/38, Painter et al. 98568/47, Warren and Drager B27873/46.
[16a] Herve and Lecomte B46855/49.
[17] König **A32639/32,** Otuka A16368/38.
[18] Prosser et al. B26618/47.
[19] Shouse et al. B27872/31.
[20] Allen and Sanderson B27871/45.
[21] Allen and Jacobson 97321/47, Cronkite B24051/48, B24042/48, Warren B27893/46.
[22] Allen and Jacobson 97321/47, Tullis B27010/48.
[23] Allen and Jacobson 97321/47.
[24] Moreau et al. B23919/48, B17718/48.
[24a] Cannon and Mendenhall 57885/14.
[24b] Cannon and Mendenhall 57886/14.
[25] Cannon and Mendenhall 57885/14.

count may not rise although there is definite polynuclear neutrophilia. This was interpreted as evidence against an appreciable storage of platelets. One group of investigators stated that: "The extreme fragility of platelets, however, renders them readily susceptible to mechanical trauma and it is possible that greatly increased circulation velocity during exercise may destroy enough platelets to mask a moderate increase in numbers. The small post-exercise decline in platelet count seen in most of our experiments is probably to be explained on this basis".[26]

Anoxia (or exposure to decreased atmospheric pressure) often causes a pronounced increase in the platelet-count. This has been ascribed to stimulation of platelet production by the megakaryocytes. It is frequently,[27] but not always,[28] accompanied by an acceleration of blood-clotting. If capillary damage is severe, anoxia may cause hemorrhagic disease without any fall in the platelet-count or derangement in clotting-time.[29]

In a variety of spontaneous diseases there exists a rather suggestive parallelism between the tendency of blood-platelets to agglutinate into clumps and the E.S.R.[30] Both the phenomena are usually a function of systemic stress. The clot-retraction time is usually also subnormal in the average hospital patient.[30a]

Purpura accompanies many acute infectious diseases and is particularly characteristic of the Waterhouse-Friderichsen syndrome (cf. p. 99).

It is often accompanied by fibrin deposition in capillaries, especially those of the renal glomeruli. Simultaneously, mural thrombi may develop in veins. This syndrome has also been compared to anaphylactic shock and to the so-called "Sanarelli-Shwartzman phenomenon".[31] Many infections cause purpura merely because of damage to the capillaries, without any interference with the clotting mechanism.[32]

The effect of an infection upon blood-coagulation, thrombus formation and the tendency to bleed, largely depends upon incidental conditioning factors, such as the sensitivity of the organism to a particular pathogen or specific effects of bacterial toxins (e.g., upon the blood-clotting system, the cells involved in the production of fibrinogen, platelets or thromboplastic substances). Hence the end-result depends upon the combined effect of stress on the one hand, and of specific actions influencing blood-clotting on the other. A recent review of this field emphasizes the importance of such conditioning factors with the statement that "the concept of mono-etiology dominates our approach to investigations of infectious syndromes. It seems that sufficient evidence has been accumulated to point out the importance of investigating the possibility that some diseases may be caused by the combined effects of plural etiologic agents, biologically remote from one another, as viruses and bacteria, or bacteria and complexes of non-bacterial protein antigens with specific antibodies. The synergism of these agents, under suitable conditions, may thus result in characteristic manifestations altogether different from the effects of each agent acting independently".[33]

[26] Gerheim and Miller **B29998/49.**
[27] van Liere **B26199/42.**
[28] Ponka and Lam B38710/48, Schönholzer and Portmann B38957/48.
[29] Haden et al. B19260/48.
[30] de Letona B37959/47.
[30a] Hirschboeck B45779/48.
[31] Shwartzman and Gerber **B19259/48.**
[32] Haden et al. B19260/48.
[33] Shwartzman and Gerber B19259/48.

Many **drugs** exert a specific influence upon blood-clotting (e.g., dicumarol, vitamin P-like substances, vitamin K, heparin and related substances), but this is not directly relevant to our problem. Yet, some drugs appear to influence blood-clotting merely by virtue of their non-specific stress effects and the resulting G-A-S. Here it is admittedly very difficult to distinguish between specific and non-specific actions, indeed, there appears to be what might be called "relative non-specificity" in this respect.

For instance, blood taken from man a few minutes after the injection of *acetylcholine* constantly undergoes fibrinolysis. This has been ascribed to the liberation of adrenergic substances during the resulting A-R.[34]

Peptone and *trypsin* render the blood incoagulable, presumably through the release of an anti-thrombin (heparin), since blood-samples taken after this type of shock counteract the clotting effect of thrombin in vitro. At the same time, the platelets disappear from the peripheral blood and extensive fibrinolysis occurs.[35]

Ascaris extracts [36] and various *antigens conducive to anaphylactic shock* [37] inhibit blood-clotting through an essentially similar mechanism. In this sense, the reaction is "relatively non-specific" and somewhat reminiscent of the derangement in blood-clotting induced by x-rays or acute infections conducive to the purpuric manifestations of the Waterhouse-Friderichsen syndrome. Incidentally, an experimental simile of the Waterhouse-Friderichsen syndrome occurs in rabbits after the injection of various *bacterial toxins* (diphtheria, meningococcic, staphylococcic, streptococcic toxin); this was accompanied by the usual extensive hemorrhages. Since the hemorrhagic tendency was produced irrespective of the specific nature of the toxin employed, the syndrome was regarded as one of "toxic hypoadrenalism".[38] It is dubious whether adrenal insufficiency in itself could explain these lesions since adrenalectomy does not duplicate them. Nevertheless, the syndrome is far from being specific for any one chemical substance.

In this connection it is noteworthy that many compounds, such as certain *allergens, snake venoms* and *quinine* can cause hemorrhages due to capillary damage without deranging the clotting system.[39]

Various *macromolecular substances,* for instance glycogen,[40] hemoglobin [41] also delay blood-clotting in experimental animals. This was considered to be part of the so-called non-specific "hemoclastic crisis". The pathogenesis of this disturbance in blood-clotting has not yet been elucidated, but its possible relationship to that caused by x-irradiation, peptone shock and anaphylactic shock would be worthy of study.

Vesicants (e.g., nitrogen mustard) cause a marked and persistant prolongation of blood-clotting time.[41a]

Following *ether* anesthesia (as after traumatic interventions) there frequently occurs a transitory shortening of the blood-clotting time,[42] which may be due to an adrenergic discharge.

[34] Soulier and Koupernik B41773/48.
[35] Rocha e Silva et al. B2575/46.
[36] Rocha e Silva et al. B2575/46.
[37] Biedl and Kraus 50209/09, König A32639/32, Nolf and Adant B26394/46, Roche e Silva B2174/47, B28507/47, Sonobe A8283/37.
[38] Lithander 97243/45.
[39] Haden et al. B19260/48.
[40] Hueper 91723/43.
[41] Hueper 91802/44.
[41a] Jacobson et al. B43939/48.
[42] Geissendörfer 34093/35.

Stimuli Influencing the Changes in Bleeding-time, Blood-clotting and Platelets during the G-A-S. — Experiments in man revealed no change in platelet-count after the injection of ACTH in amounts sufficient to cause a considerable rise in neutrophils.[43]

As already mentioned in other connections, it has been claimed that ACTH (through the adrenal-cortex) liberates a humoral substance from the spleen *"splenin-A"* which plays an important rôle during the G-A-S, inasmuch as it augments capillary-resistance and decreases capillary-permeability as well as the bleeding time. Allegedly, the spleen can also produce another hormone *"splenin-B"*, whose pharmacologic actions are essentially opposite to those of splenin-A. It is presumably identical with the *"thrombocytopen"* of earlier investigators, which decreases the platelet-count and increases the bleeding-time (cf. also, pp. 239-240). From available data it has been tentatively suggested that splenin-B is involved in the thrombocyte destruction and purpuric manifestations elicited by acute systemic stress, while splenin-A is liberated under the influence of ACTH and corticoids in the resistant stage of the G-A-S.[44] However, further experiments will be necessary to elucidate the possible rôle of such splenic "hormones" during the G-A-S.

Crude anterior-pituitary extracts delay the clot-retraction time in rabbits, but the effect is not entirely specific since salivary-gland extracts exert a similar, though much slighter, effect. The possible relationship between these actions and the G-A-S, have been analyzed.[44a]

From experiments on **adrenalectomized** rats treated with various *alarming stimuli* (e.g., formaldehyde, forced muscular exercise, cold), it was concluded that "during the stage of the alarm-reaction and the stage of exhaustion of the general-adaptation-syndrome... fibrin formation becomes very rapid in the adrenalectomized animal, but no such change is seen in adrenalectomized rats, otherwise untreated, or in those which, following an alarm-reaction, entered into the stage of resistance".[45] In other words, here, adrenalectomy in itself did not cause any significant change in fibrin-formation (an indication of blood-clotting), nor did it prevent the changes characteristic of the G-A-S.

The acceleration of blood-clotting caused by *splanchnic stimulation* is prevented by adrenalectomy,[46] while that elicited by *hemorrhage* is not.[47] In the latter instance it was assumed that the effect is due to a direct action on the liver of an inadequate blood-supply.[48] Hemorrhage does not accelerate clotting after exclusion of the liver from the circulation.[49] The decrease in clotting-time induced by *emotional excitement* or *ether* anesthesia in the rat is not influenced by adrenal de-medullation,[50] but of course this operation does not eliminate all the sources of adrenergic stimuli.

It has long been known that **adrenaline**, and many of its derivatives, accelerate blood-clotting and shorten the bleeding-time in various animal species as well as in man.[51] Indeed some oxidation products of adrenaline (adrenochromes, adrenoxyl), are even more active in decreasing capillary fragility and the bleeding-time than adrenaline itself, although these hormone derivatives no longer possess vasopressor properties.[52] Since adrenaline discharge is certainly a characteristic and constant phenomenon during the A-R it could hardly fail to influence the effect of systemic stress upon blood-clotting and bleeding-time.

Significantly, adrenoxyl markedly reduces the cutaneous purpura elicited by heavy x-irradiation in the mouse.[52a]

Singularly little is known concerning the effect of **corticoids** in this respect. In the rat DCA-overdosage may cause multiple thromboses without any significant change in the clotting-time.[53]

It has been claimed that **thyroxine** is useful in the prophylaxis of post-operative thromboses and embolisms, but the underlying mechanism has not been elucidated and indeed the claim itself has been contested.[54] On the other hand, there is no doubt that early rising after operation as well as the administration of various **anti-coagulants** (dicumarol or heparin) exert a definitely beneficial effect.[55]

[43] Greer and Brown B28267/48.
[44] Ungar 85459/44, 85460/44, 85461/44, B1173/45, B4968/47, B2263/47, B4934/47.
[44a] Caniggia and Cinaglia B45065/49.
[45] Masson 74644/39.
[46] Cannon B14905/39, Cannon and Mendenhall 57886/14, A26379/14.
[47] Gray and Lunt 59380/14.
[48] Cannon B14905/45.
[49] Nolf B26910/05.
[50] Ingle and Corwin A30265/39.
[51] Cannon and Mendenhall 57881/14. Fischer and Lecomte B46000/49, Pulaski et al. **B27703/49**, Riecker and Winters **10917/31.**
[52] Heymans **B23142/48.**
[52a] Herve and Lecomte B46855/49.
[53] Selye 35935/ND.
[54] Troell **B26678/31.**
[55] Troell **B26680/47.**

HEMOPOIETIC SYSTEM

(Including the lymphopoietic, myeloid and reticulo-endothelial systems.)

It has long been suspected that elements of the hemopoietic system play an important rôle in defense reactions. Large lymphatic accumulations notoriously tend to develop at points where the danger of bacterial invasion is particularly great (tonsils, appendix, Peyer's patches); various types of leucocytes participate in all kinds of inflammatory reactions, and the thymico-lymphatic tissue is among the first to respond to systemic stress. All these facts have been taken to suggest that hemopoietic tissues help to protect against infections and other types of damage.

Yet, according to another view such reasoning is due to a "very narrow-minded finalism" and it is considered much more probable that the reactions to damage — at least of lymphatic tissue proper — are harmful. Hence "from the point of view of the organism's defense, this tissue is not only useless but frequently even noxious" so that it would greatly improve health if the lymphatic tissues could be destroyed.[1] Such an extreme view is not shared by many; we mention it here mainly to illustrate how far we are from an unanimously acceptable theory concerning the physiologic rôle of lymphatic tissue.

It is more commonly believed that lymphatic tissue aids in defense by furnishing serologic antibodies and by phagocytosing foreign particles. Perhaps the macrophages are capable of performing both these functions and the lymphocytes may represent a mesenchymal reserve which, in emergencies, can readily be transformed into macrophages.[2]

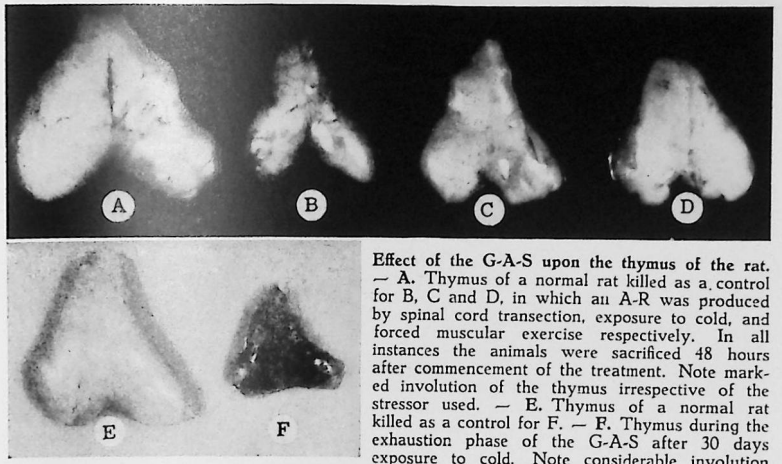
Among all organs the spleen contains the greatest single accumulation of macrophages and hence, presumably plays an important rôle both in phagocytic and in serologic defense reactions.[3]

The granulocytes are also intensely phagocytic. Hence the bone-marrow can contribute to defense in essentially the same manner as lymph-nodes and spleen, both through its granulopoietic function and through the formation of macrophages from its sessile reticulo-endothelial elements.

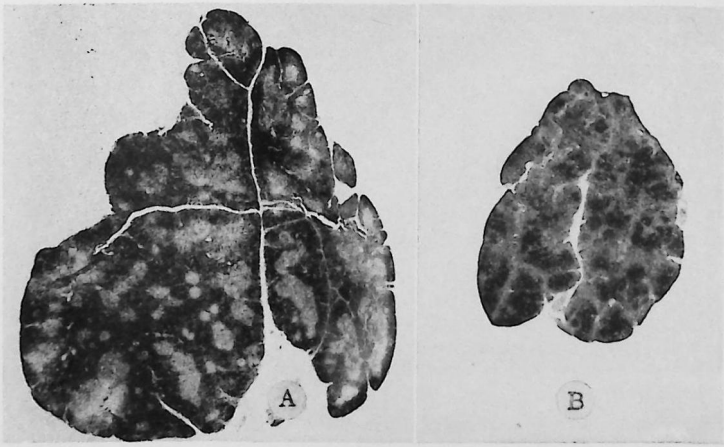
Systemic Stress

Characteristic response. — Of all the lymphatic organs, the **thymus** appears to respond most rapidly and most intensely during the A-R and therefore it received particularly careful attention in connection with studies on the G-A-S. Systematic investigations in the rat showed that the quality of the thymic response is essentially the same after treatment with a great variety of alarming stimuli (e.g., adrenaline, formaldehyde, morphine, atropine, spinal shock, surgical shock, cold, exercise). Within the first few hours after exposure, the thymocytes begin to disintegrate. If the damage is severe, after 24 hours, only the debris of their chromatin remains; partly free in the reticulum, partly in

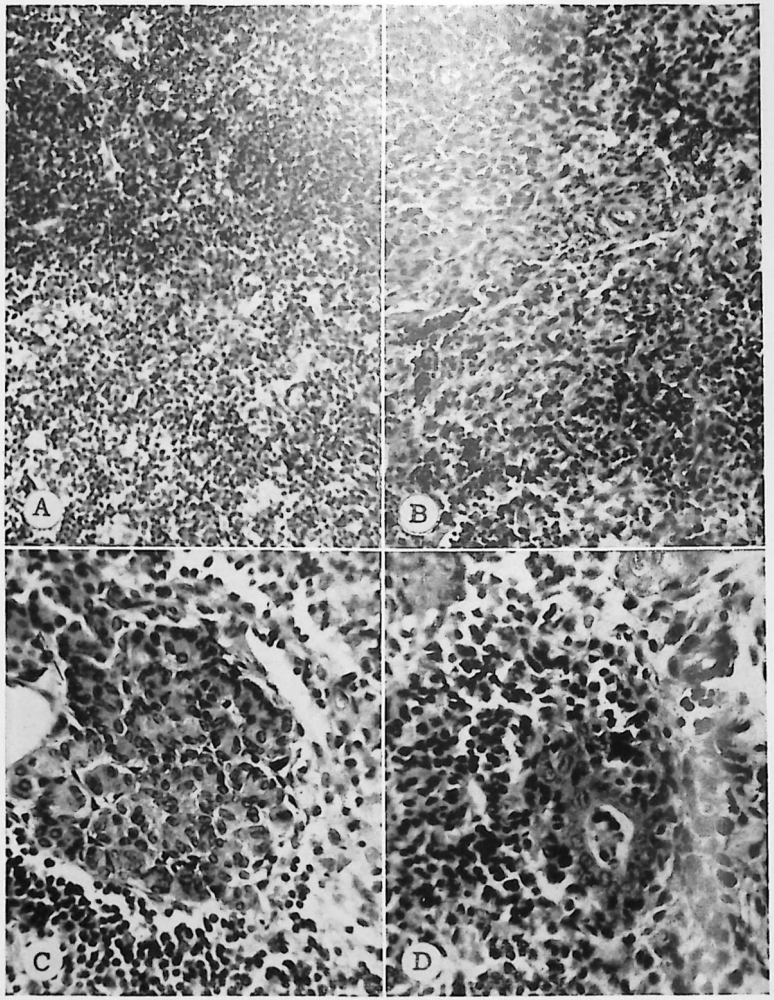
[1] Guieysse-Pellissier 99224/32.
[2] Bloom 78948/40.
[3] Perla and Marmorston-Gottesman **32161/35.**



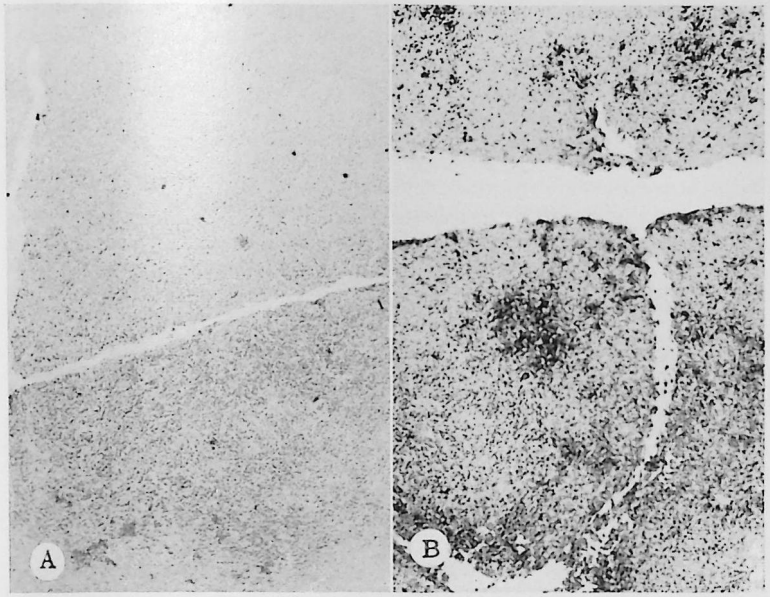
Effect of the G-A-S upon the thymus of the rat. — **A.** Thymus of a normal rat killed as a control for B, C and D, in which an A-R was produced by spinal cord transection, exposure to cold, and forced muscular exercise respectively. In all instances the animals were sacrificed 48 hours after commencement of the treatment. Note marked involution of the thymus irrespective of the stressor used. — **E.** Thymus of a normal rat killed as a control for F. — **F.** Thymus during the exhaustion phase of the G-A-S after 30 days exposure to cold. Note considerable involution of the thymus with several hemorrhages. The changes are similar but even more intense than during the A-R produced by the same agent as seen by comparison with C. (Selye 35935/ND.)



Thymus during the A-R. in the rat. — **A.** Low magnification of a cross-section through the normal thymus. Note the light medulla and dark cortical areas. The color of the latter is due to the presence of numerous thymocytes. — **B.** Cross-section through thymus in A-R produced by toxic doses of formaldehyde during 48 hours. Note the "inversion of the thymus pattern", due to depletion of the cortex of thymocytes and migration of thymocyte debris into the medulla. (Selye B1204/46.)



Thymus during the A-R, in the rat. — **A.** Normal thymus. Note the numerous and regular thymocyte nuclei in the cortical region (upper part of field). — **B.** Thymus in A-R. Note proliferation of epithelioid thymic reticulum and granular, or dust-like, debris of degenerated thymocyte nuclei. — **C.** High magnification of an area from the thymus shown in Fig. B. Note parathyroid-like cell accumulation within the proliferating epithelioid reticulum of the thymus. Surrounding it, there are pyknotic thymocyte nuclei. — **D.** Another area from the thymus shown in Fig. B. Note the cyst-like, epithelioid formation in the center, which may be a dilated Hassall body. Surrounding it there are pyknotic thymocyte nuclei. Pyknosis of the thymocytes and proliferation of the epithelioid elements in the reticulum are particularly characteristic of the A-R.
(Selye B1204/46.)



Thymus phosphatase during A-R. — **A.** Thymus of a control rat incubated with glycerophosphate, during four hours. No enzyme is present. — **B.** Thymus of a rat exposed to cold and incubated with glycerophosphate during four hours. High concentration of the enzyme is seen around the area of nuclear pycnosis, especially in the cortex.
(After Herlant and Timiras B41763/50.)

phagocytes. The latter are engaged in removing these cell-fragments through the lymphatics, so that at this time the sinusoids of the thymic lymph-nodes are filled with phagocytes containing the nuclear debris of degenerated thymocytes. At this stage, the connective tissue stroma of the organ is often so edematous that the entire organ assumes a gelatinous appearance. The cells of the reticulum, on the other hand, show signs of hypertrophy and hyperplasia. By the end of 48 hours, many of them assume an epithelioid appearance. They become round, their cytoplasm increases in volume and they form irregular strands of polygonal cells, tubules and even cysts, some of which are filled with eosinophilic colloid, similar to that seen in thyroid acini. There are many transitions between these new formations and typical Hassall bodies; they suggest a close relationship between the latter and the proliferating thymic reticulum. The epithelial structures just described may represent undifferentiated and hyperplastic precursors of Hassal's corpuscles. In the initial stages of a severe A-R, the intense thymus edema tends to mask the loss of total organ weight, but after about 48 hours, when the edema subsides, only the stroma and the modified reticulum are left so that the thymus is greatly reduced in size and weight. Occasionally, multiple petechial hemorrhages occur within the thymic parenchyme as a result of bleeding from small vessels.[4] Most of the

[4] Selye 36032/36, 38798/37, **B1204/46.** 36030/36, 66551/36, 36031/36, **94572/49.**

relevant observations have been made in rats, but essentially similar changes were found to occur in other species, e.g., in the cat, guinea-pig and rabbit.[5]

During the A-R, among all organs the thymus exhibits the greatest weight loss, nevertheless, because of its small size it contributes but little to the "protein catabolic reaction".[6] Although quantitatively the disintegration of thymus tissue thus appears to be of minor significance, qualitatively, it may be of great import by supplying special materials needed for systemic defense (e.g., antibodies, activators of the reticulo-endothelial system).

During the stage of resistance, the thymus tends to return towards the normal level, especially if the evocative stress is comparatively mild. During the stage of exhaustion, the involution of the organ becomes extremely severe again, but since here thymocyte disintegration is much less acute than in the A-R, one rarely sees as much nuclear debris (the so-called "caryoclastic reaction") as during the initial stage.[7]

Animals which become resistant to the stress effect of a certain stimulus (and whose thymus has consequently returned towards normal) develop particularly pronounced and acute thymus involution upon exposure to an alarming stimulus of a different nature. "Using the response of the thymus as an index of resistance, one may say, therefore, that during adaptation to a certain stimulus, the resistance to other stimuli decreases".[8]

The **lymph-nodes** also involute during the A-R, but not as intensely as the thymus and usually with less pronounced hyperplasia of the reticulum. Here, the disintegration of lymphocytes begins in the "germinal centers" of Flemming. Under the influence of systemic stress these are transformed into so-called "reaction centers" of Hellman. It is important to realize that this transformation is not — as had previously been thought — due to the local actions of bacteria or of their toxic products. It represents a response to any kind of systemic stress and is quite obvious after exposure to cold, trauma or muscular fatigue where such products are not introduced into the body. In the course of a severe A-R, the germinal centers may even disappear completely. Unlike in the thymus, large quantities of nuclear debris are seldom found in the lymph-nodes. Possibly many lymphocytes emigrate from the nodes without previously undergoing necrosis or the drainage is better than in the thymus so that the debris does not accumulate.[9]

Other lymphatic tissue accumulations, for instance, those seen in *Peyer's plaques*, and especially in the *appendix* undergo essentially similar changes.[10]

During an acute A-R, frequently the sinuses of the lymph-nodes are filled with erythrocytes and assume the appearance of *hemolymph-nodes*. This occurs occasionally in the rat [11] but is more common in the guinea-pig.[12] The formation of these hemolymph-nodes is greatly facilitated if the blood-volume is increased by intravenous fluid infusion prior to exposure to the alarming stimulus.[13]

In this connection, it is noteworthy that in some species, certain lymph-nodes normally exhibit most of the characteristics of a typical hemolymph-node. For

[5] Foglia and Selye A8424/38, A8055/38.
[6] Leduc and Guillemin B27410/49.
[7] Selye A8049/38, A8406/38.
[8] Selye A8049/38.
[9] Selye 38798/37.
[10] Selye 36031/36.
[11] Selye 38798/37.
[12] Foglia and Selye A8055/38, A8424/38.
[13] Selye and Foglia A8423/39, A17981/39.

instance, in the rat, such structures are always found just behind the adrenal vessels and in the pancreas. Usually the sinuses are filled with erythrophages, which contain hematogenous iron-pigment deposits. As the true hemolymph-nodes, these so-called "iron-pigment lymph-nodes" contain no germinal centers. Unilateral nephrectomy, especially when combined with adrenalectomy, causes complete disappearance of erythrocytes and pigment from the sinuses of the renal "iron pigment lymph-node", although it does not develop germinal centers. From this it has been concluded that the blood-destroying function of the renal lymph-node is dependent upon the presence of the adrenal.[14]



Iliac lymph-nodes of the rat during the A-R. — **A.** Normal control. — **B.** Transection of the spinal cord, at the level of the 7th cervical vertebra, — **C.** Exposure to cold (+ 2 C°). — **D.** Repeated, forced muscular exercise, in a revolving drum. All stressors have been applied for 48 hours, during which time food was withheld. (sensitization to stress). Note great involution of the lymph nodes, irrespective of the type of stressor used. (After Selye 35935/ND.)

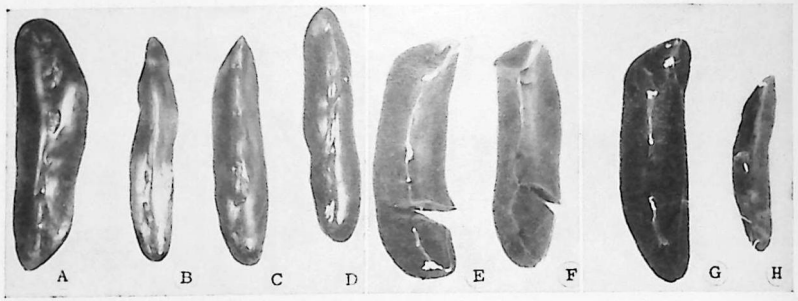
The **spleen** also involutes in the course of a typical A-R, but not as suddenly as the thymus; hence nuclear debris and edema fluid is less prone to accumulate within the splenic tissue. The disintegration tends to begin in the germinal centers of the Malpighian follicles and generally speaking, the lymphatic white pulp is much more seriously affected than the red. Contraction of the splenic musculature further decreases the size of the organ and helps to discharge its blood-reserves during the A-R.[15]

Although most of our pertinent work has been performed on the rat, other species (e.g., cat, rabbit, guinea-pig) were shown to react in essentially the same manner.[36]

On the other hand, in the acute infectious diseases of man the spleen is usually enlarged. It is interesting to note therefore that if in the rat an A-R is produced by the parenteral administration of *substances which are removed by phagocytosis* (such as blood, cholesterol emulsions, kerasin emulsions, egg-yolk or egg-white) then splenic (and lymph-node) enlargement ensues instead of the usual involution. In this respect the response to particulate (or "macromolecular") substances differs from the typical A-R although the other manifestations (thymus involution, adrenal hypertrophy, etc.) of the stress reaction develop just as after other alarming stimuli.[17] As we shall see below, it is a

[14] Selye and Schenker A15351/39.
[15] Foglia and Selye A8055/38, Selye 38798/37.
[16] Foglia and Selye A8055/38.
[17] Selye 38798/37.

characteristic feature of the A-R that the reticulo-endothelial cells are stimulated to increased phagocytic activity. Hence, perhaps exposure to stress causes splenic enlargement only if the organism is simultaneously flooded with particulate matter (e.g., colloids, bacteria), which accumulate in the activated macrophages and thus increase their volume. Here we are again dealing with a "conditioning factor" which greatly alters the appearance of the essentially stereotypical G-A-S response. The storage of phagocytosed material overcompensates for the usual loss in splenic tissue, occasioned by disintegration of the lymphatic elements and the discharge of stored blood.



Effect of G-A-S upon the spleen of the rat. — **A.** Normal control. — **B.** A-R produced by transection of the spinal cord at the level of the 7th cervical vertebra, — **C.** by exposure to cold (2° C.), — **D.** by repeated forced muscular exercise. All stressors have been applied for 48 hours, during which time food was withheld. Note great reduction in splenic size irrespective of the stressor used. — **E.** Spleen of a normal rat killed as a control simultaneously with F. — **F.** Spleen of a rat during the resistant stage of the G-A-S following 15 days of exposure to cold. Note considerable restoration of splenic tissue. — **G.** Spleen of a normal rat killed at a control simultaneously with H. — **H.** Spleen of a rat during the exhaustion phase of the G-A-S after 30 days of exposure to cold. Note that at this time the spleen (like all lymphatic organs) regresses again. (After Selye 35935/ND.)

Surprisingly little work has been done up to now concerning the response of the **bone-marrow** during the G-A-S. It has been emphasized that the myeloid elements, though damaged, do not exhibit such intense caryoclastic reactions during the A-R as the thymus and are rarely the site of pronounced edema.[18] Yet, the phagocytic ability of the reticulo-endothelial elements in the bone-marrow is markedly augmented, as judged by experiments in which the macrophages were stained by the intravenous administration of India-ink.[19] The production of "non-specific anemias", with the discharge of immature erythrocytes into the circulation (cf. Blood-count) likewise suggests that the bone-marrow participates in the G-A-S, although the precise nature of its rôle during stress has not yet been elucidated.

A local increase in the phagocytic activity of the **reticulo-endothelial system** (R.E.S.) has been noted in the thymus [20] and the Kupffer cells in the A-R.[21] More recently, experiments were performed specifically to examine the relative responsiveness of reticulo-endothelial cells in various parts of the body during the G-A-S. It was found in rats and in mice that a G-A-S elicited by a variety

[18] Selye 38798/37.
[19] Timiras and Selye B36271/49.
[20] Selye 38798/37, B1204/46.
[21] Arvy and Gabe B44853/49, Selye A15667/39.

of noxious agents (formaldehyde, adrenaline, cold, x-rays, trauma, etc.) influences phagocytosis of intravenously-injected India-ink. During the A-R the ink particles disappear from the blood more rapidly, during the resistant stage less rapidly, than in normal controls. This was confirmed in experiments on the perfused livers. The Kupffer cells of alarmed animals took up more than the normal amount of India-ink from the perfusion fluid during the A-R, while during the resistant phase, the uptake by the liver was considerably subnormal.[22]

Subsequent systematic studies designed to examine comparatively the effect of the G-A-S upon the R.E.S. in the various organs of the rat showed that during the A-R (cold, spinal-cord transection, forced muscular exercise), the phagocytosis of intravenously injected India-ink is greatly augmented in the lung, bone-marrow, adrenals, kidneys and the "hibernating gland". In the liver, there was no significant difference between the alarmed and control animals of this series, perhaps because so much ink was injected that the uptake was maximal even in the controls. However, in the spleen the storage of carbon particles appeared to be actually diminished.[23] It was concluded that the "experiments suggested active participation of the reticulo-endothelial system in the defense of the organism during the alarm-reaction".[24]

During the resistant phase this R.E.S. response is actually reversed, while in the stage of exhaustion the response is similar to that of the A-R. Presumably conditioning factors (e.g., physical and chemical properties of the particles) also play a part in determining whether the macrophages of one or the other organ system will respond most intensely.

Several observations [25] suggest that extreme stress actually depresses the phagocytic power of the R.E.S. Some workers ascribe this to an exhaustion of the phagocytic power,[26] but as we said above, such an inhibition of phagocytosis is rather characteristic of the resistant stage.

The mechanism through which stress activates the reticulo-endothelial system during the A-R is not yet known. Recent studies lead to the assumption that "the vascular endothelium, is changed by the action of *histamine* into a reticulo-endothelium, the cells acquiring the property of phagocytosing various substances which circulate in the blood. The reticulo-endothelium of the liver owes its phagocytosing properties not to histamine, but to another substance found in the liver, the chemical nature of which is not known". It has allegedly been possible to obtain active extracts of this substance which was termed *"refaktor"*.[27] Conversely, the decreased phagocytosis during the stage of resistance would be due to an endogenous anti-histaminic metabolite *"resistine"*, which is allegedly also involved in the development of resistance itself.[28] This interesting theory requires confirmation especially since other observations suggest that *sympathin* [29] or *choline* [30] liberation is responsible for the activation of the phagocyte system.

Trauma. — A marked, though transitory, involution of the thymus has been observed in "sham-hypophysectomized" rats in which the pituitary region was merely exposed under anesthesia. This was attributed to the A-R caused by

[22] Karády and Kovács B40495/48.
[23] Timiras B38907/49.
[24] Timiras and Selye B36271/49.
[25] Delaunay and Lebrun B3114/46, Eppinger B37085/49.
[26] Kindred 99940/47.
[27] Törö B28228/48.
[28] Karády and Kovács B40495/48.
[29] Golodets and Putshkow B38167/49
[30] Chèvremont B23319/48.

the stress of the surgical trauma itself.[31] Many other types of surgical interventions cause thymus atrophy through the G-A-S mechanism,[32] among these bile-duct ligature received special attention.[33]

Allegedly not only lymphocytes, but numerous other cells (e.g., fibrocytes, the Schwann cells of the nerve sheath, striated muscle cells), can transform themselves into phagocytic histiocytes under the influence of direct mechanical or chemical trauma. Here, choline, liberated from traumatized cells, was held responsible for this transformation. Since so many cells can assume the appearance of histiocytes under the influence of stress, some prefer to speak of a "histiocytic state" of diverse cells rather than consider the histiocyte as a separate, histogenetically distinct, entity. The assumption of this histiocytic state would endow the cell with new properties particularly useful in conditions of stress.[34] There is some evidence to show, however, that particularly intense damage impedes the phagocytic power of histiocytes.[35]

Hemorrhage. — Severe loss of blood causes essentially typical G-A-S changes in the hemopoietic organ.[36] In this case the splenic contraction of the acute A-R phase is particularly pronounced, and probably of great importance in that it helps to replace blood by the discharge of the splenic blood-corpuscle reserves.[37]

Burns. — The many clinical observations concerning the behaviour of the hemopoietic elements after burns, have been the subject of several extensive reviews.[38] In the lymph-nodes, Peyer's plaques, tonsils and the Malpighian corpuscles of the spleen there are necroses and edema, especially in the regions of the germinal centers. The thymus undergoes acute accidental involution. The spleen may be swollen and the reticulo-endothelial cells show increased phagocytic activity, often being loaded with erythrocyte debris. The necrotic changes noticed in the tonsils and in the lymphatic accumulations of the intestinal tract are of particular importance. They suggest that systemic stress, such as is caused by burns, may predispose these tissues to secondary invasion by microbes with the subsequent development of tonsillitis and appendicitis respectively (cf. Gastrointestinal Diseases of Adaptation).

Heat. — Exposure to high temperature may elicit the syndrome of "heat stroke" and cause typical A-R changes in the hemopoietic organs of man. The spleen is usually congested and sometimes enlarged. The bone-marrow is also hyperemic and there tends to be a particularly severe damage to the megakaryocytes, which undergo pyknosis of the nuclei with karyorrhexis. There is also depletion of the cells of the granulocytic and erythrocytic series. Since comparable bone-marrow changes were not seen in anoxic anoxia, these lesions were ascribed specifically to the action of heat.[39]

In rabbits exposed to heat (Kettering hypertherm) caryoclastic reactions were very pronounced in the lymph-nodes and bone-marrow. A pronounced increase in highly phagocytic histiocytes was observed in the lymph-nodes, spleen and liver, but not in the bone-marrow. At the same time there was polymorphonuclear infiltration of the lymph-nodes and myeloid hyperplasia, with

[31] Foglia and Houssay 81580/41, A56602/42, Houssay B19962/47.
[32] Selye 36032/36, B1204/46.
[33] Rosselli del Turco and Matteini B37478/49, B37479/49.
[34] Chèvremont B23319/48.
[35] Delaunay et al. B3114/46.
[36] Selye B1204/46.
[37] Cannon B14905/39.
[38] Harkins 82895/42, Hilgenfeldt 38008/36.
[39] Malamud et al. B18019/46.

many mitoses, in the bone-marrow. These changes were regarded as indicative of "the mobilization of the defense forces of the body" by the high temperature.[40] In another essentially similar experimental series on rabbits exposed to heat, caryoclastic phenomena and petechial hemorrhages were particularly prominent in the spleen and thymus.[41]

The phagocytic activity of blood-leucocytes is also influenced by heat and cold, but it depends largely upon "conditioning" by the protein content of the diet (see below), whether a certain change in the surrounding temperature will increase or diminish phagocytosis.[42]

Cold. — Exposure to cold proved to cause pronounced involution of the thymico-lymphatic system and proliferation of the reticulo-endothelial phagocytes, especially in fasted animals.[43]

Ionizing radiations. — Ionizing radiations exert a particularly intense destructive influence upon hemopoietic elements in the thymus, lymph-nodes, tonsils, spleen, bone-marrow, etc.[44] Their effect is not strictly comparable to that of other alarming stimuli since the destruction of hemopoietic elements by ionizing radiations is greater than could be expected on the basis of their stressor effect. Furthermore, unlike most alarming stimuli, these rays cause thymico-lymphatic atrophy even in the absence of the adrenals (see below). Indeed, degeneration of isolated lymphatic and erythropoietic cells is even obtained by direct x-irradiation in vitro.[45]

On the basis of studies in the mouse and rat, it has been especially emphasized that the thymus, lymph-nodes, spleen and Peyer's plaques respond essentially in the same manner to x-irradiation.[46] All these observations are consonant with the view that the changes in the hemopoietic organs produced by x-rays — though they are of unusual severity — are essentially similar to those caused by other alarming stimuli.

After x-irradiation, the thymus regenerates fairly rapidly in the rat[47] and rabbit.[48] In the latter species, the thymic reticulum can allegedly give rise directly not only to lymphocytes, but even to polymorphonuclear granulocytes.[49]

Most investigators agree that small doses of x-rays stimulate, while large doses destroy the reticulo-endothelial cells.[50] However, the claim that small doses of ionizing rays can also stimulate hemopoiesis has not been confirmed.[51]

A comparative study of the lesions caused by total-body irradiation during the atomic bomb test at Bikini and after total-body exposure to one million-volt x-irradiation, showed that the lesions produced in swine by these two types of exposure are indistinguishable. They are much more severe than after partial irradiation of the body and consist mainly of hemorrhage, necrosis and second-

[40] Doan A14836/38.
[41] von Haam and Frost A30282/39.
[42] Mills and Cottingham B27633/43.
[43] Leduc and Guillemin B27410/49, Reinhardt 84926/43, Selye 38798/37, B1204/46, Timiras and Selye B36271/49.
[44] Bloom **B31225/48.** Dougherty and White 95612/46, Ellinger B24015/48, Halberstaedter and Ickowicz B3383/47, Hoshi 23951/28, Leblond and Segal 82724/42, A17235/38, Lecompte and Fischer B46838/49, Luther and Lorenz B38703/47, Patt et al. B3611/47, Podljaschuk 20989/27, Reding **39925/35.**
[45] Schrek B37924/47, B37983/47, B38463/48.
[46] Dougherty and White 95612/46.
[47] Grégoire 85576/45.
[48] Downey B28249/48.
[49] Downey B28249/48.
[50] Dougherty and White 95612/46, Le Roy B37990/47, Reding **39925/35.**
[51] Bloom and Jacobson B37514/48.

ary infection. The myelopoietic elements of the bone-marrow and the lymphopoietic elements of spleen and lymph-nodes are especially sensitive. "Their destruction interferes with the cellular defense of the body and in the presence of lowered resistance, secondary infections are common". On the other hand, the reticulo-endothelial cells of the lymph-nodes and bone-marrow are comparatively radio-resistant and may serve as a matrix for subsequent regenerative phenomena.[52]

The bone-marrow is allegedly more resistant to radiation than lymphoid tissue. The rays affect both the immature granulocytic and erythrogenic elements, but following treatment with sub-lethal doses, early regenerative changes are seen within the first week. Pigment deposits, eosinophilic leucocytes and plasma cells may appear. After particularly severe irradiation, however, the marrow may assume a peculiar gelatinous appearance with subsequent connective tissue proliferation and without adequate regeneration of the hemopoietic elements.[53]

Essentially similar observations have been made in other animals and man following exposure to x-rays, the atomic bomb or U^{235}.[54]

Electro-shock. — The effect of electro-shock therapy upon the bone-marrow has not yet received much attention,[55] but there is reason to believe that here again G-A-S changes are most important.

Nervous stimuli. — Transection of the spinal cord (at the level of the seventh cervical vertebra) causes a particularly pronounced A-R with marked and rapid involution of the thymico-lymphatic apparatus.[56] Since this operation produces severe hypothermia, it is noteworthy that the thymico-lymphatic involution cannot be prevented by maintaining the body temperature at a normal level.[57] The possibility has been considered that an "alkaline shift" of the acid-base balance is the necessary prerequisite for the development of the A-R in general and the involution of the thymico-lymphatic apparatus in particular. However, exposure of rats to a high CO_2 atmosphere (which would prevent such a shift) did not inhibit the involution of the thymus, lymph-nodes and spleen, which is normally elicited in rats by high spinal-cord transection.[58]

Nervous stimuli are also effective activators of the phagocyte system, as judged by experiments on frogs in which phagocytosis (especially of leucocytes) was found to rise after splanchnic stimulation. The active principle involved here is blood-borne and apparently identical with sympathin.[59]

Muscular exercise. — Intense muscular exercise produces acute thymic involution in the rat. Since this is accompanied by adrenal enlargement [60] and other manifestations of the A-R [61] it is not considered to be a specific result of muscular work as such, but of the resulting G-A-S.

Indirect evidence suggests that muscular exercise also causes a splenic lymphocyte discharge and that this is mediated by corticoid hormones.[62]

[52] De Bruyn and Robertson B44783/49, De Coursey B38048/48, Le Roy B37990/47, Tullis B27010/48, B41901/49.
[53] Anonymous B28192/48.
[54] Bloom **B31225/48**, Lawrence et al. B41114/48, Liebow et al. B41902/49, Tobias et al. B4455/48.
[55] De Franco and Siracusano B40738/45.
[56] Selye **B1204/46.**
[57] Frank A34171/40.
[58] Fortier B24848/49.
[59] Golodets and Putshkov B38167/48.
[60] Andersen 32606/35.
[61] Selye **B1204/46.**
[62] Stone and Hechter B19207/48.

Anoxia. — In rats, decreased atmospheric pressure [63] or increased atmospheric partial pressure of CO_2,[64] cause typical thymico-lymphatic and splenic involution, accompanied by other characteristic manifestations of the A-R. Hence the response of the lymphatic organs to anoxia has also been regarded as part of the resulting G-A-S.

In dogs, the effect of acute hypoxia upon the spleen can readily be studied after exposing the organ without injury to its vascular and nervous attachments. In acute hypoxia induced by breathing pure nitrogen, the spleen of dogs so prepared did not lose weight until the arterial oxygen saturation approached zero. At that time, the organ became intensely contracted with a simultaneous rise in the systemic hemoglobin content. Blood samples taken from the splenic vein during contraction showed a hemoglobin concentration 30 to 40% higher than that of arterial blood.[65] Thus it appears that the spleen contributes significantly to the number of circulating blood-cells only when the hypoxia is extremely severe.

Increased atmospheric pressure. — In man exposed to an oxygen pressure of 2.3 atmospheres, erythropoiesis is depressed and many plasma cells appear in the bone-marrow.[66] No effort has been made to examine whether this is due to stress or to oxygen per se.

Anaphylaxis. — Numerous investigators have observed thymico-lymphatic involution, and a proliferation of the R.E.S. following re-injection of sensitized animals with foreign proteins.[67] This fact has a ready explanation in the systemic stress effect of such antigens when given to previously sensitized individuals. It is more remarkable, however, that even during the period of sensitization (that is, before the shock-eliciting second injection), typical A-R changes develop in the thymico-lymphatic tissue and R.E.S. of the guinea-pig.[68]

In the bone-marrow of guinea-pigs, the maturation of eosinophil myelocytes is accelerated during the period of sensitization; after the shock-producing re-injection, the mature eosinophils are discharged into the blood.[69] In rabbits treated with killed pneumococci, marked hyperglobulinemia developed simultaneously with diffuse, plasma cell proliferation in various organs, especially in the fat of the renal pelvis.[69a] As we shall see, this response resembles that produced by LAP.

Infectious and other diseases. — In fulminating, acute systemic infections, the thymico-lymphatic tissue usually undergoes particularly pronounced and rapid "accidental involution".[70] This is much more obvious in children than in adults, merely because the atrophic thymus of the latter contains little parenchyme even at rest. Such "accidental thymus involution" is accompanied by the usual hypertrophy and hyperplasia of the epithelioid elements which is characteristic of the A-R. The reticular fibers themselves however, disintegrate upon exposure to the systemic stress of various acute diseases.[71] Particularly marked thymico-lymphatic involution occurs, for instance, in malignant diphtheria.[72]

[63] Dohan A37744/42, Tornetta et al. 83894/43.
[64] Fortier B24848/49, B26249/48.
[65] Kramer and Luft B32779/49.
[66] Farber B38155/48.
[67] Simonin **B23373/48.**
[68] Simonin B23373/48.
[69] Vitale and Diana B37567/48.
[69a] Bjorneboe et al. B37877/47.
[70] Selye **B1204/46. 94572/49.**
[71] Fukichi 95093/28.
[72] Kettler B38029/47, Nikitin B38057/48.

A similar thymus involution occurred in rats with enlarged adrenals due to tumor transplants. It was concluded that "the tumor behaves as a non-specific stimulus inducing the changes associated with the general-adaptation-syndrome".[73] Although these findings were confirmed in rats bearing actively growing lymphosarcoma transplants, it was noted that if the tumors regressed, the lymphatic organs enlarged despite an even more pronounced adrenal hyperplasia.[74] Since histologic data have not been published, it is impossible to say whether the enlargement of the lymphatic organs was actually due to an increase in lymphocytes or to storage of tumor degradation products. In any event the combination of large adrenals and large lymphatic organs (spleen, thymus, lymph-nodes) is not unprecedented; it regularly occurs in LAP-treated rats kept on a high-protein diet [75] (cf. below).

In an effort to analyze the dynamics of the response to acute bacterial infections, the local reaction of regional **lymph-nodes** was studied in rats in which an acute popliteal lymphadenitis was produced by inoculation of the foot-pad with Type I pneumococcus. This led to rapid exudation of polymorphonuclear leucocytes from the nodal capillaries into the lymphatic sinusoids. The majority of the other inflammatory cells in the sub-capsular sinusoids came from the primary focus of infection. Importance is attached to the fact that the invading bacteria are forced to pass through the "log jam" of granulocytes in the sinuses and that the mast cells in this location appeared to discharge their heparin granules. The mast-cell reaction may account for the failure of the lymph to clot within the node, and perhaps it even plays a special rôle in the defense against bacteria.[76]

Studies with various toxic bacterial products showed that marked proliferation of the myeloid **bone-marrow** elements is usually seen, in rabbits, whenever the treatment leads to intense polymorphonuclear leucocytosis. However, in particularly intense bacterial intoxications — which lead to agranulocytosis — the bone-marrow activity is depressed.[77]

A review of the literature on focal infection suggests that even circumscribed bacterial foci can cause anemia with depression of marrow activity. Such cases have been referred to as examples of a special type of "panmyelophthisis".[78]

The **spleen** becomes rapidly enlarged in the majority of the acute infections. In human pathology, it is customary to distinguish a "red" and a "grey" type of acute splenic swelling. In its most characteristic form the red type is seen in typhoid fever. There is a great collection of erythrocytes and a marked proliferation of the endothelial cells which line the splenic sinusoids. These cells are highly phagocytic. Many of them become detached from the wall after their cytoplasm has ingested numerous erythrocytes. — The grey type of acute splenic swelling is seen in scarlet fever, acute endocarditis, general septicemia, pneumonia and many other severe infections. Here, the spleen contains large numbers of oxidase-positive cells (mature and immature granulocytes), which led to the term "pyemic form of acute splenic swelling". While very severe infections may inhibit the phagocytic power of the reticulo-endothelial cells, milder forms actually stimulate it. Thus the color of the organ depends largely upon the relative proportion of erythrocytes and leucocytes

[73] Savard B23929/48.
[74] Murphy and Sturm B39451/48.
[75] Selye B39703/49. 35935/ND.
[76] Smith and Wood B33440/49.
[77] Hoff **A14716/38.**
[78] Goia **B25571/46.**

which it contains. However, as long as the damage is not too severe, the R.E.S. is stimulated by the systemic stress of an infection, irrespective of whether the red or the grey type of splenic tumor ensues. At first, the splenic reticulum itself is broken up and this may account for the softness of the organ, but later, regeneration occurs and then induration may follow.[79]

Essentially similar splenic lesions have been produced by infections in experimental animals.[80] The stimulation of the macrophage system is particularly intense in diseases such as malaria, which cause a marked erythrocyte destruction. It has even been claimed that this effect, with a consequent improvement of immune reactions may be the principal factor in the malaria therapy of general paralysis.[81]

In outlining the splenic response characteristic of the A-R as such, we have already mentioned that normally, the spleen involutes as a result of systemic stress, but the phagocytic ability of its macrophages is increased. If systemic stress is accompanied by the flooding of the blood with particles which can be phagocytosed (foreign proteins, necrotic tissue-degradation products, cholesterol bacteria), the usual loss of weight (due to lympholysis and discharge of blood stores) is overcompensated by the deposition of phagocytosed materials. In the acute infectious splenic swelling in man, the accumulation of numerous polymorphonuclear leucocytes ("splenitis", "grey splenic swelling") or the aggregation of many, presumably damaged, erythrocytes ("red splenic swelling") contributes significantly to the increase in the weight of the organ. The significance of the erythrocyte and leucocyte accumulation in the two types of splenic tumor is not yet understood. It is suggestive to assume, however, that the leucocytes — which are potential phagocytes — participate in the defense against the bacterial invasion, while damaged erythrocytes accumulate in the spleen preparatory to their ingestion and disposal by macrophages.

Drugs. — The "caryoclastic crisis" — in the thymus, the germinal centers of the lymph-nodes and in the malpighian follicles of the spleen — has already been mentioned as being very characteristic of the A-R. Many of the earliest publications concerning the G-A-S have given prominent attention to this "lympholytic" effect.[82]

Earlier observations had shown that drugs, for instance, intraperitoneal administration of **liquid paraffin** or of **iron oleate** likewise caused typical caryoclastic reactions in the thymus, lymph-nodes and spleen of the mouse.[83] However, the non-specificity of this response was not recognized. It will be recalled that Dustin [84] believed that only a special group of drugs, the so-called **"caryoclastic poisons"** are endowed with the specific power to produce this effect. Since the response is part of the A-R to any kind of non-specific stress, this designation may be confusing. In our earlier investigations, for instance, we found formaldehyde, atropine, morphine, adrenaline, histamine and many other drugs to be endowed with such caryoclastic properties. Even cold, muscular exercise, hemorrhage and numerous other types of non-chemical stressors share this property, hence it is not specific of any particular group of drugs. Yet certain poisons are more caryoclastic than others and significantly those most active in this respect are also most potent as stimulators of the R.E.S.

[79] Boyd **99692/35.**
[80] Perla and Marmorston-Gottesman **32161/35.**
[81] Bruetsch B36457/49.
[82] Selye 36032/36. **B1204/46.**
[83] Firket and Linhoff B2390/25.
[84] B37657/31, B5348/38, A30579/39, 78614/39.

and as chemotherapeutic agents against syphilis, trypanosoma infections, etc. This led to the suspicion — almost two decades ago — that the chemotherapeutic effect of the caryoclastic drugs depended upon their ability to stimulate the "defensive energies" of the R.E.S.[85]

Subsequent studies furnished many additional data showing the non-specificity of this response. Thus, involution of the lymph-nodes, thymus and spleen has been produced in association with other A-R changes by subcutaneous injection of **formalin,**[86] **bacterial toxins,**[87] **toxic organ extracts,**[88] **colchicine,**[89] **trypaflavin, thallium, bismuth,** iodine and **mercury** compounds,[90] various **arsenicals** [91] and **alloxan,**[92] as well as with the intraperitoneal administration of **ethyl alcohol** or hypertonic **glucose.**[93]

Desoxypyridoxine also causes marked thymico-lymphatic involution, as judged by experiments in rats and mice, but here we are probably dealing with a special case since the compound appears to act merely by virtue of its anti-pyridoxine effect [94] (cf. below).

Various **vesicants** and especially sulfur and nitrogen mustards were found to produce particularly marked lympholytic effects in the thymus, lymph-nodes and spleen of the rat. Except for their extraordinary intensity, these changes were not fundamentally different from those seen in an A-R produced by other agents.[95]

Comparatively few authors examined the *bone-marrow* changes caused by drugs capable of eliciting an A-R. However, it has been shown in the rat, that the intense systemic stress caused by nitrogen or sulfur mustards damages both the erythropoietic and the leucopoietic elements of the bone-marrow, as well as the megakaryocytes.[96] "The degenerative changes of the hemopoietic organs as a whole resemble more closely those produced by roentgen rays than those caused by any other agents".[97]

Somewhat similar changes have been seen in the bone-marrow of man after **insulin** and **metrazol** shock therapy.[98] In most of these recent investigations, it was clearly recognized that the response is not due entirely to specific effects of the drugs used, but largely to the resulting G-A-S.

Interestingly an A-R caused by various drugs, especially vesicants and **urethane,** elicits similar lympholytic phenomena even in the malignant lymphocytes of mice bearing transplantable *lymphomas.*[99] Desoxypyridoxine appears to exert such an anti-lymphoma effect without causing an A-R.[100] The lympholytic [101] and antileucemic action of urethane is also much greater than could be expected merely on the basis of its stressor effect.[102] In all these instances the action of the drugs upon the white cells is not merely due to a

[85] Zylberszac B37658/31.
[86] Bass and Feigelson B28259/48, Zeckwer B1110/45.
[87] Delaunay et al. B39220/49, B36774/48, Bueno B37925/47.
[88] Simonnet 99953/47.
[89] Layani et al. B38533/47, Leblond and Segal A50424/38, MacLeod and Phillips B44307/47, Seifter et al. B32930/49.
[90] Zylberszac B37659/31, B37658/31.
[91] Ickowicz 64074/36.
[92] Arvy and Gabe B34748/48, **B44853/49.**
[93] Bass and Feigelson B28259/48.
[94] Stoerk B18187/48.
[95] DeBruyn and Robertson B44783/49, Graef et al. B39006/48, Karnofsky et al. B37880/48, Kindred 99940/47.
[96] Graef et al. **B39006/48.**
[97] Kindred 99940/47.
[98] Teilmann B35224/44.
[99] Bass and Feigelson B28259/48, B42316/48.
[100] Grégoire B38970/49, Stoerk B18187/48.
[101] Luther and Lorenz B38703/47.
[102] Moeschlin B38205/47, B38952/48.

corticoid discharge, but largely to specific, direct caryoclastic properties or a synergism (conditioning) between the endogenous corticoids and the drugs themselves.

Allylformiate, peptone, histamine and other drugs which cause a so-called "serous inflammation" diminish the phagocytic power of the Kupffer cells in the liver. Experiments on dogs in which the administration of such drugs was followed by the intravenous injection of bacteria showed that the resulting bacteremia lasted much longer than in not-pretreated animals.[103] The phenomenon of serous inflammation is closely related to the A-R, yet — as we have previously stated — in the latter, phagocytosis by reticulo-endothelial cells is usually enhanced. It must be kept in mind, however, that very severe alarming stimuli cause an inverse response and may damage the R.E.S.; [104] presumably the drugs used to produce serous inflammation were given in excessive amounts.

Diet. — Starvation has long been known to be a very effective alarming stimulus, capable of causing typical thymico-lymphatic atrophy with proliferation of reticulo-endothelial cells.[105] These observations have subsequently been confirmed and extended in the rat,[106] mouse,[107] guinea-pig [108] and in man.[109]

More recently, special attention was given to the effect of starvation upon phagocytic ability in certain territories of the R.E.S. Using the thorotrast technic it was found that in the rat the phagocytic power of the splenic macrophages is greatly increased by starvation.[110] Furthermore, in guinea-pigs and rats, fasting increases the phagocytosis of hemosiderin and lymphocyte-debris by the macrophages of the spleen, lymph-nodes and thymus. In this series no significant alterations were observed in the Kupffer cells of the liver.[111]

In chronically and severely starved men, involution of the lymphatic elements with marked hemosiderosis has also been noted in the spleen. At the same time, the bone-marrow showed a diminution of all myeloid elements, frequently accompanied by a predominance of megaloblasts. It has been suggested that this change may be responsible for the pernicious-anemia-like blood-picture which so often develops in patients suffering from hunger edema and other types of severe malnutrition.[112]

Conversely, **overfeeding** likewise causes thymus involution in the rat, and here again, the effect was ascribed to the development of a G-A-S.[113]

An essentially similar lympholytic action may become manifest in rats fed **protein-deficient** diets.[114] Indeed, to some extent, the phagocytic activity of blood-leucocytes likewise appears to depend upon the dietary protein intake.[115]

Deficiencies in **vitamins and other specific food constituents** are undoubtedly also stressors to which the organism responds with the development of a G-A-S. It had been noted many years ago — much before the discovery of the G-A-S — that in guinea-pigs fed on a corn diet (which was deficient in several vitamins) the Kupffer cells of the liver proliferate and show signs

[103] Eppinger B37085/49.
[104] Bueno B37925/47.
[105] Selye 36032/36, 38798/37, B1204/46.
[106] D'Angelo et al. B32991/49, Quimby B19203/48.
[107] Szego and White B32836/49, Dougherty and White 85504/45.
[108] D'Angelo et al. B32728/49.
[109] Uehlinger B27612/48.
[110] Gordon and Katsh B32753/49.
[111] Feder and Gordon B33046/49.
[112] Gsell B27611/48, Klotzbücher B45392/48, Overzier B45391/48, Uehlinger B27612/48.
[113] Ingle and Nezamis 98817/47.
[114] Brown B32987/49, Roofe and Brown B38187/48.
[115] Mills and Cottingham B27633/43.

of increased phagocytic activity. Frequently their cytoplasm was filled with blood-pigment granules.[116]

It has been emphasized that in the rat, the reticular cells of the thymus, unlike those in other lymphatic organs, do not readily ingest intravenously-injected carbon particles. Even if thymus involution is produced by *choline* deficiency, the thymic reticulum fails to acquire any pronounced phagocytic power.[117]

Severe *pantothenic* acid deficiency elicits characteristic manifestations of the G-A-S in the rat and causes pronounced involution of the thymus.[118] "All of these symptoms are interpreted as indicating that the pantothenic acid deficiency acts as an alarming agent".[119] On the other hand, the bone-marrow of pantothenic-acid-deficient rats remains normal or is actually hyperplastic; except for a left shift in granulocytes [120] and some hyperplasia of the erythropoietic elements [121] its cellular composition showed no consistent abnormality.

Similar changes were observed in the thymus and lymph-nodes of *riboflavin* deficient rats,[122] but here the bone-marrow activity was markedly depressed.[123] The hemopoietic organs of pair-fed controls remained essentially normal. Both in riboflavin and in *pyridoxine* deficiency the adrenal changes were mild or absent in spite of marked thymus involution.[124] It was concluded that unlike many other avitaminoses "riboflavin or pyridoxine fails to produce the adaptation syndrome".[125] If this were confirmed, it would be a remarkable exception to the general rule that every prolonged systemic stress elicits a G-A-S. It is possible, however, that the degree of deficiency was not of sufficient magnitude to produce a persistent adrenal response. Subsequent investigations confirmed that in spite of the absence or mildness of characteristic adrenal changes, the thymus of pyridoxine-deficient rats exhibits severe atrophy.[126] As an alternative interpretation it was assumed that "thymus involution need not always be attributed to a high level of secretion of the corticosterone-like hormones. Perhaps this atrophy results from inadequate protein synthesis".[127] Whatever the mechanism may be, a direct (not adrenal-mediated) lympholysis is certainly possible (e.g., after x-rays or vesicants); this may well be involved here also, but it would be unexpected if this stressor did not simultaneously elicit a G-A-S as well.

The effect of desoxypyridoxine upon lymphomatous and leucemic cells has been discussed above (cf. p. 466).

Severe *thiamine* deficiency elicits both adrenal stimulation and thymus involution in the rat, hence its effect upon the thymus was regarded as due to the development of a G-A-S.[128]

In this connection, it is of interest that the phagocytic ability of blood-leucocytes appears to be depressed in mice suffering from a variety of vitamin

[116] Rondoni and Montagnani B23143/15.
[117] Christensen 86995/46.
[118] Deane and McKibbin B1349/46, Stoerk and Zucker A94339/44.
[119] Deane and McKibbin B1349/46.
[120] McQueeney et al. B4907/47.
[121] Ashburn et al. B37602/47.
[122] McQueeney et al. B4907/47, Stoerk and Zucker A94339/44.
[123] Endicott et al. B37601/47.
[124] Grégoire B38970/49, Stoerk and Zucker A94339/44.
[125] Deane and Shaw B30043/47.
[126] Deane and Shaw B30043/47, Stoerk B18187/48, Stoerk and Eisen B37084/46, Stoerk and Zucker A94339/44.
[127] Deane and Shaw B30043/47.
[128] Deane and Shaw B30043/47, Skelton B41300/50, Stoerk and Zucker A94339/44.

deficiencies (thiamine, riboflavin, pyridoxine, pantothenic acid, choline, ascorbic acid). This was demonstrated both in vivo, by intra-abdominal inoculation with Type I pneumococcus, and in vitro, by merely mixing heparinized blood with this same organism. On the basis of these observations it was suggested that the decreased resistance of vitamin-deficient individuals to various infections may be, at least partly, due to a decrease in the phagocytic power of their blood-leucocytes.[129] It is possible that the blood leucocytes react to stress differently from other phagocytic elements, but it must also be kept in mind that it depends largely upon the intensity and duration of the stress whether it will stimulate or inhibit phagocytosis. Even the Kupffer cells of the liver lose much of their phagocytic power in severe B_1 or B_2 avitaminosis.[130] To clarify this problem, it would be important to study simultaneously and in the same animal, the effect of stress upon phagocytosis by blood-leucocytes and by other elements of the reticulo-endothelial system during all three stages of the G-A-S.

The folic acid analogues *aminopterin* and *amino-teropterin* cause pronounced involution of the thymus, spleen, inhibition of granulocytopoiesis in the bone-marrow and adrenal enlargement in the rat. This was paralleled by absolute lymphopenia and granulocytopenia. Although all these hematologic changes were diminished or abolished by adrenalectomy [131] their possible relationship to non-specific stress and the G-A-S had not been envisaged, yet we feel that it would be most misleading to accept without further proof that such changes are due to the specific effect of folic acid deficiency.

Stimuli Influencing the Response of the Hemopoietic Organs During the G-A-S

Hypophysectomy in itself, that is, without exposure to stress, causes only moderate involution of the thymus, lymph-nodes, spleen and bone-marrow. As we shall see below, several pituitary hormones do influence the hemopoietic organs, either directly or through the intermediary of other endocrine glands. Hence, the above-mentioned involutional phenomena are probably due to complex hormone deficiencies.[132]

The phagocytosis of colloidal thorium dioxide by the R.E.S. of the spleen is not detectably influenced by hypophysectomy in the rat.[133]

In hypophysectomized rats, pure *somatotrophin* tends to restore the subnormal size, protein content and nucleic-acid turnover of the thymus towards normal.[134]

ACTH on the other hand causes typical thymico-lymphatic involution even after hypophysectomy, as long as the adrenal cortex is present, hence its effect is not mediated through the anterior-lobe, but only through the suprarenal cortex.[135]

Cortical extracts increase the phagocytosis of colloidal thorium dioxide by the spleen of the hypophysectomized rat.[136] The thymolytic action of *corticoids* [137] and of *folliculoids* (e.g., estrone)[138] is not significantly prevented by hypophysectomy, as shown by experiments in the rat. These hormones appear to exert a direct thymolytic effect.

[129] Cottingham and Mills B27639/45, B27641/43.
[130] Eppinger B37085/49.
[131] Higgins and Woods B40212/49.
[132] Selye **94572/49.**
[133] Gordon and Katsh B37768/49.
[134] Li and Evans B29320/48.
[135] Selve **94572/49.**
[136] Gordon and Katsh B37768/49.
[137] Selye **B1204/46, 94572/49.**
[138] Selye et al. 38815/36.

Moderate doses of *thyroxine* cause hypertrophy of the lymphatic tissues in intact animals and it has been demonstrated that in the rat, at least the splenic enlargement is not prevented by previous hypophysectomy.[139]

Although the thymico-lymphatic apparatus of hypophysectomized animals is thus somewhat subnormal to start with, it shows little lympholysis in response to *alarming stimuli*. This is presumably due to the fact that ACTH secretion can no longer be stimulated by stress after hypophysectomy. It is remarkable, however, that some slight involution of the lymphatic organs was obtained by stress even after ablation of the pituitary.[140] This should not be ascribed to a direct thymolytic effect of these alarming agents, since adrenalectomy (cf. p. 472) completely prevents their effect upon the thymico-lymphatic tissue. Stimulation of corticoids by stress appears to be dependent upon the anterior-lobe, but some slight continuous cortical hormone secretion continues, since hypophysectomized animals do not develop as marked a hypocorticoidism as adrenalectomized or adrenalectomized-hypophysectomized individuals.[141] As we shall see later, the lympholytic action of corticoids is greatly enhanced by some (hitherto unidentified) metabolic changes which occur during the A-R; perhaps in the presence of the latter even the slight residual corticoids of the hypophysectomized animal suffice to cause thymico-lymphatic involution.

On the other hand, hypophysectomy does not influence the thymic and splenic involution normally produced in the rat by total-body *x-irradiation*, although the adrenal response is abolished.[142] This is not unexpected since even adrenalectomy fails to prevent the direct thymolytic action of ionizing radiations (see below).

Certain *transplantable sarcomas* cause thymic involution and lymph-node hyperplasia in mice. The authors eliminated the possibility that the lymphatic hyperplasia could be due to infection or metastases, but were unable to explain the "distinct dissociation of the response of the thymus and the lymph-nodes". Furthermore, allegedly, "these changes are not prevented by hypophysectomy, thereby excluding pituitary-adrenal mediation".[143] Perusal of the figures given shows, however, that the degree of thymus involution was definitely diminished by hypophysectomy, although it was not completely prevented. In this respect, the transplantable tumor did not behave in a manner essentially different from other alarming stimuli. The fact that lymph-node hyperplasia was obtained concurrently with thymus atrophy is reminiscent of the response to various foreign proteins and other materials which can be phagocytosed (cf. p. 457, 464). It will be recalled that these cause an enlargement of the lymph-nodes and spleen, while the thymus (whose reticulum is not very phagocytic) remains essentially uninfluenced and still responds to stress by acute accidental involution. In the light of these considerations, it does not appear necessary to postulate that transplantable tumors affect the thymico-lymphatic tissue in a manner qualitatively different from other stressors.

Anterior-pituitary extracts exert different effects upon the thymico-lymphatic system depending upon the hormones which they contain. In rats treated with LAP, we usually note a pronounced enlargement of the spleen and lymph-nodes. The thymus is usually very well developed, but not necessarily larger than it would be at the height of its physiologic development before involution due to

[139] Swann A30182/39.
[140] Selye 38798/37, 36032/36.
[141] Selye **94572/49.**
[142] Patt et al. B33711/48, Tyree et al. B33116/48.
[143] Savard and Homburger B31735/49.

age has commenced.[144] This is often accompanied by intense myeloid metaplasia in the spleen and the connective tissue, especially around the renal pelvis, the liver and the adrenal cortex. Simultaneous treatment with testosterone or thyroxine (preferably both) greatly enhances this tendency towards the formation of ectopic myeloid tissue. In all these locations, and especially in the spleen, the extraordinarily pronounced development of megakaryocytes was always striking in these experiments.[145] The peculiar stimulating action of LAP upon the lymphopoietic and erythropoietic elements is not yet fully understood. It should be kept in mind, however, that somatotrophin stimulates thymus development, while thyroxine and testosterone enhance the proliferation of myeloid tissue, especially in animals simultaneously treated with anterior-pituitary extracts (cf. p. 337). The crude LAP preparation contains thyrotrophin and gonadotrophin; through these it may augment thyroxine and testoid formation. The protein impurities in the LAP undoubtedly further enhance lymphopoiesis. These stimulating actions could overcompensate for the lympholytic effect of the ACTH contained in the LAP. It should also be kept in mind that DCA tends to cause splenic enlargement in the rat, while gluco-corticoids (e.g., cortisone) cause intense involution of the spleen. Interestingly, LAP also imitates many other effects of the mineralo-corticoids (such as DCA), perhaps through the preferential endogenous production of these adrenal hormones. This may further contribute to the complex mechanism by which LAP stimulates the development of the lymphopoietic and hemopoietic tissues.[146]

The bone-marrow of LAP-treated rats is also hyperplastic, with a particularly marked increase in neutrophils.[146b]

Purified *growth hormone* has a definite thymotrophic effect in the intact rat and it has been assumed that the thymus enlargement obtained with crude extracts[147] is due to the presence in such preparations of growth hormone.[148]

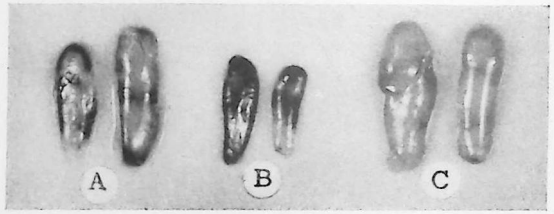
Purified *ACTH* on the other hand, causes pronounced involution of the thymus, lymph-nodes and spleen presumably due to the resulting discharge of corticoids, since the effect is prevented by adrenalectomy,[149] and parallels the degree of cortical stimulation.[150] In three groups of intact rats, receiving high-fat, high-carbohydrate and high-protein diets respectively, a given amount of purified ACTH caused the same degree of thymus involution, irrespective of the diet ingested.[151] This observation is in agreement with the concept that the corticotrophic action of pure ACTH itself is uninfluenced while that of LAP (or of systemic stress) is generally enhanced by a high protein intake.[152]

ACTH presumably also stimulates the R.E.S., at least in regions directly exposed to injury. This was noted in rats in which an arthritis had been produced by the juxta-articular injection of a formalin solution containing India-ink. Here the staining of the regional lymph-nodes with carbon particles was excessively rapid if the development of the arthritis was mitigated by ACTH.[153] Indeed perhaps the improvement of lymphatic drainage and phagocytosis participates in the anti-arthritic effect of this hormone.[154]

[144] Selye A75044/44, **94572/49.** B39703/49.
[145] Selye and Stone B29705/50.
[146] Selye B39702/49.
[146a] Carey B46475/50.
[147] Selye **94572/49.**
[148] Li and Evans B29320/48.
[149] Dougherty and White **B18513/47.**
[150] Bergner and Deane B23875/48.
[151] Ingle et al. B2709/47.
[152] Henriques et al. B27603/49, Selye 94572/47.
[153] Selye B39702/49.
[154] Paulley B43495/49.

The bone-marrow of intact rats undergoes atrophy and becomes gradually replaced by fat in rats treated with purified corticotrophin. This atrophy is particularly striking in the center of the shaft, but may extend to the sub-epiphyseal regions and sometimes assumes the character of "serous atrophy". It was especially noted that the megakaryocytes tended to persist, in spite of intense marrow atrophy and that the diet did not consistently affect these structural changes.[155]

The marrow eosinophil count, allegedly rises after ACTH treatment, both in the rat and in man, while the eosinopenia of the blood develops. The latter is claimed to result from a rise in the eosinophil threshold of the bone-marrow.[155a]



Effect of ACTH and LAP upon the reaction of regional lymph-nodes to a local inflammatory focus. Iliac lymph-nodes of rats which were injected with formaldehyde and India ink into the joint region of the hind leg, for the production of topical irritation arthritis. — **A.** Not hormone-treated control. — **B.** ACTH pretreated and — **C.** LAP-pretreated animals. Note that ACTH increases phagocytosis (indicated by black discoloration), but diminishes the size of the lymph-nodes, while LAP exerts contrary effects. (After Selye B39702/49.)

Vasopressin-containing posterior-lobe extracts cause hyperplasia of the bone-marrow in the rabbit. It has been suggested that this may be due to a specific posterior-lobe hormone which regulates hemopoiesis.[156] However, such extracts produce an A-R and severe gastric hemorrhages, so that their effect upon the bone-marrow is presumably non-specific and secondary.[157]

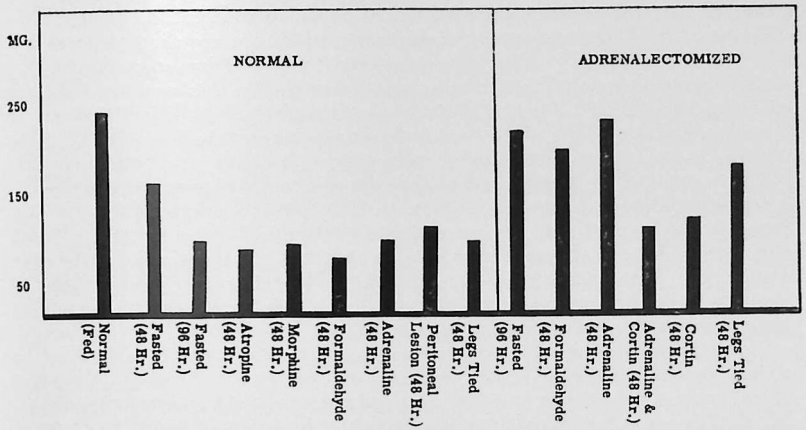
Adrenalectomy has long been thought to cause actual hypertrophy and hyperplasia of the thymico-lymphatic apparatus, but re-examination of the published data and repetition of the crucial experiments revealed that this is only partly true. What actually happens is that adrenalectomy protects the thymus against those influences which would normally produce involution, namely, advancing age, the hormones produced during the sexual cycle, and the various stresses and strains encountered in the course of life. Thus, in the adrenalectomized animal, the thymus constantly remains in a state of full development; in the intact organism, this is attained only at a certain age and in the absence of any incidental stressors.[158]

Even some recent investigators who observed larger thymuses and lymph-nodes in adrenalectomized than in intact rats, were led to conclude again that adrenalectomy causes true thymico-lymphatic hyperplasia,[159] but none of the thymus weights recorded by them are above the normal range for the healthy rat. Further re-examination of this problem on rats kept on various standard laboratory diets showed that an apparent hyperplasia is only obtained if the composition of the food is not optimal. Here, of course, the inadequacy of the diet acts as a stressor (even though a mild one) which causes some degree of

[155] Baker and Ingle B29436/48.
[155a] Tronchetti and Rossi B45524/49.
[156] Dodds and Noble 54523/35.
[157] Selye et al. 58020/36.
[158] Selye 36032/36.
[159] Houssay et al. 82751/41. Rapela B38491/44.

thymus involution capable of being inhibited by adrenalectomy. In rats kept under optimal laboratory conditions, whose thymus was perfectly developed, adrenalectomy caused no further enlargement.[160]

It has been shown that neither *alarming stimuli* (treatment with atropine, morphine, formaldehyde, adrenaline, surgical trauma, nervous stimuli, starvation, etc.),[161] nor *ACTH*[162] cause thymus involution after ablation of the adrenals.



Prevention by Adrenalectomy of Thymus Atrophy Normally Seen During A-R in the Rat. The black areas indicate the weight of the thymus under various experimental conditions and have been obtained from averages of large groups of rats. (After Selye 36032/36.)

At the time these investigations were begun, the only hormone known to be discharged in response to "emergency situations" was *adrenaline*. Hence considerable importance was attached to the fact that in the adrenalectomized animal, adrenaline was unable to produce the usual thymus involution. Curiously, upon exposure to stress, rats in which only the adrenal medulla was removed, showed much less pronounced thymus involution than intact controls, although their adrenal cortex remained well preserved. This observation in conjunction with the fact that the thymolytic action of adrenaline depends upon the presence of adrenal tissue, agrees with the view that adrenaline discharge during emergencies, though not directly responsible for the thymus involution, may further aggravate it through its effect (via the hypophysis) upon the adrenal cortex.[163]

Corticoids given in the form of the relatively inert early extracts available at the time this work was done, caused little thymus involution, either in intact or in adrenalectomized rats, though in the latter, some effect was definitely distinguishable.[164] In later experiments, complete, acute involution was achieved in adrenalectomized rats only when as much as 600 dog units of corticoid activity were administered in the form of an adrenal extract. This showed that the

[160] Stoerk A88905/44.
[161] Pellegrino B46742/49. Selye 36032/36, 66551/36, 36030/36.
[162] Dougherty and White B18513/47, Rapela B38491/44. Selye 94572/49.
[163] Selye 36032/36.
[164] Selye 36032/36, 66551/36.

thymolytic action of the corticoids is not mediated by the adrenals and requires large amounts of hormone.[165] The question arose why maintenance doses of cortical extract (or oral administration of NaCl) fail to permit thymus involution upon exposure to stress in adrenalectomized animals. It was concluded that either exceedingly high quantities of corticoids are required for this particular effect, or it is due to a special type of cortical hormone of which only small quantities are present in commercial extracts.[166]

Subsequent experiments with pure corticoids showed that in the adrenalectomized rat, maintenance doses of DCA cause no detectable change in the structure of the lymphatic organs [167] and toxic doses are required to produce a significant involution.[168] The gluco-corticoids (e.g., dehydro-corticosterone, corticosterone, cortisone) are much more effective in this respect than the mineralo-corticoids.[169] Yet it is unlikely that the thymolytic effect is merely a subordinate action of the gluco-corticoid potency; as we shall see below, many steroids devoid of any corticoid effect also possess a direct lympholytic activity.

The increase in the number and phagocytic power of the macrophages, which is normally induced by chronic inanition, is diminished by adrenalectomy in rats. Subsequent treatment with cortical extracts (but not DCA or saline solutions) was highly effective in preventing this impairment.[170] It remains to be seen whether the stimulation of the reticulo-endothelial elements by other types of stress is also under adreno-cortical control, and to what extent the cortex participates in the regulation of phagocytosis.

The thymolytic effect of gluco-corticoids is apparently much augmented by certain metabolic changes which occur during the A-R. Although the effect of corticoids is a direct one — a fact especially evident from in vitro experiments (cf. p. 478) — it is dependent upon the simultaneous action of some conditioning factors that appear to arise during the A-R. Thus, adrenalectomized rats treated with threshold doses of a cortical extract show little thymolysis, and an A-R (exercise, cold) has no thymolytic action in the absence of the suprarenals. Yet, if the same threshold dose of cortical extract is administered during an A-R (exercise, cold) marked thymolysis results, even after adrenalectomy. From this it was concluded that the stressors affect the thymus through a dual mechanism: (1) they cause a discharge of gluco-corticoids, (2) they sensitize the thymus to the lympholytic effect of the corticoids by some extra-adrenal mechanism.[171]

Even after adrenalectomy natural and artificial *folliculoids* (estrone, estradiol, stilbestrol, etc.) are very potent thymolytic and lympholytic agents, as shown by experiments on rats. At the same time they cause particularly pronounced proliferation of the thymic reticulum.[172]

Testoids (e.g., testosterone) and *luteoids* (e.g., progesterone) also exert a direct lympholytic action in the rat,[173] but systematic investigation of a large number of steroids revealed that in all of them the lympholytic and folliculoid potencies run parallel; hence it was postulated that the former effect is merely a subordinate action dependent upon the folliculoid properties of these compounds.[174] In the literature, the thymolytic action has emphatically been related to corticoid potency; yet, weight for weight, folliculoids are much more potent in this respect than the most active gluco-corticoids so far tested. Of course the intense thymico-lymphatic involution produced by cortisone [175] or non-specific stressors is unaccompanied by any manifestation of hyperfolliculoidism; hence, it would be unwarranted to assume that the lympholytic phenomena of the A-R are due to increased folliculoid production by the adrenal cortex. It is more probable that both corticoids and folliculoids effect lymphatic cells through an essentially similar mechanism.

Since the thyroid also has an important effect upon lymphatic structures, it is noteworthy that in the rat, *thyroidectomy* does not influence the inhibiting action which adrenalectomy exerts upon the involution of the lymphatic organs during the A-R.[176] Conversely, thyroxine stimulates the growth of lymphatic organs in the adrenalectomized mouse.[177]

As previously mentioned, adrenalectomy prevents the thymico-lymphatic involution caused by most agents, except that produced by some steroid hormones. However, folliculoid stilbenes (which are not steroids) also possess a direct lympholytic action. This suggests that it is not so much the chemical structure as the pharmacologic activity of a compound that counts. This may explain why even non-steroidal folliculoids are highly lympholytic. There are, however, a few entirely unrelated agents which likewise possess direct lympholytic properties. Thus adrenalectomy fails to prevent the thymico-lymphatic involution produced by *x-irradiation* in the rat.[178] Yet, the effect of very small doses of x-rays is at least partly inhibited by adrenalectomy in the mouse and rat.[179] Furthermore, if the thymus itself is shielded from the rays, while other tissues are exposed, adrenalectomy also diminishes the resulting thymus involution. Presumably x-rays affect the thymico-lymphatic organs both through a direct action and through the production of a G-A-S; only the latter effect is inhibited by adrenalectomy.[180] After severe involution has been produced by x-irradiation, the regeneration of the thymus is accelerated by adrenalectomy in the rat.[181]

Even apart from the hormones and hormone-like compounds previously mentioned, there are a few chemical agents which appear to possess direct thymolytic properties. Thus *colchicine*, which at first was thought to act only through the adrenal cortex [182] was later shown to cause some measure of thymus involution in adrenalectomized rats.[183] Certain *vesicants* (e.g., nitrogen and sulfur mustards) can cause considerable thymico-lymphatic involution in adrenalectomized rats, hence their action is likewise, at least partly, a direct one.[184]

Aminopterin and *amino-teropterin* (two folic acid analogues) which cause marked thymico-lymphatic involution in intact animals, lose much of this effect after adrenalectomy in the rat [185] and mouse.[186] However, since the effect is not completely abolished by ablation of the suprarenals, it was con-

[165] Selye A8610/37, Selye et al. 38815/36.
[166] Selye A8610/37, Selye et al. 38815/36.
[167] Dougherty and White B18513/47.
[168] Dontigny 94204/46, Rapela B38491/44.
[169] Wells and Kendall A33542/40.
[170] Gordon and Katsh B32753/49, B32006/49, B37768/49.
[171] Herlant B38905/49, B44951/50.
[172] Schacher et al. A231/37, Selye A8610/37, Selye and Masson A18204/39, Selye et al. 38815/36.
[173] Schacher et al. A231/37, Selye and Masson A18204/39.
[174] Selye A57606/43.
[175] Selye 35935/ND.
[176] Selye 38798/37.
[177] Marder B43583/49.
[178] Leblond and Segal A17235/38.
[179] Dougherty and White 95612/46.
[180] Halberstaedter and Ickowicz B3383/47, Leblond and Segal 82724/42.
[181] Grégoire B579/43.
[182] Leblond and Segal A50424/38.
[183] Leblond and Segal A17235/38.
[184] Bass and Feigelson B42316/48, Karnofsky et al. B19945/46, B37880/48, Kindred 99940/47.
[185] Higgins and Woods B40212/49.
[186] Dougherty and Dougherty B40101/49.

cluded that part of its lympholytic effect is direct, and also partly mediated through the discharge of corticoids as a result of the ensuing stress.

The administration of *desoxypyridoxine* causes an acute *pyridoxine* deficiency. In the mouse and rat this is accompanied by a pronounced thymico-lymphatic involution, which is not prevented by adrenalectomy.[187]

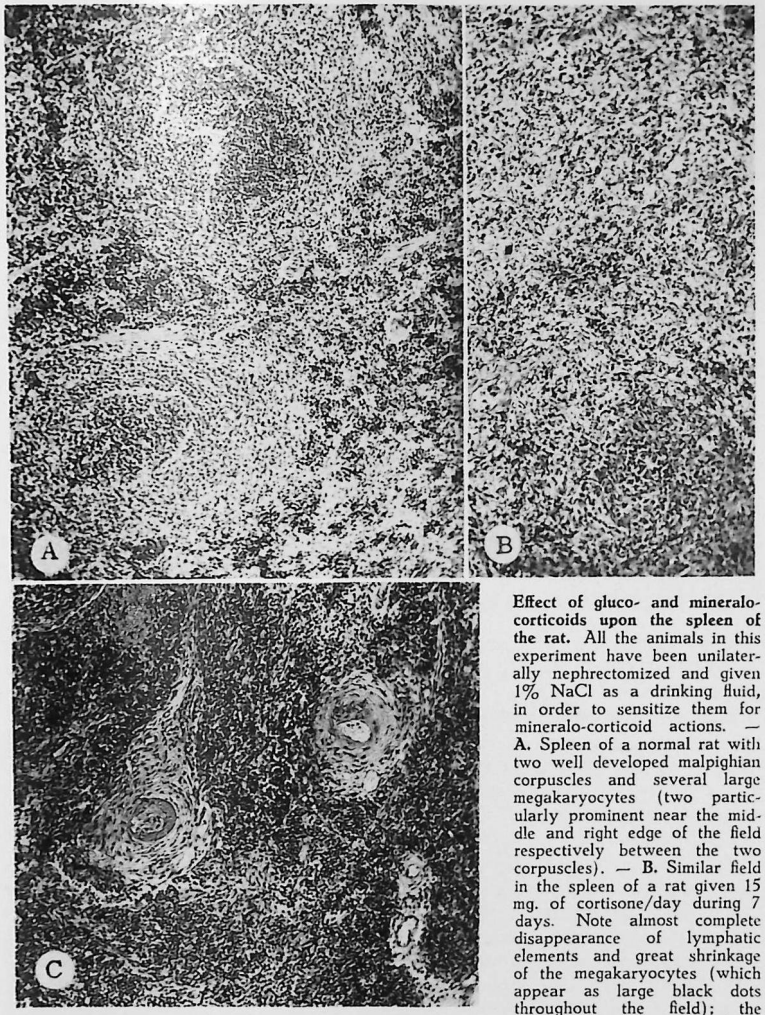
It is tempting to assume that the various direct lympholytic agents (e.g., folliculoids, gluco-corticoids, x-rays, vesicants, colchicine, aminopterin, desoxypyridoxine) affect the lymphatic tissue through the same mechanism, perhaps by severely damaging the desoxynucleic-acid frame-work of the lymphocyte nuclei.

That **adrenaline** causes marked thymico-lymphatic involution in the intact animal,[188] has already been mentioned in connection with the fact that adrenalectomy prevents this action. It is possible that during emergencies, excessive discharge of endogenous adrenaline could increase their stressor effect and thus further enhance ACTH production. It is unlikely, however, that discharge of ACTH during the A-R is solely regulated by adrenergic stimuli (cf. antonomic drugs", pp. 481-482).

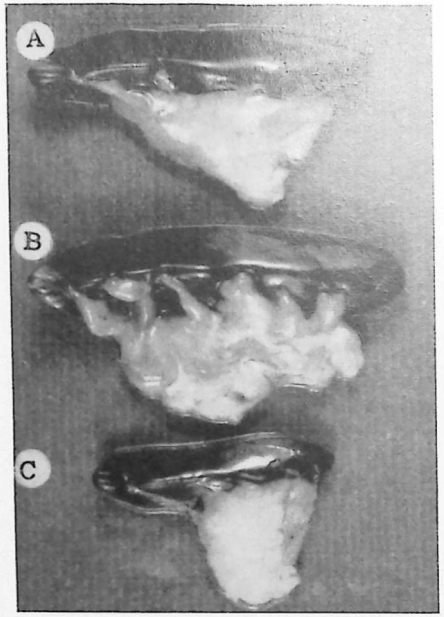
Splenic contraction is produced by adrenaline (and many of its derivatives) even in doses insufficient to cause any marked rise in blood-pressure.[189] This effect is due to a direct, specific pharmacologic action of adrenergic compounds and not to their stressor action.[190]

All active **corticoids** so far tested, produce thymico-lymphatic involution in the intact animal, gluco-corticoids being much more effective than mineralocorticoids. In this respect, the intact animal responds in the same manner as the adrenalectomized one (see above). Although the nephrosclerotic and cardiovascular actions of DCA are greatly augmented by simultaneous *NaCl* administration, the slight lympholytic effect of this steroid is not further enhanced by excess sodium.[191] In the event of chronic treatment with DCA, the thymus involution of the first few weeks tends to disappear; in fact, later, the thymus may become larger than that of untreated control animals. This apparent loss of sensitivity does not develop in all organs at the same time; for instance, the adrenal cortex remains atrophic throughout the treatment period. Such observations have been interpreted as examples of a selective *"dissociated adaptation"* of certain organs to overdosage with the hormone. The increase in thymus weight above the control level may be a result of the adreno-cortical involution. This mineralo-corticoid is comparatively inert as a thymolytic agent, but it depresses the secretion by the adrenal of more active gluco-corticoids.[192] Desoxocortisone, another mineralo-corticoid, it likewise very poor in thymolytic potency.[193] Conversely gluco-corticoids, e.g., cortisone, cause very pronounced involution of the thymus, lymph nodes, Peyer's plaques and spleen in mice,[193a] and rats.[193b]

[187] Stoerk B18187/48.
[188] Delaunay et al. B36774/48, Selye 36032/36, Zeckwer B19293/48.
[189] Stabilini and Monti B37188/48.
[190] Selye **94572/49.**
[191] Rapela B38491/44, Selye A31129/40. **94572/49.** Selye and Hall A56583/43. A57551/44.
[192] Selye A36209/41, Selye and Beland A57605/43.
[193] Selye B43385/50.
[193a] Antopol B47052/50, Molomut et al. B47636/50.
[193b] Selye 35935/ND.



Effect of gluco- and mineralocorticoids upon the spleen of the rat. All the animals in this experiment have been unilaterally nephrectomized and given 1% NaCl as a drinking fluid, in order to sensitize them for mineralo-corticoid actions. — **A.** Spleen of a normal rat with two well developed malpighian corpuscles and several large megakaryocytes (two particularly prominent near the middle and right edge of the field respectively between the two corpuscles). — **B.** Similar field in the spleen of a rat given 15 mg. of cortisone/day during 7 days. Note almost complete disappearance of lymphatic elements and great shrinkage of the megakaryocytes (which appear as large black dots throughout the field); the macrophages in these spleens were loaded with brownish blood-pigment derivatives. — **C.** Similar field from the spleen of a rat killed 30 days after implantation of a single DCA pellet, weighing 50 mg. Note persistence of lymphatic elements and two splenic arterioles showing pronounced hyalinization and fibrosis. (After Selye 35935/ND.)



Effect of **mineralo- and gluco-corticoids upon the spleen and its vessels in** the rat. All the animals in these experiments were unilaterally nephrectomized and given 1% NaCl as a drinking fluid, in order to sensitize them to the mineralo-corticoid actions. — **A.** Spleen with the attached tail of the pancreas, through which the vessels reach the hilum, in an untreated control. — **B.** Corresponding tissues of a rat having received 1.25 mg. of DCA/day in the form of a microcrystalline suspension during 33 days. Note slight enlargement of the spleen and intense periarteritis nodosa of its vessels. This was accompanied by sclerosis and edema of the surrounding pancreatic stroma. — **C.** Corresponding tissues of a rat which had received the same amount of DCA as the animal shown in fig. B, but at the same time was also treated with an equivalent amount of cortisone acetate. Note great reduction in the size of the spleen and complete absence of periarteritic lesions.
(After Selye 35935/ND.)

Indirect evidence suggests that the effect of corticoids upon serologic immune reaction (cf. G-A-S → Serologic reactions) is largely due to stimulation of the *R.E.S.*[194]

The intense thymus involution produced by chronic *starvation* in the rat is not further aggravated by DCA.[195] Furthermore, cortical extract does not alter either the thymolytic effect or the stimulation of the macrophage system in acutely starved guinea-pigs and rats.[196] This is perhaps merely due to the fact that starvation in itself suffices to cause an optimal endogenous corticoid hormone discharge.

Transplantation of the adrenals from their normal location into the spleen causes a particularly pronounced lympholysis in the immediate vicinity of the grafts but no generalized involution of lymphatic tissues.[196a] Presumably in this case the corticoids acted directly upon the lymphatic cells but could not reach other organs, because (being implanted into the portal area), they had to traverse the liver, and were here detoxified, before reaching the systemic circulation.

In vitro observations have shown that cortisone inhibits the migration of lymphocytes from explants of rabbit lymph-nodes in tissue culture. This inhibition is associated with an increased rate of degeneration of lymphocytes while the macrophages are not damaged.[197] Studies concerning the effect

[194] White B38901/48.
[195] D'Angelo et al. B32991/49.
[196] Feder and Gordon B33046/49.
[196a] Bomze and Friedman B47281/50.
[197] Heilman 86759/45, 86709/45.

of adreno-cortical extracts and various purified corticoids upon the lysis of isolated lymphocytes in vitro yielded inconsistent results,[198] hence it was concluded that the lympholysis during the A-R cannot solely depend upon a direct action of such steroids. However, gluco-corticoids do regularly accelerate the breakdown of lymphocytes in vitro, provided that lymphoid stroma is present in the system.[199] These observations raise the question whether the hypothetical "co-factor" which enhances the lympholytic effect of gluco-corticoids is derived from the stroma of lymphatic organs.

While active cortical extracts are claimed to cause involution of the lymph-nodes in mice with spontaneous *lymphatic leukemia,* no such effect was seen in patients. "It is suggested that mouse lymphoid leukemia differs significantly from the human variety".[200]

Renal hormones appear to play no specific rôle in the responses of the hemopoietic organs during the G-A-S. Nephrectomized animals respond with the usual thymico-lymphatic involution when exposed to alarming stimuli.[201] In fact experimental kidney lesions can cause marked thymus involution, simultaneously with other A-R changes.[202]

It is true that in rats bearing an "endocrine kidney" the thymus, lymph-nodes and the spleen undergo pronounced involution, but this response is prevented by adrenalectomy and appears to result merely from the systemic stress caused by an abnormally increased renal-pressor-substance production. Only the splenic contraction is so intense that it suggests the intervention of some specific factor and interestingly, this response is not prevented by ablation of the adrenals. Perhaps the R.P.S. which are known to contract various smooth muscle cells, also affect the spleen by a direct effect upon the smooth musculature of its vessels and capsule.[203]

It has already been mentioned that **gonadal hormones,** particularly *folliculoids,* are very active in causing thymico-lymphatic involution even in hypophysectomized or adrenalectomized animals. Of course, this effect is also manifest in the intact organism. Here again, the particularly pronounced proliferation of the epithelioid cells in the thymic reticulum are especially striking.[204] Often one gains the impression that very many large, new Hassall bodies are formed from the reticulum under the influence of such treatment.[205]

The erythropoietic activity of the bone-marrow is inhibited by folliculoids, especially in certain animal species,[206] but the possible relationship of this effect to the G-A-S has not yet been examined.

Luteoids [207] and *testoids,*[208] cause thymolysis, but are quantitatively less effective. The regeneration of the rat thymus after an involution which had been produced by x-irradiation is also inhibited by testosterone.[209] The erythropoietic activity of the bone-marrow, on the other hand, is often stimulated by testoids.[210]

[198] Delaunay et al. B39220/49, Robertson B37686/48, Schrek B39399/49.
[199] Hechter and Johnson B43538/49.
[200] Hellman B32769/49.
[201] Selye 35935/ND.
[202] Rosselli del Turco and Matteini B37480/47.
[203] Selye and Stone B44270/ND.
[204] Persson B37703/49, Rapela B38491/44, Selye A8610/37.
[205] Selye and Beland A57605/43, Selye et al. 38815/36.
[206] Selye and Beland A57605/43.
[207] Selye **94572/49.**
[208] Selye et al. 36745/36.
[209] Selye A31129/40, A35221/41, Rapela B38491/44.
[210] Grégoire 85576/45.
[210] Selye **94572/49.**

In either sex, castration tends to increase the development of the thymico-lymphatic apparatus in various species.[211] However, the removal of the ovary or testis fails to prevent the thymico-lymphatic involution normally seen during an A-R caused by non-specific stress,[212] though it may partially inhibit it.[213]

Thyroidectomy does not cause involution of the thymico-lymphatic tissue in the rat, but it augments the lympholytic effect of an A-R produced by various stressors.[214] Thyroid deficiency severely deranges metabolism, hence it is quite possible that this augmentation of the lympholytic effect is merely due to the fact that resistance to any damaging agent represents a greater stress for the thyroidectomized than for the intact animal.

In very young rats, thyroidectomy or treatment with a goitrogenic agent (aminothiazole), causes definite thymus involution, although the lymph-nodes and spleen are not markedly affected.[215] During the G-A-S the thymus always responds much more intensely than the lymph-nodes and the spleen. In young rats, in which the growth impulse is very intense, the metabolic derangement due to thyroid deficiency may represent a greater stress than in adults and thus cause a mild G-A-S, which would suffice to explain the changes observed.

Small doses of **thyroxine** on the other hand, tend to cause thymico-lymphatic hyperplasia,[216] similar to that frequently seen in Grave's disease; myelopoiesis may also be stimulated by this hormone.[217]

In rats receiving repeated doses of **insulin,** severe thymico-lymphatic involution develops. This has been ascribed to the fact that the resulting hypoglycemia produces a G-A-S.[218]

The effect of **anti-pernicious-anemia principle** of the liver and of pteroylglutamic acid upon the changes in the hemopoietic organs, has not yet been investigated during the G-A-S, although such studies would promise to be rewarding (cf. folic acid analogues, p. 469).

In the mouse **splenectomy** allegedly protects the thymus against the caryoclastic effect of such stressors as trypoflavine, but it has no effect upon lympholysis in other tissues.[219]

The usual effects of x-irradiation in the mouse are significantly influenced if the spleen is exteriorized and protected by placing it in a lead box during irradiation. Under these conditions marked ectopic erythropoiesis and granulopoiesis developed in the spleen, while the lymphatic tissue involuted. The latter effect was regarded as an indirect action of irradiation. Obviously, the splenic response represents a compensation for the destruction of the bone-marrow by the rays, but it is not known what humoral factors are responsible for the stimulation of the splenic myeloid tissue.[220] In any event, in the above experiments, only the involution of the splenic lymphatic tissue could be regarded as due to increased corticoid secretion.

Among the pharmacologic agents capable of influencing the response of the hemopoietic organs during the G-A-S, the **autonomic drugs** are particularly important. It will be recalled that some investigators expressed the opinion

[211] Persson B37703/49.
Selye 38798/37, **94572/49.**
[212] Selye 38798/37, Zeckwer B1110/45.
[213] Szego and White B32836/49.
[214] Selye 38798/37, Zeckwer B1110/45.
[215] Grégoire B36686/49.
[216] Marder B43583/49.
[217] Selye **94572/49.**
[218] Zeckwer B19293/48.
[219] Dustin and Zylberszac 8668/31.
[220] Jacobson B33422/49.
Jacobson et al. B47629/50.

that during the A-R, ACTH is discharged as a result of adrenergic stimulation. This could occur either through adrenaline secretion by the adrenal medulla, or as a result of adrenaline (or nor-adrenaline) discharge in the nerves of the pituitary itself. It is interesting, therefore, that "the histological changes of the A-R in the thymus and the adrenals, provoked by epinephrine, were reversed by *dibenamine* but those provoked by colchicine were not".[221] Since exogenous adrenaline was effectively inhibited by the adrenolytic agent under the conditions of this experiment, it is unlikely that the thymus involution caused by colchicine — which remained uninfluenced by dibenamine — could have been occasioned by overproduction of endogenous adrenaline.

As regards possible mediators involved in the stimulation of the R.E.S. during the G-A-S, we already mentioned that *choline, acetylcholine* [222] and *histamine* [223] are allegedly capable of causing similar hypertrophy and hyperplasia of the macrophage system. Significantly, the effect of the latter is inhibited by anti-histaminics. However, other investigators obtained diametrically opposite results at least with histamine [224] and further work will have to take into account that responses during the G-A-S are usually triphasic.

We have already discussed the various **nutritional derangements** which can influence the hemopoietic organs through their stress-effect. Let us merely point out here that the thymico-lymphatic atrophy produced by other alarming stimuli is in turn influenced by the diet. The most striking conditioning action of this type is the marked sensitizing effect of *fasting* upon the thymico-lymphatic involution caused by various stressors.[225] It is probable that this sensitization is largely, if not entirely, due to the fact that fasting increases the ACTH secretion of the pituitary in animals exposed to stress; hence the resulting overproduction of lympholytic corticoids is also augmented.

Exposure to a hot environment greatly increases the phagocytic power of the blood-leucocytes in the rat, but only if the animals are kept on *high-protein* diets.[226] Unfortunately, comparable observations have not yet been made concerning the behaviour of other phagocytic elements.

Hemopoietic Diseases of Adaptation

The possible rôle of systemic stress in the pathogenesis of blood dyscrasias has been discussed in connection with the blood-count under the heading "Blood Diseases of Adaptation" (cf. page 432). This appeared justified since any major derangement in the function of the hemopoietic organs generally reflects itself in the blood-count. Here we shall merely mention a few derangements of the hemopoietic organs, which are not regularly accompanied by prominent hematologic changes.

Status thymico-lymphaticus. — As we stated in connection with the adrenal diseases of adaptation, the "status thymico-lymphaticus" appears to be closely related to the G-A-S. It has often been observed that adreno-cortical hypoplasia is accompanied by excessive development of lymphatic tissue and that

[221] Seifter et al. B32930/49.
[222] Chèvremont B23319/48
[223] Biozzi et al. B39116/48,
Jancsó B38168/47,
Piemonte B38649/46,
Törö B41276/42, B38648/43, B28228/48.
[224] Eppinger B37085/49.
[225] Selye A8406/38.
[226] Mills and Cottingham B27633/43.

this syndrome predisposes to sudden death upon exposure to some acute stress situations. There has been much argument about the nature of this syndrome; some regard it as a special disease, others believe that whenever an individual dies very suddenly (without previous disease) the adrenal cortex merely appears hypoplastic, and the thymico-lymphatic apparatus hyperplastic, in comparison with the averages reported for autopsy material. In other words, the latter school holds that the organ weights of patients with status thymico-lymphaticus are actually normal and that the average, as listed in pathology texts, is the abnormal figure, since in most patients death was preceded by a disease which, through the G-A-S mechanism, caused adreno-cortical enlargement and thymico-lymphatic involution.[227] Be this as it may, the possibility must be acknowledged that a hypoplastic and hypofunctional adrenal cortex could simultaneously decrease resistance and cause excessive development of the thymico-lymphatic apparatus, due to interference with the normal G-A-S response to stress.

Thesauroses, reticulo-endothelioses, lymphomatoses. — Excessive phagocytosis of various metabolites or abnormal proliferation of the R.E.S. have been described under these headings. The various types of xanthomatoses, Schüller-Christian's syndrome, Gaucher's disease, Niemann-Pick's disease, are largely characterized by the abnormal storage of various lipids by the histiocytes of the R.E.S.[228] On the other hand, Hodgkin's disease, Boeck's sarcoid and various allied "reticulo-endothelioses" [229] are chiefly characterized by a proliferation of the R.E.S., frequently accompanied by hyperplasia of the lymphoid tissue.

The relationship of these diseases to the G-A-S has not yet been sufficiently examined to justify any detailed discussion here. However, the possibility exists that they may, to some extent, be diseases of adaptation. Both the proliferation and the phagocytic power of the macrophage system are largely dependent upon corticoids and exposure to any stressor exerts a marked influence upon the physiology of the R.E.S. It is highly probable, therefore, that diseases which are chiefly characterized by abnormal proliferation or excessive storage phenomena in reticulo-endothelial cells, are at least influenced — if not precipitated — by exposure to stress. In view of these considerations, it would appear most promising to re-examine the pathogenesis of such diseases from this point of view. Presumably — as in so many similar instances — the stereotypical G-A-S response leads to specific disease manifestations only in the presence of specific "conditioning factors", for instance, the accumulation of abnormal metabolites which lend themselves to phagocytosis by the R.E.S.

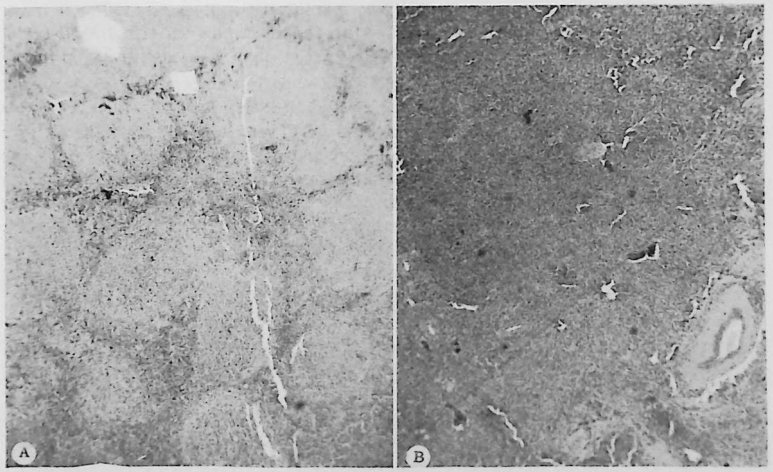
More or less prolonged remissions have been obtained with *ACTH* or *cortisone* in patients with **lymphosarcoma** and **Hodgkin's disease.**[230] In agreement with expectations *DCA* proved ineffective in Hodgkin's disease.[231]

In guinea-pigs injected with extracts from the urine of patients with Hodgkin's disease, lymphoid or myeloid leukemia, there developed a "Hodgkin-like reaction" in various organs. This was ascribed to the presence in such urine extracts of myelokentric and lymphokentric acids, substances allegedly promoting myeloid and lymphatic growth respectively.[232] Judged by the

[227] Selye 94572/49.
[228] Thannhauser 91509/40.
[229] Cazal B31651/46.
[230] Pearson et al. B46975/50, B46309/50.
[231] Frada B46147/50.
[232] Miller and Turner B46901/49.



Follicular lymphosarcoma. — **A.** Before treatment. — **B.** After 10 days of ACTH (100 mg./day). (After Pearson et al. B46975/50.)



Follicular lymphosarcoma. — **A.** Lymph-node biopsy before ACTH shows germinal follicles. — **B.** Lymph-node biopsy after 17 days of ACTH shows disappearance of germinal follicles and decrease in cellularity. No cytologic changes noted. (Courtesy of Dr. O. H. Pearson.)

illustrations given, these Hodgkin-like changes strikingly resemble those caused by LAP in the rat. The cause of this similarity should be investigated.

DCA has little if any effect in Hodgkin's disease (or in lymphatic and myeloid leukemias) even if given simultaneously with ascorbic acid. On the other hand, allegedly, "sensational and permanent relief" has been obtained with DCA in a rare disorder, the so-called giant **follicular lymph-adenopathy** (Brill-Symmers disease).[232a] If confirmed, this observation would be of the utmost importance since DCA is normally devoid of any significant lympholytic effect.

In mice, transplantable lymphosarcomas involute more markedly upon colchicine treatment then the normal lymphoid tissue of the spleen. "As reduction in weight of the spleen in the mouse is consistently seen when 'alarming' stimuli are employed", this was ascribed to a specific action of the drug.[233]

In cases of **acute porphyria,** decreased plasma Na and Cl was found to occur conjointly with functional and morphologic signs of adreno-cortical hyperfunction. These findings have been analyzed in the light of the G-A-S concept, but it was concluded that "the disordered electrolyte metabolism is not primarily adrenal in origin".[234]

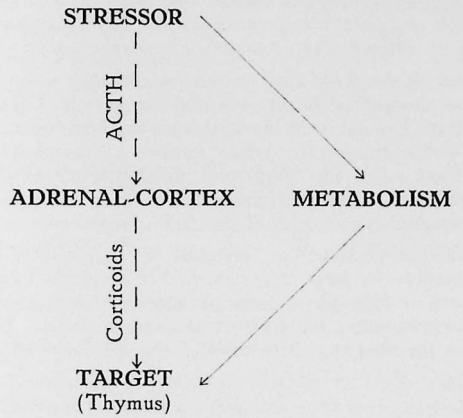
Theories Concerning the Participation of the Hemopoietic Organs in the G-A-S

Here again, we may refer the reader to the corresponding discussion in the chapter "Blood-count", since during the G-A-S the circulating blood-cells are subject to essentially the same regulatory mechanism as the sessile elements of the hemopoietic organs. Indeed, most of the changes in the blood-count (illustrated in the drawing on page 438) are largely the result of primary actions upon the hemopoietic organs themselves.

As regards the very prominent lympholytic phenomena of the A-R, available evidence suggests that these affect sessile lymphocytes much more than those freely circulating in the blood. Even the lymphocytes of the various lymphatic organs do not respond to stress or gluco-corticoids with equal intensity. The thymus, the germinal centers of lymph-nodes or Payer's plaques and other lymphatic tissues respond with decreasing intensity in the order mentioned. There is much to suggest that the R.E.S. cells, which are so plentiful in the stroma of the lymphatic tissues, contribute considerably to the lympholysis produced by stressors or gluco-corticoids.

In vitro observations revealed that certain "co-factors" present in the stroma of lymphatic organs, are necessary for the full lympholytic effect of gluco-corticoids. Abundance of such hypothetical "co-factors" in the thymus and the germinal centers of lymph-nodes, may explain why both stress and gluco-corticoids cause maximal lymphocyte destruction in these locations.

Observations in vivo suggest that during the A-R, some such conditioning factors arise, which augment the lympholytic effect of gluco-corticoids. Apparently, in the intact animal thymolysis can be induced through a dual mechanism: (1) increased gluco-corticoid production, (2) peripheral activation of the circulating gluco-corticoids. In gluco-corticoid-treated animals (not exposed to stress) the first mechanism is effective although the second is absent. In untreated adrenalectomized animals both mechanisms are inactivated and the target no longer responds to stress. In the diagram below these two pathways are represented by interrupted and solid lines respectively.



In previous chapters of this book we mentioned several similar instances of a peripheral sensitization to corticoids and ACTH by some hypothetical metabolites produced during the A-R. Thus pure ACTH fails to cause persistent degranulation of the adrenal-cortex in the absence of some "degranulation factor" which appears to be produced by tissues in the course of exposure to stress. Similarly, the hyperglycemic action of corticoids is mild in adrenalectomized animals unless they are simultaneously exposed to alarming stimuli. It would be desirable to establish whether, in the instances mentioned above, the factors sensitizing for lympholysis, adreno-cortical degranulation and hyperglycemia are related to each other. The chemical nature of these peripheral synergists is not known, but it is suspected that their production is related to the intense catabolic phenomena characteristic of the A-R, since all these sensitization phenomena are at their maximum when cell disintegration is at its peak.

Because of its great importance for defense, special interest attaches to the stimulation of the R.E.S. during certain stages of the G-A-S. Only few experimental studies have so far dealt with this aspect of the problem, but it is already obvious that the gluco-corticoids are important activators of the phagocytic system. Hence a discharge of gluco-corticoids during stress probably helps to promote phagocytosis (e.g., of microbes) by the R.E.S. and the production of serologic antibodies against exogenous antigens.

[232a] Frada B47665/50, B46147/50.
[233] Bass and Place B44857/49.
[234] Prunty B37297/49.

Summary of Observations Concerning the Participation of the Hemopoietic System in the G-A-S

During exposure to stress, the hemopoietic, and especially the thymico-lymphatic organs, undergo important variations which are obviously non-specific and due to the G-A-S itself. This is shown by the fact that a great variety of stressors produce essentially similar lesions in the hemopoietic system and that interference with the G-A-S response (e.g., by hypophysectomy or adrenalectomy) inhibits these reactions.

During the A-R, there is an acute disintegration of lymphocytes, especially those situated in the thymus and the germinal centers of various **lymphatic organs.** The debris of the disintegrating lymphocytes is subsequently engulfed by mobile phagocytes, which remove it through the lymphatics. During the resistant stage, the lymph-cell population of the lymphatic organs tends to return towards (though rarely to) normal, while during the exhaustion phase, the marked lympholysis of the A-R is repeated.

The "caryoclastic" or "lympholytic" response of the A-R can be accurately reproduced by large doses of *ACTH* or *gluco-corticoids* even in the absence of stress. *Hypophysectomy* or *adrenalectomy* prevent the lympholytic effect of most stressors, but not that of gluco-corticoids. Hence stressors presumably affect the lymphatic cells through the discharge of corticoids.

There are a few notable exceptions to this general rule. For instance, ionizing radiations, vesicants, and several steroid hormones devoid of gluco-corticoid action (e.g., folliculoids, testoids) cause marked lympholysis in animals deprived of their suprarenals. Other agents (e.g., pyridoxine antagonists, folic acid antagonists, colchicine) take an intermediate position; they lose only part of their lympholytic effect after adrenalectomy. Presumably, the lympholytic effect of most stressors is primarily dependent upon the discharge of gluco-corticoids, but other *"co-factors"* are also of importance. During the A-R the relative rôle played by these two types of agents may depend upon the nature of the stressor used.

Although the chemical identity of such "co-factors" has not yet been elucidated, their participation in lympholysis is clearly shown by several types of experiments. Thus, in adrenalectomized animals, threshold doses of gluco-corticoids cause no lympholysis unless an A-R is simultaneously produced by some stressor; yet, in itself the latter likewise fails to induce lympholysis in the absence of the suprarenals.

In vitro observations revealed furthermore that addition of gluco-corticoids to lymphocyte suspensions causes no marked lympholysis unless certain — in themselves inert — tissue products are simultaneously present. Such sensitizing substances appear to be especially plentiful in the stroma of lymphatic organs.

The phagocytic activity of the **R.E.S.** is likewise greatly stimulated in the A-R and the exhaustion phase in most organs, particularly the lung. During the resistant stage, on the other hand, there appears to be a diminution of phagocytosis. The mechanism through which the R.E.S. is regulated during exposure to stress has not yet been fully elucidated, but there is ample evidence to suggest that the *gluco-corticoids* participate in this response.

Much less is known concerning the truly characteristic reactions of the **erythropoietic** elements during the G-A-S. Exposure to a great variety of stressors has been shown to cause some depression of erythropoiesis and transformation of red into inactive gelatinous or fatty bone-marrow. With most stressors, these responses are comparatively mild, but curiously, ionizing radiations, vesicants and other agents capable of causing lympholysis in the absence of the adrenal, produce particularly severe degenerative changes in the erythropoietic elements. It remains to be shown whether there is any causal connection between the "direct lympholytic effect" and the ability of certain agents to produce especially severe destruction of the erythropoietic system.

The participation of hormonal factors in the regulation of erythropoiesis during the G-A-S has not yet been adequately studied. It is known that *ACTH* and *gluco-corticoids* can cause erythrocytosis due to a stimulation of the bone-marrow. *Testoids* and *thyroxine* likewise stimulate the erythropoietic system, but we do not know whether these latter hormones play any important part in the regulation of bone-marrow function during the G-A-S. The erythropoietic effect of crude pituitary extracts is much greater than that of purified ACTH. It has been tentatively assumed that protein impurities, or contamination with other anterior-pituitary hormones augment the erythropoietic effect of ACTH in such impure extracts.

As regards the **hemopoietic diseases of adaptation,** we referred the reader to the corresponding section of the chapter on blood-count. Here we merely mentioned *status thymico-lymphaticus,* certain *thesauroses* and *reticulo-endothelioses* in which the G-A-S may exert at least a modifying influence upon the development of the disease manifestations.

LYMPHATIC VESSELS AND LYMPH-FLOW

Dilatation of lymphatic capillaries and medium sized lymph-vessels is rather characteristic of the A-R produced by various stressors, e.g., in the rat.[1]

All those agents which elicit a **"serous inflammation"** augment the volume and protein content of the thoracic duct lymph. Since these same agents are also alarming stimuli, this observation is of considerable interest in the interpretation of the G-A-S.[2]

Among other stressors **hemorrhage** was found to cause a marked increase in systemic (and particularly in pulmonary) lymph-flow.[3] Curiously **insulin** allegedly diminishes both the volume and the protein content of the lymph, although it causes considerable stress.[4]

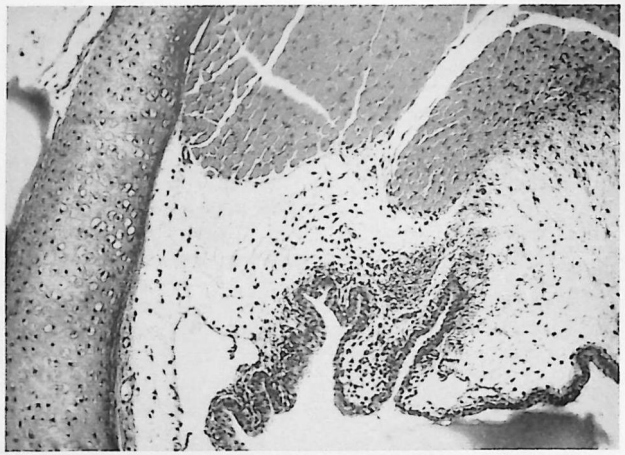
Anoxia increases lymph-flow even when it is severe enough to cause a collapse of the blood-pressure.[4a]

It is probable that during the A-R (as in the so-called "serous inflammation") the permeability of capillaries is increased so that a large amount of plasma leaks into the intercellular spaces. When this is absorbed by the lymphatics, the volume and protein-content of the lymph increases. A recent survey of the literature concerning changes in the lymphatics during the A-R rather supports this view.[5] The formation of hemolymph-nodes during the A-R

[1] Selye 35935/ND.
[2] Eppinger **B37085/49.**
[3] Eaton B37563/47.
[4] Eppinger B37085/49.
[4a] Malméjac et al. B43984/48.
[5] McMaster **B23173/43.**

(cf. previous section) suggests that even erythrocytes may traverse from the blood-capillaries into the lymphatic vessels.

The factors regulating lymph-flow during the G-A-S are incompletely known, but the mineralo-corticoids are presumably among them. In rats given large doses of desoxocortisone, there was a marked dilatation of the lymphatic vessels throughout the body, which paralleled the simultaneous development of tissue edema. This response was particularly pronounced in the glottis region and the lung, hence acute glottis- or lung-edema during the A-R may be related to excess mineralo-corticoid secretion.[6]



Glottis edema produced by desoxocortisone in the rat. Note intense edema of the stroma with marked dilatation of lymphatic vessels (lower left corner between cartilage and epithelial lining) in the glottis region. (After Selye B43385/50.)

Since mineralo-corticoids tend to increase the pharmacologic actions of sodium, it is noteworthy that ingestion of excess NaCl is one of the most active means of promoting lymph-flow in the rat.[7]

[6] Selye B43385/50.

[7] Reinhardt and Bloom B44796/49.

CARDIOVASCULAR SYSTEM

Cardiovascular changes are among the most important manifestations of the G-A-S and its diseases, hence we shall discuss them in some detail.

Adequate oxygenation and nutrition of tissues depends largely upon the maintenance of blood-pressure, blood-flow and capillary permeability. The normal adjustment of these factors to varying requirements is indispensable for the maintenance of physiologic homeostasis; conversely, derangements of these adjustments are probably the most common pathogenic factors which can lead to diseases of adaptation (e.g., the hypotension of shock, the various types of hypertension and arteriosclerosis caused by chronic exposure to stress).

Pertinent observations have been made ever since man became aware of the fact that the heart-rate is accelerated by excitement or that the pulse becomes weak and the skin pale in shock. It is not surprising therefore that the literature concerning the behaviour of the cardiovascular system during exposure to stress is truly enormous. However, we shall limit ourselves here to a discussion of data which are particularly instructive for the evaluation of cardiovascular phenomena as components of the G-A-S or of the diseases of adaptation. In many organs (e.g., kidney, brain, hemopoietic tissue) the vascular changes form an integral part of the local lesions characteristic of the response to systemic stress; hence the chapters specifically devoted to these organs should also be consulted.

Systemic Stress

Characteristic response. — In discussing the cardiovascular responses characteristic of the G-A-S, it is important to emphasize that almost all the published facts are concerned with the A-R stage. At this time, the type of response depends largely upon the intensity of the alarming stimulus. The cardiovascular system always appears to exhibit the "shock-phase type" of reaction after severe, and the "counter-shock type" after comparatively mild exposure.

According to the classical concept, a stimulus of average intensity first causes manifestations of shock which, in the event of recovery, are followed by countershock. Frequently, however, an initial period of counter-shock-like manifestations precedes shock. Probably an initially well tolerated agent gradually builds up its stressor effect to a severely damaging level, due to a cumulative action. Indeed, if the stress effect rapidly increases to a fatal intensity, the initial counter-shock phenomena are followed by gradually increasing, and eventually lethal, manifestations of shock.

Of course the severity of the stressor does not depend so much upon its intensity in absolute terms as upon the resistance the body can put up against it. Thus a stimulus which causes predominantly counter-shock manifestations in a healthy intact organism, may produce exclusively shock phenomena in an organism whose resistance has been weakened, e.g., by previous exhaustion, adrenalectomy, hypophysectomy or malnutrition. Essentially the same con-

siderations apply to almost every manifestation of the G-A-S, but they are particularly evident as regards the responses of the cardiovascular system.

Because of the frequent overlapping of shock and counter-shock phenomena, it is somewhat artificial to make an absolute distinction between so-called "primary" and "secondary" shock. Both are characterized by essentially the same cardiovascular manifestations, only that in primary shock these occur immediately after injury and are generally regarded as due to nervous insults (especially pain and psychic factors). Conversely, in secondary shock, there is a period of several hours of relative well-being between exposure to stress (trauma, burns, etc.) and the onset of shock. However, nervous insults may also cause shock after a latency period and irrespective of etiology there are many transitional types between immediate "primary" and delayed "secondary" shock. Hence, it is perhaps inadvisable to conclude with finality that primary and secondary shock are fundamentally different conditions.

In the most extensively studied type, the so-called "secondary" **shock,** the pulse is rapid and feeble but upon opening the chest, the heart is found beating vigorously, although its cavities, as those of the great veins, are incompletely filled. The venous pressure is low, the cardiac output reduced and there is widespread dilatation of capillaries and small venules. The systolic arterial blood-pressure falls considerably, often below 60 mm. Hg. This is preceded by slowing of the peripheral blood-flow and reduction of cardiac output in spite of a strong heart beat. Hence the hypotension is presumably due to sequestration of blood in the dilated vascular territories, with a concomitant decrease in peripheral resistance, a diminished inflow of venous blood to the heart and consequently a decrease in "stroke volume".

Hemoconcentration is not a constant accompaniment of shock nor is there necessarily any evidence of plasma loss into the tissues. The circulating blood-volume is markedly reduced even if no hemorrhage has occurred, but this is not due to leakage from the vascular system, but to stagnation of blood in the dilated peripheral vessels. This latter factor is also responsible for the great slowing of the circulation and the resulting interference with the nutrition of tissue.

Frequently, there is constriction of the arterioles, especially in the splanchnic and cutaneous areas, but this is probably a compensatory response (stimulation of sympathetic nerves, adrenaline liberation, decreased tonus of depressor nerves) and hence, a counter-shock phenomenon. The skin is cold but may be pale or cyanotic, depending upon whether peripheral vasoconstriction or vasodilatation prevails.

Essentially this same type of response is seen in "traumatic shock",[1] "burn shock" [2] as well as in the various types of "medical shock" caused by fulminating infections, intoxications, etc.[3]

On the other hand, the cardiovascular manifestations of **counter-shock** are perhaps most characteristically typified by the so-called "emergency reaction" of Cannon.[4] Here the pulse rate is also rapid, but the "stroke volume" is greatly increased. There is vasoconstriction in most organs, especially in the splanchnic and cutaneous territories; as a result of this the peripheral resist-

[1] Cannon and Cattell 13334/22, Cannon et al. **57880/18,** Moon **A16304/38.**

[2] Harkins **82895/42.**

[3] Manceaux and Jorda B23176/48, Stamler et al. B46212/50.

ance and blood-pressure rise. In case of injury, the constriction of the skin-vessels minimizes bleeding, while the rise in blood-pressure tends to counteract any possible hypotension of shock. The simultaneous splenic constriction pours erythrocytes (better tissue oxygenation) and leucocytes (phagocytosis and other defense phenomena) into the circulation. Conversely, the vessels of the heart and skeletal muscles are dilated, presumably in preparation for the physical effort of fight or flight to cope with emergency situations.

To summarize, let us re-state that in comparing the cardiovascular phenomena of the shock and counter-shock phases, the hypotension of the former and the hypertension of the latter are most striking. The arterial blood-pressure depends primarily upon the balance between the amount of blood pumped into the arteries and the resistance to the outflow from them. During the shock-phase the peripheral resistance is low and the skeletal musculature is relaxed, hence insufficient amounts of blood return to the heart and the stroke-volume falls. During counter-shock, vasoconstriction causes a marked rise in peripheral resistance and the venous return is simultaneously accelerated due to pressure by incidental contractions of skeletal muscles. Contraction of the abdominal muscles and diaphragm tend to press the venous blood back from the abdominal cavity towards the heart, while contraction of other skeletal muscles compresses the vessels within them with the same result. "The laboring muscles act as if they were outlying hearts, receiving more blood when they work and pumping that blood back to the central heart and the lungs for refreshment and new service".[5]

In this sense, it is probably of adaptive value that restlessness and hypermotility are almost constant accompaniments of all types of stress. In fact this may serve a dual purpose, in conditioning "preparedness" during emergencies, partly through the above-mentioned cardiovascular changes and partly by "limbering up" the musculature for offense or defense.

As regards the morphologic changes accompanying shock-like conditions, endothelial damage is considered of primary importance by many observers. A comparative study of various kinds of traumatic and medical shock led to the conclusion that "the pattern of changes indicative of endothelial damage included dilatation and engorgement of capillaries and venules in the thoracic, abdominal and cranial viscera, petechiæ in serous and mucous surfaces and within parenchymatous tissues, and edema of soft viscera".[6] The pathogenesis of this capillary damage is incompletely understood, but perhaps interference with intercellular cement substances may play a major rôle.[7]

Degeneration of the myocardium is inconstant. When it occurs, the cross striations become indistinct and the fibers assume a granular appearance. The cytoplasm tends to be of uneven density, sometimes showing basophilia or apparent liquefaction, with transverse fragmentation of the fibers. The nuclei may be swollen or distorted.[8]

Systematic studies concerning cardiovascular responses characteristic of the **resistant stage** of the G-A-S have not yet been published. Various animal experiments and clinical observations suggest that certain types of hypertension, cardiac hypertrophy, arteriosclerosis and "rheumatic-like" cardio-

[4] **B14905/39.**

[5] Cannon **B14905/39.**

[6] Moon B19951/48.

[7] Chambers and Zweifach **B26122/47.**

[8] Moon B19951/48.

vascular lesions are caused by derailments of the G-A-S. These will be discussed below, in connection with the factors (mostly hormonal and dietary) which can effect such a derailment, as well as in the section on "Cardiovascular diseases of adaptation". Yet, it would be artificial to make a sharp distinction between normal and abnormal adaptive phenomena, since any stimulus requiring adaptation is, by definition, somewhat outside of the "normal base level" of physiologic life. In this sense, even the mildest phenomena of shock and counter-shock could not be clearly delimited from the abnormal. On the other hand, life at the "base level" of complete rest, could not be long maintained nor could it be called normal. Therefore we must outline the manifestations of the G-A-S, and of its diseases, as parts of a single picture in which the normal and abnormal imperceptibly merge into each other.

The morphologic changes in the cardiovascular system, which often develop during the resistant stage of the G-A-S, are interpreted as pathologic (hence as "diseases of adaptation") by most students of this field. Yet, even here, it is a matter of opinion whether for instance an arteriosclerotic lesion in the aorta should be considered as "abnormal", irrespective of its severity or of the patient's age.

It would lead us too far afield into philosophy if we were to attempt any definition of physiologic norms, but few physicians would consider it "normal" if, at the autopsy of a man aged 90, not the slightest degenerative change could be observed in the cardiovascular system. As we have repeatedly stated in other connections, the stresses and strains of daily life are in themselves alarming stimuli and hence the comparative resistance of maturity and the exhaustion of senility, may well be compared to the corresponding stages of the G-A-S. We have said in the "Foreword" that adaptability is one of the most characteristic features of life, but it is perhaps equally characteristic of living matter that it cannot maintain this adaptability indefinitely. Hence the greatest possible deviation from the "norm" of life, namely eventual death, is also one of its most typical features.

But let us extricate ourselves from the realm of philosophy and return to our more immediate problem. Even if we took the extreme attitude that any morphologic change caused by exposure to stress is a "disease" of adaptation rather than part of the physiologic G-A-S, we would have to admit that at least the tendency to develop such lesions is an integral part of the adaptation-syndrome. For this reason, we shall discuss the important cardiovascular **"hyalinosis"** syndrome here. Since its characteristics are essentially the same be it produced by stress (e.g., cold) or hormones (e.g., LAP, DCA, desoxocortisone, the "endocrine kidney") this procedure will also help us to avoid unnecessary repetition. Later, when we come to consider individual stressors and hormones we will only have to mention such minor differences as do occur in this syndrome.

Numerous animal experiments and clinical observations have shown that the tendency to develop persistent hypertension, cardiac hypertrophy and what we call "hyalinosis" of the cardiovascular system, is typical of the stage of resistance. There is deposition of "hyalin" or "fibrinoid" material beneath the intima of various vessels, especially the arteries of medium size. Frequently, large portions of the media are likewise infiltrated with this material or actually transformed into a homogeneous, hyalin substance. In the myocardium, entire groups of muscle fibers may become homogeneous as a result of what is known as *"fibrinoid necrosis"*.

At the same time a granulomatous tissue develops, especially around the cardiac arterioles and in the vicinity of the hyalin plaques. As part of this granuloma in the heart, but rarely in extracardiac tissues, two curious, special cell-types appear. One is the polymorphonuclear giant-cell, which resembles the *"Aschoff cell"* of acute rheumatic fever; the other is the *"Anitschkow cell"* (myocardial reticulocyte, cardiac histiocyte, cardiac myocyte or caterpillar cell). It is well to keep in mind, however, that contrary to earlier opinion such Anitschkow cells can occur outside the heart, for instance, in the muscularis of the stomach, the mucosa of bronchi and the intima of arterioles.[9]

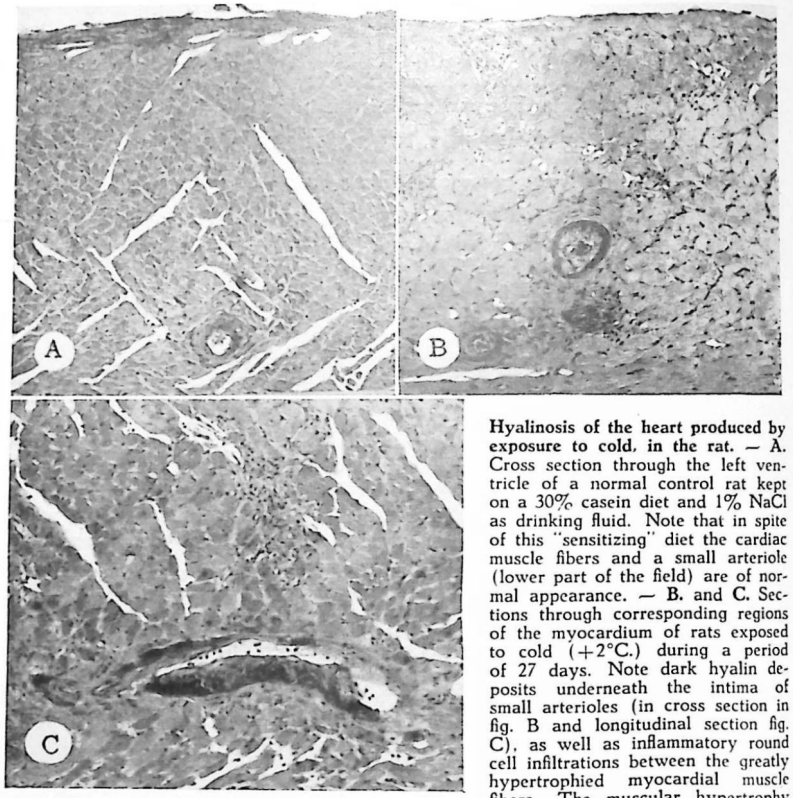
Some investigators considered both the Anitschkow cell and the Aschoff cell to be characteristic of acute rheumatic fever, but this is certainly not correct. It is true that the development in the heart of numerous and typical Aschoff nodules containing characteristically formed Aschoff cells and Anitschkow cells is almost pathognomonic of acute rheumatic fever. Yet various non-specific injuries to circumscribed areas of the myocardium can produce "foreign body granulomas" with "foreign body giant cells" and histiocytes which are practically indistinguishable from those of rheumatic fever. Such lesions are especially prone to develop during the stage of resistance of the G-A-S and after overdosage with certain hormones (LAP, mineralo-corticoids) which are known to be produced in excess during exposure to systemic stress.

In the coronary system of man there are small arterial branches, the walls of which contain layers or *"cushions" of so-called epithelioid cells.* They have also been observed outside the heart, especially in vascular territories where *arterio-venous anastomoses,* or "shunts" occur.[10] Excessive development of these "epithelioid cells" has likewise been considered to be a consequence of non-specific systemic stress and part of the G-A-S.

Although hyalinosis is particularly frequent in the cardiac arteries and arterioles, those of the kidney, mesentery and brain are also often involved. Among the larger arteries, only those of the splanchnic territory are frequently affected. The veins and the aorta appear to be almost entirely immune.

From our experimental material the *histogenesis of the hyalinosis* may be reconstructed in the following manner: The typical lesion develops in medium-sized or small arteries, frequently at a bifurcation, perhaps because the mechanical damage caused by the constant impact of the blood (local stress) predisposes these sites. In the earliest stages, the muscle cells of the media become rounded. They often contain basophilic granules or rods and their nuclei assume a vesicular appearance. Sometimes basophilic threads seem to form bridges between nuclei of cells situated in different strata of the media. Almost at the same time, a thin layer of hyalin "fibrinoid" material is deposited underneath the intima; it also infiltrates between the muscle cells of the media. At a later stage, a rather cellular, granuloma tissue develops in the adventitia and subsequently infiltrates into the media from the outside. Within this granuloma, many polynuclear giant-cells appear, but these do not resemble Aschoff cells as closely as those in the heart, since they are comparatively small and rarely contain more than two or three nuclei. In very acute cases, many polymorphonuclear leucocytes invade the granuloma tissue, thus giving it the appearance of an acute inflammation. Only exceptionally does this reaction proceed

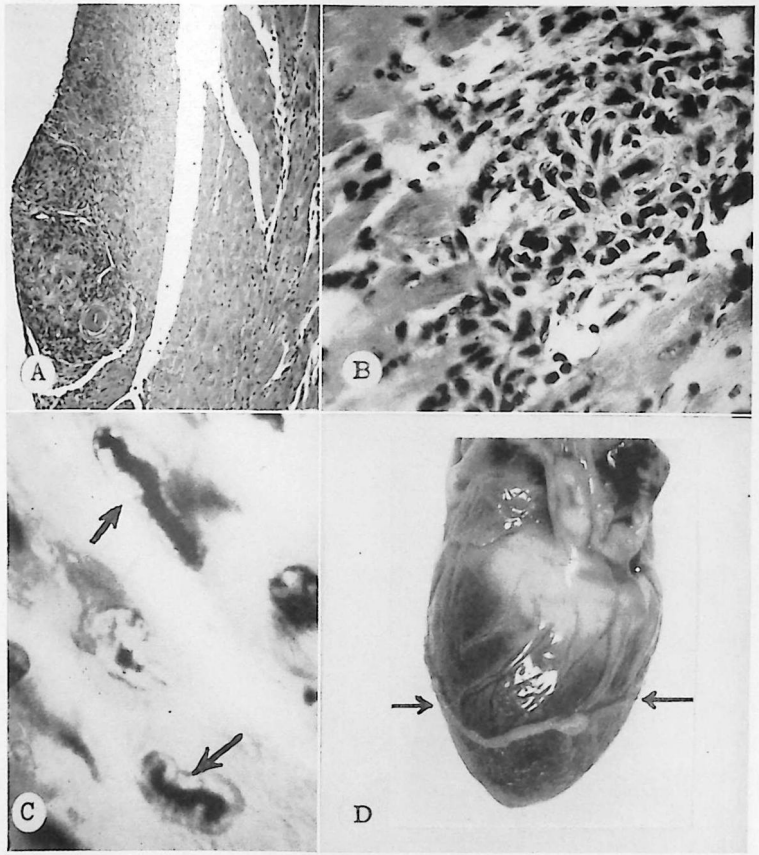
[9] Zak 99899/47. B23130/42.
[10] Hirsch B24132/42, B24133/42,



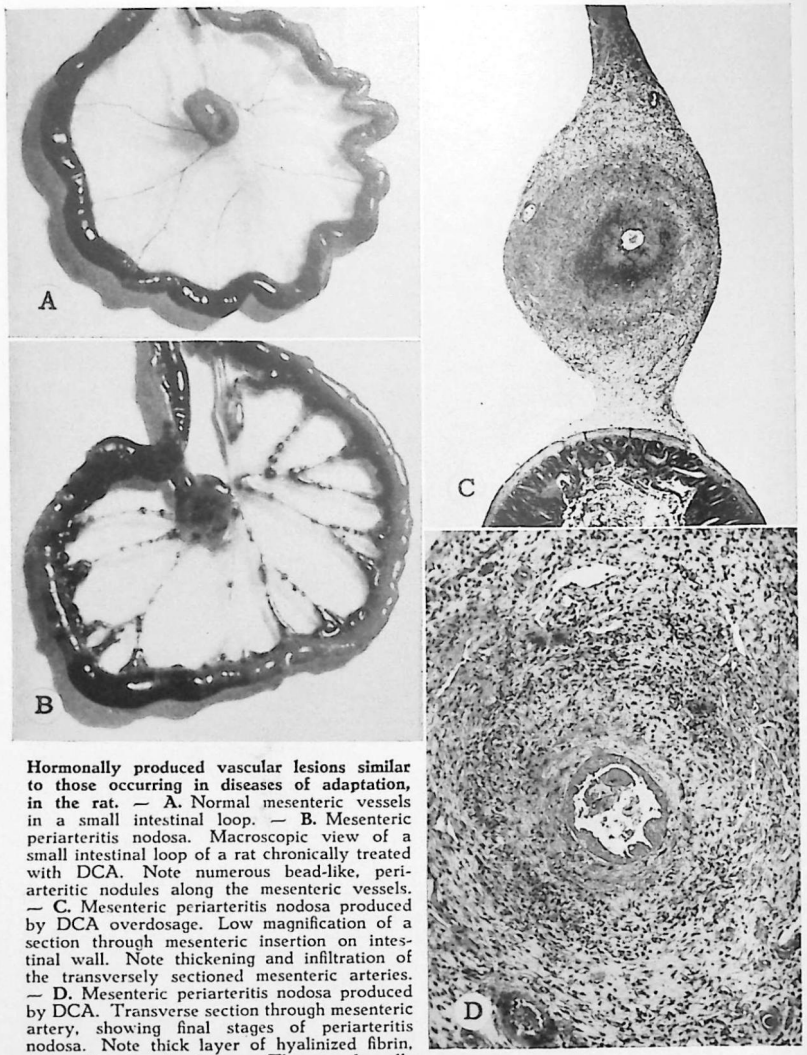
Hyalinosis of the heart produced by exposure to cold, in the rat. — **A.** Cross section through the left ventricle of a normal control rat kept on a 30% casein diet and 1% NaCl as drinking fluid. Note that in spite of this "sensitizing" diet the cardiac muscle fibers and a small arteriole (lower part of the field) are of normal appearance. — **B.** and **C.** Sections through corresponding regions of the myocardium of rats exposed to cold (+2°C.) during a period of 27 days. Note dark hyalin deposits underneath the intima of small arterioles (in cross section in fig. B and longitudinal section fig. C), as well as inflammatory round cell infiltrations between the greatly hypertrophied myocardial muscle fibers. The muscular hypertrophy in such animals is most obvious in regions where arterial hyalinization has occurred. (Selye 35935/ND.)

to actual suppuration. Sometimes the entire granuloma is interspersed with lymphocytes or eosinophils, but this is rare and usually limited to circumscribed vascular territories. As the lesion progresses, the sub-intimal layer of hyalin increases in thickness and more and more of the media is invaded, both by the homogeneous fibrinoid substance (from within) and by granulomatous cellular infiltrates (from without). Whenever the vascular involvement becomes very severe, the endothelium tends to be shed off and thromboses occur. The latter usually take the form of mural thrombi, but occasionally they occlude the vascular lumen completely. Mural thrombi are likewise quite common in the heart, especially in the right auricle. Here one may also find "ball thrombi" which are free or attached to the wall only at one point. Occasionally, fibrin deposits or even partially organized thrombi are noted in the other cardiac cavities, or on the surface of valves. One of the most common causes of death in animals affected by these lesions is coronary thrombosis.

The pericardium is frequently filled with a large amount of yellowish fluid; less often, there is fibrinous pericarditis.



Hormonally produced cardiac lesions similar to those occurring in diseases of adaptation. — **A.** Myocarditic nodules (Aschoff?) in subendocardial layer of a papillary muscle produced in the rat by DCA and NaCl. Note characteristic eccentric location of the (partially hyalinized) blood-vessel in this nodule. The center of the nodule consists of hyalinized material, in which several giant cells are detectable. — **B.** High magnification of a nodule similar to that shown in Fig. A. Note several, slightly basophilic, polymorphonuclear giant cells (Aschoff cells?) with characteristic fringy cell borders. — **C.** Myocarditic (Aschoff?) nodule produced by DCA overdosage in the rat. Note "caterpillar cells" (arrows). — **D.** Experimental fibrinous pericarditis produced with DCA and NaCl in the dog. The animal died with an enormous amount of pericardial transudate containing excessive quantities of K, Na, Cl and fibrin. The fibrinous coating was rolled down towards the apex (arrow). (After Selye B1204/46.)



Hormonally produced vascular lesions similar to those occurring in diseases of adaptation, in the rat. — **A.** Normal mesenteric vessels in a small intestinal loop. — **B.** Mesenteric periarteritis nodosa. Macroscopic view of a small intestinal loop of a rat chronically treated with DCA. Note numerous bead-like, periarteritic nodules along the mesenteric vessels. — **C.** Mesenteric periarteritis nodosa produced by DCA overdosage. Low magnification of a section through mesenteric insertion on intestinal wall. Note thickening and infiltration of the transversely sectioned mesenteric arteries. — **D.** Mesenteric periarteritis nodosa produced by DCA. Transverse section through mesenteric artery, showing final stages of periarteritis nodosa. Note thick layer of hyalinized fibrin, lining the vascular lumen. The vessel walls have undergone partial necrosis and hence, appear somewhat homogeneous.

(After Selye B1204/46.)

In most of our experiments, treatment was continued until the animal was killed or died spontaneously. However, in a few instances, where treatment was interrupted, we were able to follow the histogenesis of healing in these cardiovascular lesions. Here, the most characteristic changes were the gradually decreasing cellularity of the granuloma and the substitution of the sub-endothelial hyalin deposit by concentric layers of fibroblast and connective tissue fibers. Eventually, the architecture of the outer vascular layers, which had been completely disorganized by the infiltrations, also began to approach normalcy, but the thick layer of sub-endothelial connective tissue persisted for a long time and gave the arteries an aspect typical of endarteritis obliterans. The fibrinous thrombi gradually became organized by invading blood vessels and fibrous tissue. Essentially similar substitution by scar-tissue was noted in the myocardial nodules.

The photographs on pp. 494-496 and 525-528 show how closely the lesions produced in our experimental animals resemble those seen in man suffering from periarteritis nodosa, lupus erythematodes, rheumatic arteritis, allergic arteritis and (during healing) endarteritis obliterans. We should like to point out in this connection that extensive studies of autopsy material from patients who died of the above-mentioned diseases failed to convince us that the actual morphologic lesions in these maladies are essentially different from one another. We are inclined to believe that all these are non-specific reaction forms to injury and that pathologists tend to label the same vascular lesion with the name of one or the other of these diseases, depending upon the extravascular manifestations which happened to dominate the clinical and anatomic picture. Thus a certain lesion is called "rheumatic arteritis" if it occurs in a patient who died of acute rheumatic fever, but this same lesion is labelled "allergic arteritis" if it develops in conjunction with other manifestations of allergy, or "periarteritis nodosa" if there is a tendency to form distinct nodules along the course of the arteries, while it will be referred to as "endarteritis obliterans" if phenomena of healing predominate. That all these are not fundamentally different vascular changes is perhaps best demonstrated by the fact that several of these "diseases" are often found side by side in the same patient. Similarly in experimental animals all these changes can be produced with the same pathogenic agent (e.g., DCA, desoxocortisone), the character of the lesion depending merely upon such incidental factors as: the length and intensity of treatment, diet, heredity, species-predisposition for one or the other type of reaction, etc.[11]

All these experimental cardiovascular changes differ most markedly from the common types of clinical arteriosclerosis and atheromatosis in that the large vessels, and particularly the aorta, are rarely affected and that lipid deposition and calcification of the lesions is quite exceptional in the "hyalinosis syndrome". Further experiments are required however, to show whether these are truly fundamental differences or whether they are also merely due to incidental "conditioning" factors (e.g., species-predisposition, duration of exposure, diet).

Almost nothing is known concerning the nature of the cardiovascular changes characteristic of the **stage of exhaustion.** If the hyalinosis syndrome develops in the stage of resistance it tends to continue into the stage of exhaus-

[11] Selye A62756/43, B1204/46, 94572/47, Dontigny B25570/48, B25568/48.

tion, unless death occurs earlier as a result of some complication (e.g., coronary thrombosis, brain hemorrhage, incidental infections). The only change which is characteristic of the exhaustion stage is the reappearance of the generalized endothelial damage with capillary leakage, similar to that which sometimes (not always) occurs during the shock-phase of the A-R.

In the preceding paragraphs we attempted to give an outline of those cardiovascular lesions which are apparently typical of the three stages of the G-A-S, irrespective of the eliciting agent. The resulting picture is necessarily somewhat onesided since it is based largely on observations in experimental animals (mostly the rat), treated with a few stressors (e.g. protein injections, exposure to cold). As we have said, the cardiovascular changes produced by diverse stressors are essentially similar among themselves; they also resemble those caused by exogenous overdosage with those hormones which we believe to be produced in excess during the G-A-S (e.g., ACTH, corticoids, renal pressor substances and perhaps even adrenergic hormones). However, in spite of this fundamental similarity, there are certain differences in the cardiovascular changes caused by these agents. Now that the fundamental pattern of response has been outlined, we shall be able to appreciate such dissimilarities. While we consider these, it will also be possible to survey many scattered experimental and clinical observations which have not been hitherto considered from the point of view of the G-A-S concept.

Trauma. — After extensive traumatic injuries, the cardiovascular changes correspond quite accurately to those outlined above as characteristic of the shock-phase. In the tissues directly exposed to injury, the vascular damage, and especially the increased capillary permeability, are most pronounced. This, however, is unrelated to systemic stress effects. On the other hand, the changes in parts of the cardiovascular system, which are at a distance from the site of direct injury, are identical with those described above as typical of the shock-phase; hence they need not be discussed here in detail.[12]

It is perhaps worth mentioning, however, that in patients with the syndrome of post-operative alkalosis, hypochloremia and hypopotassemia, certain **electrocardiographic changes** occur. These are characterized by a depression of T-waves, prolongation of the QT-interval, depression of ST-segments, inversion of P-waves, frequent extrasystoles and auriculo-ventricular block. The clinical condition of the patients and the electro-cardiographic anomalies were beneficially influenced by potassium administration. It was concluded that "these results suggest that the pathogenesis of this syndrome in post-operative patients is due to the alarm-reaction, producing hyperfunction of the adrenal cortex, with loss of potassium and chloride (or retention of sodium) in the urine, associated with a low intake of potassium".[13] In this sense, such a syndrome would correspond to the counter-shock rather than to the shock-phase of the A-R. In the dog, the E.C.G. changes produced by traumatic shock were of a different pattern,[13a] perhaps due to differences in K-intake.

On the other hand, "it is now definitely established that a reduction in minute cardiac output and stroke volume is a constant and contributing factor of the shock-syndrome". Furthermore, during tourniquet shock in

[12] Cannon et al. 57880/18, König A32639/32, Mocn **A16304/38**, B19951/48, Page and Abell 84114/43.
[13] Pearson and Eliel B33432/49.
[13a] Jourdan et al. B44315/49.

dogs, x-ray examination reveals an initial decrease in **cardiac size** which was attributed to the loss of circulating blood-volume. Later the heart size increases, however, perhaps because of myocardial ischemia due to diminished blood-flow in which the coronary circuit shares so that the cardiac tone suffers.[14]

Among the **histologic changes in the hearts** of patients who died of traumatic shock, cloudy swelling and fatty degeneration are most conspicuous.[15] In dogs, subendocardial hemorrhages tend to prevail.[15a]

Clinical observations on traumatic and post-operative shock indicate that an initial increase in **blood-pressure** (counter-shock ?) usually precedes the period of hypotension.[16] It is possible that the renal pressor mechanism participates in this response since tourniquet shock in animals opens the *"renal shunt"* and allows the blood to bypass the cortex on its way to the medulla of the kidney.[17] Be this as it may, the initial *vasoconstriction* of the larger arteries, especially in the mesentery and skin, persists into the shock-phase. Indeed this may act somewhat like a tourniquet and thus, through tissue anoxia, favor the development of irreversible shock.[18] The blood-flow in the skin may fall to zero before the development of shock and indeed before the drop in blood-pressure or the tachycardia.[19] These are additional examples of overlapping between shock and counter-shock phenomena.

In various types of traumatic shock there is a greater reduction in circulating red-cells and plasma than can be accounted for by measurable hemorrhage. This has been ascribed to the "trapping" of blood in the **capillaries** throughout the body.[20] The question whether capillary permeability is increased, even at a distance from the site of direct injury has been much debated. Recent observations with dyes show quite clearly, however, that both in experimental animals [21] and in man,[22] capillary leakage at a distance from the injury is not an essential feature of shock, "a marked increase in the rate of dye loss was observed only in cases of burns and abdominal injuries with peritonitis. In these conditions, it will be noted that there is direct damage to extensive areas of the capillary bed and evidence of continued 'weeping' from the injured surfaces".[23]

The **circulation-time** is invariably prolonged in traumatic shock and a progressive delay in the circulation-time is a prognostically very unfavorable sign.[24]

Hemorrhage. — Severe hemorrhage likewise causes pronounced **hypotension** such as is characteristic of the shock-phase.[25] However, this hypotension in itself activates various compensatory mechanisms, such as the renin-angiotonin system.[26] the sympathetic vasoconstrictor nerves,[27] adrenaline secretion [28] and perhaps also the production of VEM by the kidney.[29] All these factors have

[14] Kondo and Katz **88842/45.**
[15] Kalaja B37977/47.
[15a] Jourdan et al. B44315/49.
[16] Schneider 8972/32.
[17] Trueta et al. **99193/47.**
[18] Freeman B314/39, 44351/33, Freeman et al. B27053/36.
[19] Kondo et al. B38556/48.
[20] Gibson et al. **B26950/47.**
[21] Engel and Forrai **B26864/43.**
[22] Noble and Gregersen **93259/46.**
[23] Noble and Gregersen 93259/46.
[24] Wang et al. B3052/46, B38209/47.
[25] Aggazzotti B19554/39, Cannon **B14905/39**, Collins et al. A71604/44.
[26] Collins et al. A71604/44.
[27] Freeman B314/39, Freeman et al. B27052/38, B27053/36, Wiggers et al. B23362/48.
[28] Cannon B14905/39.
[29] Zweifach et al. B19254/48.

already been discussed in the section on hormone metabolism changes during the G-A-S.

It is generally agreed that as a result of such compensatory (counter-shock) mechanisms, hemorrhage causes widespread **vaso-constriction** in various vascular territories. This may produce changes in "pulse contour",[30] a decrease in the blood-flow through the limbs [31] and severe ischemia and blanching of the skin.[32] A similar vasoconstriction is readily demonstrable by direct inspection of the exteriorized mesentery immediately after moderate hemorrhage, for instance, in the dog and cat.[33] The intensity of this vasoconstriction varies of course in the different vascular territories, largely in accordance with the vasomotor response described above as typical of the counter-shock phase. Extensive studies on dogs and rats have shown that after removal of little blood (equivalent to 1-2% of the body weight) the first vascular change is a constriction of the larger arteries (100-300μ), the reaction being more rapid and more intense in the skin than in the splanchnic area. After withdrawal of more blood (2-3% of the body weight) the larger arteries and veins undergo a progressive narrowing to about one half of their original width. The terminal arterioles and muscular venules remain open, however, and the flow through them is not much affected. Only in the case of excessive blood loss (4% of the body weight and more) does circulatory failure develop, despite the great increase of the peripheral vascular reactivity which is so characteristic of severe hemorrhage. Yet, even when the animal dies, the peripheral vessels still retain their irritability and the animals can be saved by re-injecting the blood withdrawn during the experiment (reversible shock). In the case of repeated, graded hemorrhages, however, the initial hyper-reactive "compensatory state" is eventually replaced by a hypo-reactive "decompensatory state" of the peripheral vascular bed. The onset of vascular decompensation is evidenced by a progressive diminution of the reactivity of the terminal arterioles to such pressor stimuli, as for instance, adrenaline. This is accompanied by a slowing of the spontaneous vasoconstrictor rhythm in the terminal arterioles and precapillaries and the vessels remain in a state of partial relaxation. The opening of the precapillary sphincters allows increasingly more blood to be diverted into capillary side-channels, where it is trapped and removed from active circulation. If hypotension is long maintained at or below a certain "critical level", subsequent infusions can no longer save life (irreversible shock).[34]

It is not yet clear why the **circulation time** is not prolonged by hemorrhage as much as by trauma conducive to an equal degree of shock. Perhaps the sympathetic nervous system is not as readily activated by the former as by the latter.[35]

Burns. — The cardiovascular changes produced by extensive burns also follow the previously described pattern characteristic of the A-R with its shock-phase and counter-shock-phase manifestations.[36] It is striking that the very diverse types of acute damage so far considered (traumatic shock, hemorrhage, burns) tends to produce fundamentally similar cardiovascular responses.

[30] Alexander and Webb B40922/47.
[31] Eckstein et al. B38558/46.
[32] Mann B33702/15, Meek and Eyster B33703/21.
[33] Page and Abell 84114/43, Page **B40258/49.**
[34] Chambers B45911/48, Wiggers and Werle B33701/42, Wiggers et al. B23362/48, Zweifach et al. **B19254/48**, 89023/45.
[35] Wang et al. B38209/47.
[36] Abell and Page 84395/43, Harkins **82895/42.**

This is yet another indication that the changes elicited by all these agents are probably due to the only feature they have in common, namely systemic stress, rather than to any of their specific effects.

In man, burns may cause immediate "primary shock", but this is rarely, if ever, the case in animals; perhaps because such experiments are usually performed under anesthesia, which eliminates the immediate action of pain. It may also be of importance that most species of experimental animals appear to be emotionally less affected by a burn than man. In animal experiments, instead of the primary shock with hypotension, an initial, transitory but pronounced rise in **blood-pressure** occurs; [37] the "hypertension en flèche" of the French literature.[38] This is subsequently followed by the usual hypotension of secondary shock. As in the case of traumatic and hemorrhagic shock, this inversion in the normal sequence of events suggests that counter-shock phenomena can precede shock, whenever an initially effective compensatory mechanism gives way later to a secondary breakdown.

Earlier investigators frequently noted intense **capillary** dilatation and leakage as well as the occurrence of petechial hemorrhages and multiple capillary thrombi following extensive surface burns.[39] Special emphasis has been placed upon the frequent occurrence of brain edema in burned animals and man.[40] However, direct observations of the retinal vessels,[41] studies with radioactive tracers,[42] and many other observations [43] suggest that a markedly increased capillary permeability, at a distance from the direct site of injury, is not a constant manifestation of shock caused by burns. The edema and capillary leakage reported by earlier investigators was probably due to excessive transfusions. (Cf. also "Inflammation, Phagocytosis and Capillary permeability".)

On the other hand, it is a rather characteristic feature of burns that they often cause considerable loss of fluid due to direct capillary damage at the site of scalding. It is largely because of this factor that burns tend to produce an extraordinarily marked hemoconcentration and decrease in plasma volume.[44]

In the **heart,** focal necrosis, calcification and even the formation of granulomatous nodules (containing polynuclear giant cells!) has been observed in rabbits.[45] Some authors consider a "serous myocarditis" with valvular edema to be quite characteristic of burns. It is often accompanied by panarteritis at a distance from the directly injured area, e.g., in the kidney.[46] Less prominent degenerative lesions, such as fragmentation of the myocardium have been noted in various species, including man.[47]

Freezing. — Localized exposure to comparatively mild cold causes vasoconstriction especially of the arteries. Upon more intense freezing (chilblains, immersion foot, trench foot), severe degenerative and even inflammatory lesions develop in all vessel wall layers and eventually thrombosis and gangrene may ensue. Fibrinoid degeneration of the arterial walls is likewise common.[48] Upon more chronic exposure, and especially in the course of healing, the lesions

[37] Harkins **82895/42.**
[38] Lambret and Driessens B33765/37.
[39] Harkins **82895/42,** Kabat and Hedin A56063/42, Prinzmetal et al. B37979/48, Simonart 63360/30.
[40] Barac B24076/46, Gibson B33762/45.
[41] Humblet and Barac B24102/46.
[42] Cope and Moore B26912/44.
[43] Harkins **82895/42.**
[44] Harkins **82895/42,** Simonart B33766/37.
[45] Fain 75452/39, Harkins 82895/42.
[46] Eppinger B37085/49, Zinck B37654/40.
[47] Buis and Hartman A36295/41, Zinck B33767/38, B33768/40.
[48] Hueper **91730/45.**

simulate the picture of "endarteritis obliterans".[49] The fact that such a non-specific local stimulus as freezing causes vascular lesions of this type strongly supports our view that hyalinosis and endarteritis obliterans are non-specific responses of the vessel wall. Hence, we have no valid reason to attribute such changes to the action of some hypothetical, specific pathogen when they happen to be produced by some systematically acting agent (exposure of the whole body to cold, the "endocrine kidney", or injection of LAP, DCA, desoxocortisone, etc.). They are what we designated as typical "non-specific changes" (cf. Definition, p. 7) and various agents causing a derangement in the nutrition of the vessel walls may elicit them. The only "specific" feature about their production by DCA, LAP, the "endocrine kidney" or non-specific stress is that all these agents are rather selectively "vasotropic" inasmuch as they tend to damage the vessels more than other tissues.

Temperature variations. — Exposure to much **heat** — especially if conducive to "heat stroke" — tends to produce focal myocardial degeneration, multiple purpuric hemorrhages especially in the brain, lung and gastrointestinal tract, simultaneously with other typical manifestations of the A-R. Most of the cardiovascular changes caused by exposure to heat are probably manifestations of the G-A-S. However the edema, hyperemia and hemorrhages in the brain are much more common and intense after exposure to heat than in other stress situations; hence they may be regarded as somewhat specific of this particular stimulus.[50]

Exposure to **cold** regularly causes typical G-A-S changes in the cardiovascular system. Indeed, this stimulus proved to be so effective in this respect that it is routinely used in a great variety of investigations as a type of stressor especially suitable for the study of the G-A-S and its diseases.

Exposure to even moderate chilling greatly accelerates the *heart rate* in the rat. This is not merely due to incidental muscular hyperactivity since it is also obvious in quietly resting animals.[51]

The so-called *"cold pressor test"* is based upon the observation that brief immersion of a hand in ice-water causes a rise in systolic blood-pressure often accompanied by various manifestations of vasospasm.[52] The response varies considerably even among normal individuals, but hyperreactors are believed to possess a hypersensitive vasomotor system, which renders them especially liable to the subsequent development of essential hypertension. A rise of 22 mm. Hg. in non-pregnant or of 29 mm. Hg. in pregnant individuals is considered to be the upper limit of the normal. Indirect evidence suggests that vasospasm within the kidney is particularly pronounced during the "cold pressor test".[53]

In shipwrecked mariners who suffered prolonged immersion in cold seawater, the blood-pressure tends to be high and they exhibit an increased vasomotor response as gauged by the cold pressor test. Since exposure to cold is known to produce constriction of the renal vessels, it was assumed that such reactions may play a part in this type of vascular hyperirritability.[54]

[49] Staemmler B29879/44, Vagliano B29862/47.
[50] Gore and Isaacson B41903/49, Haymaker et al. B37920/47, Malamud et al. **B18019/46**, Moon B19951/48.
[51] Moses B26384/46.
[52] Dieckman et al. B33770/38, Hines B33769/39, Odel B33771/43, Wolfe and Hardy B33772/41.
[53] Odell and Aragon **B26603/47**.
[54] Garai B33780/45.

Continuous exposure to cold was found to be a particularly effective type of stress for the production of **persistent hypertension,** nephrosclerosis, cardiac hypertrophy and cardiovascular **hyalinosis** in the rat, especially under certain conditions of sensitization which will be discussed below.[55] During the A-R stage of a G-A-S elicited by cold, the **weight of the heart** shows no significant change; unlike most other organs, presumably the cardiac muscle is very resistant to the factors which cause tissue breakdown at the time of the "catabolic phase".[56]

Ionizing radiations. — The cardiovascular changes produced by exposure to ionizing radiations differ from those elicited by the previously mentioned acute stressors (trauma, hemorrhage, burns, cold) in that they develop more slowly and that endothelial damage is especially prominent. The toxic effects of ionizing rays (e.g., x-rays) become fully manifest only after a certain latency period; hence acute shock and counter-shock phenomena, such as sudden variations in blood-pressure, are not prone to develop. The prominence of **endothelial damage** (leakage of capillaries, petechial hemorrhages, etc.) is presumably due to the direct effect of rays upon tissues, since such manifestations are rarely seen at a distance from the site of injury.[57] Only in the event of extremely intense x-irradiation does marked hypotension and death occur immediately.[58]

Observations at the Bikini atomic bomb test showed that the hemorrhagic syndrome is increasingly more readily produced in the rat, goat, pig and guinea-pig, in this order.[58a]

Capillary dilatation is a constant finding in acute irradiation injury and results in the well-known erythema within 10 to 20 days. This may be accompanied by swelling of capillary endothelia, stasis and extravasation of blood. Preterminally, multiple subcutaneous and internal petechial hemorrhages are very characteristic in all species and sometimes massive hemorrhages occur, especially in the gastrointestinal tract, the lymph nodes, the heart and the skin. Prior to death, the heart-rate tends to increase, for instance in the dog, as much as 50%. There may also be **electrocardiographic changes** such as a reversal of the P-wave.[59] Essentially similar changes have been seen in animals and man exposed to the effects of the atomic bomb.[60]

Allegedly the hemorrhagic syndrome caused by acute ionizing radiations in the dog is favorably influenced by rutin and other flavonoids of the "vitamin-P" group,[61] but this has not been confirmed in the mouse.[62]

Electric injury. — The important cardiovascular changes which occur during electro-shock therapy are rather similar to those seen during other types of acute stress. There is a pronounced initial rise in blood-pressure and this is followed by hypotension only if the patient responds poorly. Sometimes there are also severe electrocardiographic changes.[63]

Experimental observations on rats revealed that periarteritic lesions and cardiac infarcts are rather regularly produced by repeated stimulation with the faradic current in a specially constructed cage.[64]

[55] Gilson B47691/50, Selye B17771/48, A62756/43.
[56] Leduc and Guillemin B27410/49.
[57] Graham A63324/43.
[58] Prosser et al. B26618/47.
[58a] Tullis and Warren B41776/47.
[59] Prosser B26618/47.
[60] Anonymous B26330/48, B28192/48, Tullis B27010/48.
[61] Field and Rekers B37300/49, Rekers and Field B33764/48.
[62] Cronkite et al. B31726/49.
[63] Delmas-Marsalet **B26881/46**.
[64] Hirsch B33742/49, Hirsch and Zylberszac B4973/47.

Nervous stimuli. — It has long been known that nervous and emotional stimuli exert very powerful influences upon the cardiovascular system. The relevant literature has become so voluminous that we shall have to limit ourselves to a few observations which are of particular interest in connection with the G-A-S concept. Such a limitation of our scope will hardly be felt as a loss, since the problem of neurogenic hypertension has been very adequately outlined in several excellent monographs.[65] Some of the most important nervous mechanisms which regulate the course of the cardiovascular response to systemic stress will be discussed below (cf. Stimuli Influencing the Cardiovascular G-A-S Response p. 552). Here, we shall merely consider some representative observations illustrating the type of cardiovascular change which is presumably due to the non-specific systemic stressor effect of nervous and emotional stimuli.

Under the influence of **emotional excitement,** such as fear or anger, the heart rate rapidly increases. This response is not prevented by denervation of the heart; indeed, due to removal of vagal inhibition it is augmented. This tachycardia is presumably mediated through the liberation of adrenergic hormones. Simultaneously, emotional excitement elicits that typical vasomotor response which we described above as characteristic of the counter-shock phase.[66] Such vasomotor reactions have long been considered to result from increased muscular activity, but it was found that the mere thought of taking exercise leads to the shrinking of the abdominal viscera and the expansion of the limbs,[67] while the arterial pressure rises.[68] On the other hand, the volume-flow of blood through the hand is markedly reduced by fear or pain.[69] These observations are not necessarily contradictory. As previously stated, the vasomotor response during the counter-shock phase is characterized by dilatation of muscle and constriction of skin vessels. Presumably in the limb as a whole the muscle vessels, while in the hand, the skin vessels play the predominant rôle.

Until quite recently, it was rather unanimously agreed that the tachycardia, hypertension, and the vasomotor response characteristic of the counter-shock phase are mainly due to the liberation of *adrenaline* and to the direct effect of sympathetic nerves upon the cardiovascular system. A simultaneous diminution in the *vagal tonus* presumably sensitizes the vascular system to such effects of adrenergic stimuli.[70]

The *renal pressor mechanism* may also be involved since stimulation of the "pressor area of the cerebral cortex increases limb volume but diminishes kidney volume during the resulting pressor response in cats and monkeys".[71] Subsequent experiments in cats, confirmed the occurrence of a pronounced renal vasoconstriction as evidenced by virtual exclusion of intra-arterially injected India ink from the renal-cortical vascular bed. Here the best vasopressor responses were obtained by electrical stimulation of foci on the gyrus proreus, gyrus sigmoideus. It was concluded that "possibly certain abnormal cerebral activity in man may result in persistent or recurrent cortical ischemia, and this mechanism may lie at the basis of essential hypertension".[72]

[65] Delrieu **78582/39**, Dexter **91416/46**, Grimson **B33775/41**, Heymans **75530/38**, **B33776/38**, Heymans and Bouckaert **89592/39**, Heymans et al. **A2429/33**.
[66] Cannon B14905/39. A19828/29.
[67] Weber B33777/06. B33781/07.
[68] Cannon B14905/39.
[69] Freeman et al. B27053/36.
[70] Cannon B14905/39.
[71] Green and Hoff B33778/37.
[72] Hoff et al. B32772/49.

Trueta et al.[73] suggested that under the influence of nervous stimuli (as it is during tourniquet shock) the vascular pattern of the kidney is so rearranged that blood is shunted away from the cortex, through the medulla. This renal vessel response is similar to that obtained in the "endocrine kidney" operation and may well cause hypertension through the activation of the renal pressor mechanism.

Even persistent hypertension can be produced experimentally by constant nervous irritation (e.g., audiogenic stimulation by air blasting), especially in the "emotional gray Norway rat" and particularly in the emotional animals.[74] It was concluded "that an auditory stimulus applied over a prolonged period of time may produce an increase in the systolic and diastolic pressure of the rat".[75] In guinea-pigs, audiogenic stimulation elecits rather characteristic vasomotor responses in the capillary bed of the mesenteric serosa.[76]

Repeated emotional stimuli (irritation with an electric current) can allegedly even produce periarteritis and cardiac infarcts in the rat. This was considered indicative of the importance of similar etiologic factors in the production of angina in man.[77] Many other experimental and clinical observations suggest that nervous strain can cause arteriosclerotic lesions.[78]

Clinical observations in man also brought forth a good deal of evidence that "situations provocative of frustration and anger" raise the blood-pressure, while they diminish renal blood-flow.[79] These responses have been correlated with the G-A-S and were mentioned in support of the view that hypertension can be a disease of adaptation due to a psychosomatic derailment.[80] This interpretation received additional support from systematic investigations on 695 men from an Armoured Brigade who had experienced at least a year of desert warfare. Among these, 27% proved to have a symptomless hypertension at rest and in most cases the blood-pressure remained high even after two months of freedom from battle anxieties.[81] Here we are clearly dealing with a rather persistent blood-pressure elevation caused by emotional stress.

These observations, and the findings concerning the production of hypertension by mineralo-corticoids, suggest that nervous and emotional stress can raise the blood-pressure through various essentially different mechanisms and particularly through the liberation of adrenaline, sympathin, renal pressor substances, and mineralo-corticoids.

The acute hypertension caused by **cerebral ischemia** is not abolished after elimination of the carotid sinus reflexes. It is allegedly due to a cerebral pressoreceptor response.[82]

The often very intense hypertension produced by **transection of the depressor nerves** fails to cause any severe morphologic changes in the cardiovascular system. Even after the blood-pressure had been elevated for months or years, some hypertrophy and fibrosis of the heart and arteries is usually the only detectable change.[83] Indirect evidence suggests that the blood-pressure regula-

[73] **99193/47.**
[74] Farris et al. B1132/45, McCann et al. B31793/48, Medoff and Bongiovanni 91713/45, Yeakel et al. B29450/48.
[75] Yeakel et al. B29450/48.
[76] Lee B39071/49.
[77] Hirsch B33742/49, Hirsch and Zylberszac B4973/47.
[78] Hueper **91730/45.**
[79] Pfeiffer et al. B33779/47.
[80] Wolf B26123/48.
[81] Graham B2425/45.
[82] Guyton B23020/48, Rodbard B45939/49.
[83] Heymans B37954/47, Heymans et al. A2429/33.

tion by carotid sinus reflexes is not mediated through adrenergic substances or renin.[84]

Muscular exercise. — Fatigue is also particularly capable of producing rapid and intense counter-shock manifestations such as intense **tachycardia** with a great increase in the stroke volume. In man, heavy muscular exercise may raise the pulse rate from 70 to 140 per minute within a very short time.[85] This is not only due to adrenergic stimulation, but also to the fact that the normal tonic, inhibitory vagal stimuli are suppressed during exercise. Simultaneously, there is a pronounced increase in arterial **blood-pressure** accompanied by that particular change in the tonus of different vascular territories which we previously described as characteristic of counter-shock. There is dilatation of **arterioles and capillaries** in the active muscle, while the splanchnic vessels contract.[86] This response is not entirely a systemic one since vasodilatation occurs selectively in active muscles and not to an equal degree in others. Thus, in comparing an inactive muscle with its active counterpart on the other side, it was found that during work, the number of open capillaries may be 40 to 100 times as great as in the muscle at rest.[87]

As with other types of stress the **renal plasma-flow** is diminished during the pressor response to exercise in man,[88] but it has not yet been shown whether this contributes to the formation of R.P.S.

In the case of often repeated exercise, the acceleration of the pulse rate during each muscular effort becomes progressively less pronounced, as a result of **adaptation,** both in man [89] and in experimental animals, for instance, in the rat.[90] Trained athletes usually even exhibit some bradycardia during rest perhaps due to increased vagus tonus as a result of overcompensation.

It is well known, furthermore, that muscular activity is a strong stimulus for the development of **cardiac hypertrophy.** This has also been noted both in athletes [91] and in animals, e.g., the rat,[92] which is a species frequently used in pertinent experiments.

Allegedly **arteriosclerosis,** especially of the coronary arteries, thromboses in various vessels, and even typical rheumatic-fever-like changes may be precipitated by muscular effort among athletes.[93] It has been claimed that in rats cardiac **infarcts** can be produced at will by overexertion.[94] If rabbits are forced to run in a treadmill, the papillary muscles and the ventricular septum of the heart often show foci of **hyalinization,** or even necrosis. This change has been ascribed to local anoxemia since it is produced with particular ease by exercise after hemorrhage.[95] It must be pointed out, however, that although muscular exercise is especially effective in raising the blood-pressure — and of course represents considerable excess work for the heart — we found it less effective in producing cardiovascular hyalinosis in the rat (especially sensitized by partial nephrectomy and high sodium intake) than other alarming agents, for instance, exposure to cold.[96] In other words, we

[84] Bein B37510/47.
[85] Cannon B14905/39, Michailesco and Alexiu A15436/38.
[86] Cannon B14905/39, Heymans 89593/39, Lee B39071/49, Liljestrand B37509/48.
[87] Krogh 39493/29.
[88] Chapman et al. **B24881/48.**
[89] Michailesco and Alexiu A15436/38.
[90] Moses B26384/46.
[91] Jokl B19917/47.
[92] Hatai A10936/15, Korényi A35132/39.
[93] Jokl B19917/47.
[94] Hirsch and Zylberszac B4973/47.
[95] Buechner B33773/33, Buechner and Lucadou B33774/34.
[96] Selye A62756/43.

note that at least under the conditions of our experiments, muscular exercise — though an active alarming stimulus (as judged by the production of acute thymus involution, adrenal-cortical enlargement, gastric ulcers, etc.) is not particularly conducive to derailments of the G-A-S with generalized hyalinosis. Perhaps muscular exertion is more conducive to the overproduction of glucocorticoids than of the vasotoxic mineralo-corticoids. It is also possible that changes in the intermediate metabolism incident to physical exertion tend to antagonize the toxicity of mineralo-corticoids somewhat like Na deficiency does.

Anoxia. — Acute anoxia causes tachycardia, an increase in blood-pressure and other vasomotor phenomena typical of the counter-shock phase. However, under conditions of chronic, continuous or interrupted oxygen-want, adaptation occurs and all these phenomena tend to disappear. This has been observed in various animal species as well as in man exposed to reduced atmospheric pressure or breathing oxygen-poor air under normal pressure.[97]

Allegedly, acute anoxia "shunts" the renal blood-flow toward the medulla and renders the cortex ischemic in the normal rabbit, but not after denervation of the kidney.[98]

In dogs exposed to acute anoxia, cardiac edema and hemorrhages tend to occur, presumably as a result of capillary damage.[99]

The acute hemorrhagic lung edema produced by acute severe anoxia in experimental animals will be discussed below (cf. Lung). Only very severe anoxia causes a generalized increase in capillary permeability.[100]

Diseases. — Hypotension and focal myocardial necroses,[101] as well as generalized endothelial damage with serous effusions, ecchymoses, edema and hemoconcentration [102] are often caused by *various severe infections.* These are manifestly non-specific lesions and resemble those produced by other alarming stimuli (e.g., traumatic injuries, burns, intoxications). The very concept of "serious inflammation" (cf. p. 24) was based upon the observation that vascular damage, with the accompanying tendency to produce serous transudates, is observed in a number of apparently unrelated infections and that essentially similar changes can be reproduced in animals by compounds isolated from pus (e.g., allylamine).[103] Hence the production of these changes does not appear to depend upon any specific substance elaborated by a certain microörganism, but rather upon the intensity and duration of the resulting systemic stress. Myocardial necrosis, myocarditis, endarteritis, panarteritis, hyalin necrosis of arterial walls, multiple thromboses, sub-endocardial hemorrhages, generalized capillary damage and hypotension, are clear-cut examples of this kind of lesion, which often occur in the "malignant" or "toxic" types of *diphtheria.*[104] Essentially similar cardiovascular changes have been noted (in combination with other manifestations of the G-A-S) after *streptococcus infection,*[105] in *spotted fever,*[106] *tick typhus* or *"rocky mountain spotted*

[97] Freeman et al. B27053/36, van Liere **B26199/42,** Liljestrand B37509/48, Markwalder and Starling A2059/14, van Middlesworth B29440/48, Scano B37538/47, Stacy et al. B25994/48.
[98] Franklin et al. B37737/49.
[99] Gale et al. B37571/48.
[100] Henri et al. B37513/47.
[101] Meessen B23957/47.
[102] Brown B45581/47, Moon A33122/39.
[103] Eppinger **B37085/49,** Eppinger et al. B26941/34.
[104] Gore B38112/48, Kienle **B31236/47.**
[105] Jaffe and Holtz B38049/48, Kesareva B37570/48.
[106] Wajnapel B31243/47.

fever",[107] *typhus*,[108] *paratyphoid* [109] and *measles*.[110] (Cf. also, myocarditis, Waterhouse-Friderichsen etc., under "Cardio-vascular Diseases of Adaptation", p. 558 ff.)

In rabbits which became very ill following successive skin infections with several types of "group A" streptococci, there developed cardiac lesions resembling those of rheumatic fever. It is perhaps significant that in these animals the adrenal-cortex was extremely large.[111] The essential similarity of the cardiac lesions caused by various pathogens should not be overlooked. Yet, they are not equal in degree and quality, hence these changes can not be due solely to the G-A-S. Presumably conditioning factors also play an important rôle in their pathogenesis.

Serologic reactions. — It had long been noted that anaphylactic shock in the dog is accompanied by a marked **hypotension** similar to that seen in traumatic shock. This fall in blood-pressure remains almost entirely unaffected by splanchnic stimulation or the injection of adrenaline, hence it was ascribed to a "paralysis of the peripheral vasomotor mechanism".[112]

Additional observations on animals and man revealed that various types of *sera, foreign proteins, bacterial toxins, sulfonamides* and other compounds capable of producing "hypersensitivity reactions" can cause an "allergic myocarditis and panarteritis". Such lesions in the cardiovascular system, are remarkably similar to the **"hyalinosis"** or rheumatic-like changes and periarteritis nodosa elicited by the "endocrine kidney", DCA, desoxocortisone or LAP.[113]

Drugs. — Various drugs likewise cause cardiovascular damage of a non-specific nature. Those substances which cause **"hypersensitivity reactions"** have already been discussed in the preceding paragraph. Many others (e.g., **snake venoms, quinine**) appear to exert a similar toxic effect upon the endothelium and thus increase capillary permeability.[114]

The so-called **menstrual toxin** (an atypical globulin found in the endometrial debris discharged at menstruation) elicits a typical A-R if administered parenterally in experimental animals. At the same time ' edema, hemorrhage and necrosis, such as occur in the menstruating endometrium, characterize the local and systemic reactions".[115]

Various **bacterial toxins** (e.g., typhoid endotoxin) cause vasomotor reactions in the rabbit which closely resemble those of anaphylactoid or traumatic

[107] Harrell B2189/47, Harrell et al. B24806/44, B24807/45, Kelsey and Harrell B24821/48, Lillie B33782/41.
[108] Golden B28034/45.
[109] Eppinger et al. B26941/34.
[110] Macciotta 90290/31.
[111] Murphy and Swift B37498/49.
[112] Biedl and Kraus 50209/09.
[113] Betz B26164/48, Bras and Lie Kian B37897/48, Cavelti B4227/47, B38103/48, Delaunay et al. B39216/49, Ehrich et al. B37492/48, Eppinger **B37085/49**, Fashena et al. B37975/48, Griep and Mayer B38223/49, Hamilton et al. B47285/50, Jaffe and Holtz B38049/48, B46361/48, B46042/49, Kerr and Cavelti **B23078/47**, Kesareva B37570/48, Klinge B33784/33, Lucherini and Pala B33489/48, McKeown B38104/47, McLean and More B39074/49, More and McLean **B38772/49**, Rich A61362/42, A61361/42, **B41723/47**, Rich and Gregory B526/44, **A71373/43**, B7063/43, **84496/43**, B41772/47, van Rijssel and Meyler B40122/48, Sullivan et al. B27058/48.
[114] Haden et al. B19260/48.
[115] Smith and Smith 92761/46.

shock.[116] This response is not inhibited by sympathectomy and is accompanied by loss of adrenal chromaffinity, hence it has been ascribed to an adrenaline discharge, such as occurs in the A-R.[117]

We have already mentioned that **allylamine** has allegedly been prepared from certain types of pus.[118] Furthermore "the intracutaneous injection of allylamine in the rabbit leads to a necrotizing arteriolitis strikingly similar to that conventionally present in certain human infections (the streptococcoses especially), which have prominently, in their background, the phenomena of hypersensitiveness".[119] Following repeated injections of allylamine, hyalinizing coronary artery necrosis occurs in dogs. Since this response is not inhibited by nephrectomy, it can hardly be attributed to the secondary liberation of R.P.S.[120] Allylamine, or similar substances, may arise as cleavage products of protein during intense catabolic reactions and hence they could play a rôle in the pathogenesis of hyalinosis, but this possibility has not yet been adequately investigated.

Many other vasopressor and vasotoxic drugs produce more or less typical arteriosclerotic lesions in animals. Among these, **ergot, lead, barium, calciferol, nicotine, S-methylisothiourea** and certain adrenaline derivatives such as **ephedrine** and **tyrosine** have received particular attention.[121] Most of these drugs obviously have direct vasotropic effects. It remains to be shown, however, whether some of the cardiovascular lesions which they produce are not also, at least partly, mediated through the production of endogenous substances.

Prolonged administration of **cholesterol** produces an atheromatous type of arteriosclerosis in various experimental animals, especially readily in the rabbit [122] (cf. Diet, p. 511). Essentially similar lesions have been seen after intravenous administration of diverse **macromolecular substances** (e.g., polyvinyl alcohol, methyl cellulose, pectin acacia). All these compounds display distinct film-forming properties and allegedly coat the surface of erythrocytes, thus interfering with the speed of oxygenation. "Their introduction into the blood elicits the hematic macromolecular syndrome, which includes increased sedimentation and pseudo-agglutination of the erythrocytes and colloidoclastic leucopenia, as well as reticulo-endothelial and parenchymatous thesauroses, similar to those produced by cholesterol and other lipoids".[123] Here again we are probably dealing with direct actions of the foreign substances and not merely with secondary manifestations of the G-A-S which they produce. It may be fruitful to consider the possibility, however, that endogenous macromolecular substances, similar to those mentioned above, might be involved in the pathogenesis of the cardiovascular lesions produced by exposure to stress.

The effects of **sodium chloride** overdosage deserve special attention, since Na salts accentuate the cardiovascular damage caused by exposure to stress or injection with LAP or DCA.[124] Most animals tolerate comparatively large doses of NaCl, but in the chick, pronounced nephrosclerosis and cardiovascular damage was produced by the mere expedient of giving an excess of NaCl in

[116] Boquet and Lehoult B24114/48, Delaunay et al. B38020/47, B39216/49.
[117] Boquet et al. B24109/48.
[118] Eppinger et al. B26941/34, **B37085/49**.
[119] Mellon et al. B26940/35.
[120] Waters B26939/48, Waters and McAllister B28162/48.
[121] Hueper **91730/45**.
[122] Hueper 91730/45.
[123] Hueper **91730/45**.
[124] Selye and Stone A56585/43.

the drinking water. This also led to pronounced cardiac hypertrophy and typical nephrosclerosis.[125] Mammals are much more resistant to Na-intoxication. However, in dogs in which hypertonic (25%) NaCl was injected subcutaneously, pronounced cardiovascular damage was noted during the resulting "dehydration shock". There were sub-epicardial, sub-endocardial and sub-pleural hemorrhages, with some leucocytic infiltration in their surroundings, pronounced dilatation of the cardiac capillaries, lung edema and intense congestion of the stomach and brain.[126] It would hardly be permissible to ascribe all these lesions to the toxicity of Na as such, since a comparable degree of dehydration by other means may well be conducive to a similar syndrome.

Although mammals are rather resistant to the hypertensive action of sodium, rats given hypertonic NaCl (1.5% or 2%) as a drinking fluid, gradually develop a slight degree of hypertension accompanied by a modest increase in the relative weight of the heart and kidney. Allegedly, this type of hypertension is not prevented by adrenalectomy.[126a] Perhaps it is due to an increase in blood-volume, but this possibility has not yet been examined.

Diet. — Some of the dietary factors which can produce G-A-S lesions in the cardiovascular system have already been described in the section on drugs, others will be considered in "Stimuli Influencing the Cardiovascular System", p. 554 ff.

Suffice it to state here that **starvation** is a particularly effective alarming stimulus and as such, it should also produce non-specific cardiovascular changes. However, even complete starvation acts too slowly to produce acute shock phenomena. Prolonged (complete or partial) withdrawal of food, on the other hand, does not cause hypertension or arteriosclerosis, perhaps because inanition notoriously exerts a rather specific antihypertensive effect,[127] tending to prevent the development of arteriosclerotic lesions. In a sense this is a negative "conditioning" or "deconditioning" of the stress effect upon this target.

It is probably because of these factors that inanition fails to cause typical G-A-S responses or "diseases of adaptation" in the cardiovascular system, although it is most effective in eliciting other manifestations of this syndrome, such as: thymus involution, loss of adrenal lipids, protein catabolism, etc. Indeed, during the second World War, among the undernourished populations of Belgium,[128] Soviet Russia [129] and German concentration camps [130] there was a definite tendency towards hypotension and bradycardia, while the incidence of hypertensive disease was extraordinarily low. Atrophy of the myocardium, often accompanied by brown ("wear-and-tear") pigmentation or fatty degeneration of the heart were comparatively common. Only in a few instances were the signs of myocarditis, myocardial fibrosis, thrombophlebitis or E.C.G. changes characteristic of diffuse myocardial damage among the very severely undernourished, but since the resistance of these patients was very low, it is somewhat difficult to determine whether the cardiovascular lesions were due to starvation as such or to complicating infections.[131]

[125] Selye A56426/43.
[126] Davis A37428/41.
[126a] Sapirstein et al. B46262/50.
[127] Brozek et al. **B37858/48.**
[128] Brull and Lambrechts B26140/45.
[129] Anonymous B27051/44, B27050/43, Brozek et al. B23241/46.
[130] Gsell B27611/48, Overzier B45391/48, Uehlinger B27612/48.
[131] Eggers B46650/49, Gömöri et al. B37886/47, Gsell B27611/48, Uehlinger B27612/48.

While during starvation the blood-pressure tends to fall, even in normal individuals, it frequently rises well above the upper limit of normal during recovery. Particularly striking are the descriptions of a veritable "epidemic of hypertension and hypertensive cardiovascular disease" which occurred after the lifting of the Siege of Leningrad in 1943.[132] Perhaps this is due to sudden withdrawal of the "deconditioning" effect of malnutrition.

Several investigators found that the acute renal damage caused by **choline** deficiency in the rat is unaccompanied by hypertension.[133] It is of especial interest however, that if rats are fed a choline-deficient diet during six days at ages of three to four weeks and are then placed on a normal diet, they eventually develop marked hyalinosis and hypertension, similar to that elicited by mineralo-corticoids. Thus a temporary nutritional defect early in life may result in hypertensive disease much later. It has been suggested that the fibrotic organization of capsular and sub-capsular hemorrhages could eventually so compress the kidney that a renal hypertension (similar to that caused by cellophane or silk perinephritis) would result.[134] As we shall see later, cholesterol-atheromatosis is inhibited by choline so that this food constituent certainly exerts an important effect upon the development of cardiovascular changes similar to those seen during the diseases of adaptation.

Cholesterol feeding undoubtedly causes atheromatous arteriosclerotic lesions — especially in certain predisposed species, such as the rabbit and fowl.[135] Golden hamsters and guinea-pigs are less sensitive, while rats, gophers and most other experimental animals are even more resistant to this action of cholesterol.[136]

The underlying pathogenic mechanism is still poorly understood. Allegedly, in the cholesterol-fed rabbit, the phagocytes of the liver and adrenals become loaded with cholesterol esters and these cells are then discharged as such into the circulating blood. Such *storage cells* " ... having entered the blood stream, pass through the lung filter and selectively invade the arterial intima. This invasion is favored by stresses, but is apparently dependent on a positive chemotaxis of the arterial wall for cells carrying cholesterol esters". ... "Stresses determine the localization of lesions and influence the degree of the sclerotic processes".[137] Here, the word stress was used in the sense of a local strain upon the vessel wall, but probably the blood-pressure variations occasioned by systemic stress could also act as predisposing factors, if we accept the above theory. Other observations on the rabbit also suggest that "a relationship between cholesterol deposition and areas of probable turbulent blood flow is indicated".[138] However, histochemical studies of the arterial walls, during different stages of atheroma development, failed to support the phagocytic-invasion theory. They led to the assumption that the lipid-storing "foam cells" arise locally in the arteries of cholesterol fed rabbits and that proliferation of fibroblasts and collagenous elements occurs after initiation of the lesions.[139]

In the chick, cholesterol feeding likewise causes pronounced and extensive atherosclerosis of the aorta and other great vessels, especially if this sterol is

[132] Brozek et al. B37858/48.
[133] Sobin and Landis B37533/47.
[134] Best and Hartroft **B43574/49.**
[135] Dexter 01416/46, Hueper 91730/45, Leary B44516/49.
[136] Altschul B28173/48, Dragstedt B34232/45, Goldman B46712/50.
[137] Leary B30226/41.
[138] Taylor and Stewart B33114/48.
[139] Kuntz and Sulkin B42310/49, Sulkin B33030/49.

given in oil. Observations on chicks suggested that the major factors which influence the development of the atheromata are the degree of hypercholesterolemia, a disturbance in the ratio of plasma-lipid fractions, and the ability of tissues to esterify cholesterol. The absolute value of the blood-cholesterol is perhaps least important.[140]

The degree of atherosclerosis produced by cholesterol, under given experimental conditions, in the rabbit, shows a high net correlation with the gain in body weight.[140] Emaciation may therefore be the chief factor in the inhibition of this type of arteriosclerosis by various supposedly specific agents.

Simultaneous feeding of *"lipocaic", choline* or *inositol* tends to prevent atherosclerosis in the rabbit [141] and chick [142] although such "lipotropic factors" increase the hyper-cholesterolemia that develops on standard high-cholesterol diets. Furthermore, in rabbits fed a high-cholesterol diet and simultaneously given intravenous injections of a detergent ("Tween 80"), the latter aggravated the hyper-cholesterolemia [143] and inhibited the development of atherosclerosis. In the animals receiving the detergent, the blood phospholipid-level was as high, indeed higher, than the corresponding cholesterol-level, while in the controls the former reached only about half the level of the latter. This led to the suspicion that the *cholesterol:phospholipid* ratio is an important factor in experimental atherosclerosis and that phospholipids may inhibit the development of this type of atherosclerosis.[144]

Unlike cholesterol, the related **stigmasterol** does not cause atheromatous lesions in the rabbit.[145]

Overdosage with **vitamin D_2** or **irradiated ergosterol** produces pronounced "metastatic calcification" in the rat, with the deposition of calcium salts in the subintimal layers of the arteries, the cardiac muscle, the kidney and many other organs.[146] Similar observations have been made on various other species, although not all are equally sensitive to this effect. Such calcification may or may not be accompanied by a rise in blood-pressure.[147]

This change is somewhat reminiscent of the metastatic calcification produced by high calcium diets as well as by food predisposing to **acidosis.**[148] In the former case, the fed calcium itself, in the latter, the salts liberated from the skeleton are responsible for a flooding of the organism with calcium and the tendency of it to precipitate in soft tissues, especially in blood-vessels.[149] Vitamin-D overdosage (and incidentally, also parathyroid hormone intoxication) probably acts through a very similar mechanism since here again calcium is liberated from the bones. **Phosphate**-rich diets cause calcinosis because the resulting hyperphosphatemia precipitates even normal amounts of blood-calcium in the form of highly insoluble calcium salts.[150]

Various other vitamin deficiencies have been shown to exert a more or less specific effect upon the cardiovascular system. For instance in **vitamin-C**-deficient guinea-pigs, carditis and valvular lesions arise much more readily than in normal controls, after infection with a hemolytic streptococcus.[151]

[140] Paterson et al. B41804/48, Stamler et al. B33112/48.
[140a] Firstbrook B44610/50.
[141] Dragstedt **B34232/45**, Morrison and Rossi B28170/48, B28278/48, B28171/48, Morrison B37802/49, Steiner B41803/48.
[142] Bolene et al. B32711/49.
[143] Kellner et al. B37986/48.
[144] Ladd et al. B32952/49.
[145] Altschul B28173/48.
[146] Selye **1270/29.**
[147] Briskin et al. A56871/43, Dexter **91416/46**, Hueper **91730/45.**
[148] Rabl 827/24.
[149] Hueper **91730/45.**
[150] Rabl 827/24.

The cardiovascular lesions produced by **vitamin-E** deficiency in experimental animals [152] have assumed some interest in connection with the diseases of adaptation when it was claimed that vitamin E administration may have beneficial effects in patients with cardiovascular disease.[153] However, on the whole, systematic re-investigation of this field failed to confirm these claims.[154] It has even been reported that high doses of a vitamin-E concentrate produce an atherosclerosis, in the rat, which can be prevented by cholesterol feeding.[154a]

Rhesus monkeys maintained for six months or longer on a **pyridoxine**-deficient diet develop arteriosclerotic lesions "with surprising similarity to those seen in man". Allegedly this is due to the disturbance in protein metabolism which results from pyridoxine deficiency.[155] Since pyridoxine is also involved in cholesterol metabolism, such lesions may be related to the atheromatous changes produced by cholesterol feeding.

The effect of various **electrolytes** upon the cardiovascular system has already been discussed in connection with drug actions. Let us merely emphasize here that the well known cardiac and skeletal muscle changes caused by *potassium*-deficiency [155a] are qualitatively different from those produced by mineralo-corticoids or R.P.S. This is noteworthy since the lesions induced by DCA have often been ascribed to the resulting hypokalemia. However, as we have stated elsewhere, the endocrine kidney produces similar lesions without depressing the blood-K level and the changes caused by DCA are not prevented by the feeding of excess potassium.

Stimuli Influencing the Cardiovascular System During the G-A-S

Hypophysis. — **Hypophysectomy** tends to diminish the resting blood-pressure somewhat, but it rarely produces as pronounced a hypotension as adrenalectomy. From this it was concluded that some cortical activity persists even in the absence of ACTH. The acute pressor responses to stress which are mediated by adrenaline liberation, are not prevented by hypophysectomy since the secretion of the medulla is regulated by the splanchnics and not by the pituitary.[156]

Both the heart and the vessels undergo some atrophy after hypophysectomy. It would be difficult to examine, however, whether *stress* could still cause hyalinosis in the absence of the pituitary, because hypophysectomized animals cannot survive the exposure to severe chronic stress necessary to produce such cardiovascular changes.

ACTH prevents hypotension after hypophysectomy in the rat; hence it was concluded that the fall in blood-pressure usually occasioned by hypophysectomy is due to lack of corticoids.[157]

Experiments with *DCA* showed that the hypotension of hypophysectomy is abolished by it in the rat.[158] Indeed typical hyalinosis can be produced by

[151] Rinehart and Mettier B36732/33, Schultz B36730/38, B36731/36.
[152] Bragdon and Levine B44737/49, Gullickson and Calverley 93016/46, Mason and Emmel B4984/45.
[153] Vogelsang et al. B1791/47.
[154] Donegan et al. B37083/49.
[154a] Marx et al. B46044/49.
[155] Rinehart and Greenberg B36355/49, B37453/49.
[155a] Smith et al. **B46713/50.**
[156] Selye **94572/49.**
[157] Braun-Menendez and Foglia B182/44.
[158] Braun-Menendez and Foglia B182/44.

this mineralo-corticoid compound in the absence of the pituitary.[159] Curiously, the hypotension caused by hypophysectomy is less readily prevented by DCA than that which follows adrenalectomy. From this it was postulated that the pituitary does not exert its pressor action exclusively through the adrenal cortex.[160] Perhaps the rôle of the posterior-lobe would deserve to be more seriously examined in this connection.

For technical reasons it has not yet been possible to study the production of hyalinosis by the "endocrine kidney" after hypophysectomy. It is known, however, that *experimental renal hypertension* is greatly diminished by ablation of the whole pituitary,[161] though not by isolated posterior-lobe removal.[162] In rats with experimental renal hypertension the blood-pressure always falls after hypophysectomy, but not quite to normal levels except when the hypertension has been of less than a month's duration. ACTH (but not prolactin) restores the hypertension to the pre-hypophysectomy level.[163]

The cardiac hypertrophy normally caused by *thyroxine* in the rat remains demonstrable after hypophysectomy.[164] This action is therefore not entirely dependent upon the anterior-lobe.

Various impure **anterior-lobe extracts** have been shown to produce cardiac hypertrophy in different animal species. This is probably due to the combined effect of the somatotrophin, ACTH and thyrotrophin contained in such preparations since all three of these hormones tend to enlarge the heart.[165] In itself this treatment has very little tendency to cause hypertension, hyalinosis or nephrosclerosis, hence, most experiments designed to study the production of arteriosclerotic changes by anterior-pituitary extracts have been performed on animals specially sensitized to these toxic actions by partial nephrectomy and excess NaCl (cf. pp. 515, 516). Let us reemphasize here that in most of the pertinent animal experiments the cardiac hyalinosis and nephrosclerosis run parallel. Hence, unless otherwise stated, the term "hyalinosis" as employed in this book, includes nephrosclerosis. However, outside the heart and kidney hyalinosis (e.g., in the brain or mesentery) is rarely produced by anterior-lobe extracts, presumably because gluco-corticoids inhibit this particular effect of the mineralo-corticoids and these hypophyseal extracts cause a simultaneous discharge of both these cortical hormones.

In intact mice chronically treated with a purified *ACTH* preparation (without dietary sensitization), the cardiac weight showed no increase, but definite coronary sclerosis was present in all cases. There was also considerable arteriosclerosis (hyalinization, calcification) in the arteries of the testes and the splanchnic territory, as well as some nephrosclerosis.[166] In unilaterally nephrectomized rats kept on 1% NaCl as drinking fluid, chronic ACTH treatment caused a marked rise in blood-pressure.[167] In man no such effect was obtained after administration of a large single dose,[168] but the blood-pressure usually rises following more prolonged ACTH treatment.[168a]

Adrenalectomy prevents the cardiovascular hyalinosis otherwise produced by anterior-pituitary preparations such as LAP, as shown by experiments in

[159] Selye 35935/ND.
[160] Leathem and Drill A94493/44.
[161] Page and Sweet A9430/37.
[162] Ogden et al. B6972/44.
[163] Anderson et al. B6973/44.
[164] Swann A30182/39.
[165] Dontigny **B25570/48.** Hall B18146/46, Selye **B1204/46. 94572/49.**
[166] Dougherty B27068/48.
[167] Guillemin and Ducommun B44419/ND.
[168] Sayers et al. B37710/49.
[168a] Spies and Stone B45101/50.

the rat. This is so even in animals kept in good condition by the administration of maintenance doses of adreno-cortical extracts.[169] It was concluded that the cardiovascular hyalinosis and hypertension caused by LAP are "... probably mediated by the adrenal cortex, through the secretion of desoxycorticosterone-like compounds. However, our experiments do not exclude the possibility that both pituitary and mineralo-corticoid adrenal hormones are necessary for the development of these lesions".[170] Only one investigator claims to have prepared an anterior-lobe preparation which raises the blood-pressure of the rat even after adrenalectomy if small doses of DCA are simultaneously administered. These observations led him to conclude "... that the adaptation diseases are not induced by the salt active corticoids alone, but by their co-operation with a hypophyseal synergist, probably our blood-pressure principle of the anterior pituitary".[171]

The production of myocarditis and periarteritis nodosa by *DCA* is inhibited in rats simultaneously treated with ACTH;[171a] this is presumably due to the fact that ACTH is predominantly gluco-corticotrophic.

Simultaneous treatment with *thyroxine* considerably augments the cardiovascular hyalinosis and cardiac enlargement normally produced by LAP[172] in the rat. It is of special interest, therefore, that the cardiovascular effect of LAP, though diminished, is still very manifest after thyroidectomy.[173]

Numerous experiments have shown that, at least in the rat, *unilateral nephrectomy* increases the ability of LAP to produce persistent hypertension, cardiac hypertrophy, cardiovascular hyalinosis and nephrosclerosis.[174] It is especially noteworthy, however, that even under optimal conditions of sensitization (by unilateral nephrectomy and a high Na intake) mesenteric periarteritis nodosa is extremely difficult to produce with LAP in the rat. This was all the more unexpected since in this species, systemic stress,[175] DCA overdosage and the "endocrine kidney" operation (cf. below) all manifest a particular tendency to elicit periarteritic changes in the mesenteric vessels. Curiously, LAP produces such arterial lesions in the kidney, pancreas, adrenals and heart. The possibility has been considered that the comparative resistance of the mesenteric vessels to the action of this impure preparation may be due to some specifically inhibitory principle contained in it.[176] More recent observations show, however, that cortisone inhibits the production of mesenteric periarteritis nodosa by DCA, even in rats which develop hypertension, myocarditis and nephrosclerosis under the influence of this combined hormone treatment. Hence the selective absence of such mesenteric lesions in LAP-treated rats may well be due to the simultaneous discharge of mineralo- and gluco-corticoids.[177]

Castration does not prevent, and may even increase, the hyalinosis-producing effect of LAP in the rat.[178]

In rats bearing an *"endocrine kidney"*, the administration of LAP causes even more pronounced cardiac hyalinosis, pancreatic periarteritis nodosa and cardiac hypertrophy than in intact or unilaterally nephrectomized controls;

[169] Dontigny B25570/48. Dontigny et al. B1214/46, Hall et al. B1215/46.
[170] Hall et al. B1215/46.
[171] Hase B19303/48.
[171a] Woodbury et al. B47201/50.
[172] Selye B1204/46, Selye et al. B124/45.
[173] Hay 86717/45, B1216/46.
[174] Corcoran B44416/49. Selye et al. B124/45.
[175] Selye B1204/46.
[176] Selye A75044/44.
[177] Selye **B41762/49.**
[178] Hall and Selye B22454/45.

only the vessels of the "clamped" kidney are protected.[179] Curiously, in intact (unlike in hypophysectomized) rats, purified ACTH allegedly diminishes the intensity of renal hypertension.[180] One wonders whether this could be due to the same predominantly gluco-corticoid type of discharge which is responsible for the beneficial effects of ACTH in patients with rheumatic and rheumatoid conditions.

The *diet* exerts a particularly pronounced influence upon the cardiovascular actions of LAP. Most of the pertinent observations have been made on rats sensitized to the production of hypertension and hyalinosis by unilateral nephrectomy. In these it was found that all the cardiovascular actions of LAP-overdosage are greatly augmented by the administration of excess NaCl[181] and are counteracted by acidifying salts (e.g., NH_4Cl or $CaCl_2$) which cause a sodium loss.[182] The pressor effect of ACTH in man is similarly conditioned by Na.[182a]

Large amounts of carbohydrate, such as glucose or starch, counteract the hyalinosis-producing action of LAP. In rats kept on various natural food stuffs such as muscle, "purina fox chow", peas, lentils, corn, lima beans or rice, the degree of hyalinosis and cardiac hypertrophy roughly paralleled the protein content of the food.[183] Control experiments showed that the hyalinosis-producing action of the LAP was specifically due to pituitary principles as it could not be obtained on any of these diets when similar lyophilized preparations of liver were injected.[184]

Continuation of this work with synthetic diets revealed that "the hypertension produced by LAP treatment on a 30% protein ration was prevented by decreasing the casein concentration to 15%".[185] Here the decrease in the protein (casein) concentration of the diet was effected by increasing the carbohydrate (corn starch) content. It is important to note therefore that when the corn starch was substituted by wheat starch, or even by an equicaloric amount of fat, this remained without any influence upon the hyalinosis-favoring action of the diet in the LAP-treated rat. Various protein preparations differed in their ability to promote cardiovascular hyalinosis; casein, egg albumin and wheat gluten were more effective than lactalbumin, gelatin or zein.[186]

As previously stated, even in rats sensitized to the hyalinosis effect of LAP by unilateral nephrectomy and a high NaCl diet, cardiovascular damage could not be produced if the protein (casein) concentration of the food mixture was kept down to 15%. However, if in addition to the 15% protein, completely hydrolyzed protein preparations are administered in an amount equivalent to 15% protein (thus bringing up the total amino-acid-N to that of a 30% casein diet), then LAP produces marked hypertension and hyalinosis. Addition, to the 15% protein basic diet, of individual amino-acids did not permit the production of cardiovascular hyalinosis by LAP. Glutamic acid, glycine, methionine, cystine, tryptophane, valine, histidine, lysine, leucine, phenylalanine, aspartic acid, isoleucine, norleucine and arginine all proved ineffective in this respect.[187] However, even if rats are maintained on a completely protein-

[179] Selye and Stone 94202/46.
[180] Corcoran B29330/48.
[181] Selye A71896/44, A75044/44, **B1204/46.**
[182] Hall and Selye B22454/45, Selye and Stone A95909/46.
[182a] Ransahoff et al. B47896/50.
[183] Berman et al. 86716/45, Selye and Stone A95909/46.
[184] Hay and Seguin B1220/46, Selye and Stone A95909/46.
[185] Dontigny et al. 99356/48.
[186] Hay et al. 96831/48.
[187] DeGrandpré et al. B19699/48, B3479/48 Selye B1433/48.

free diet, but are given mixtures of the purified essential amino-acids or protein hydrolyzates, in adequate amounts, then LAP produces hyalinosis.[188] Hence, artificial hydrolysis of protein does not destroy the factors indispensable for the production of anterior-pituitary hypertension and hyalinosis; protein is apparently effective as a sensitizing agent only by virtue of its constituent amino-acids.

It is known from every day clinical experience that hypertensive changes are adversely influenced by overeating. Since LAP increases food consumption, it is noteworthy, therefore, that it produces hyalinosis and cardiac hypertrophy in the rat even if the total caloric intake is maintained at a given level by "paired feeding".[189]

Vasopressor posterior-lobe extracts cause constriction of the coronary arteries with rather characteristic changes in the E.C.G. At the same time, the cardiac output is greatly increased following an initial transitory decrease. In evaluating the possible rôle of endogenous vasopressin in the cardiovascular response to stress, it is important to remember that this hormone causes a marked blood-pressure rise only under certain conditions (e.g., in the ether-anesthetized cat or dog); in unanesthetized animals and man, the pressor effect is minimal or replaced by hypotension and bradycardia. Not even all anesthetics permit the production of increased blood-pressure by posterior pituitary extracts. The pressor action is not mediated by the nervous system, since it also occurs after destruction of the brain or spinal cord and after paralysis of the vasomotor ganglia by nicotine. Probably the pressor action depends largely upon an increase in the capillary tonus and to a lesser degree, upon constriction of larger arteries and arterioles. To some extent, the hormone may even act by increasing the production of R.P.S., since it causes marked constriction of the renal arteries and this is known to stimulate R.P.S. production. It remains to be shown what rôle, if any, vasopressin plays in the maintenance of the normal blood pressure and in the vasopressor responses during stress.[190]

Several investigators maintain that vasopressin can produce arteriosclerotic lesions in experimental animals,[191] although this effect is quite inconstant. Yet, as we have said above, vasopressin is undoubtedly a powerful vasoconstrictor, particularly of the coronary arteries; it is because of this action that it uncovers latent cases of coronary disease.[192] Overdosage with vasopressin may even cause fatal myocardial infarction in man[193] as well as renal, splenic and other infarcts in the rat;[194] hence endogenous overproduction of this hormone may well play a part in the pathogenesis of certain cardiovascular diseases of adaptation.

Some relationship between vasopressin and R.P.S. is also suggested by in vitro experiments, indicating that the pressor effect of the former is abolished by hypertensinase-containing renal extracts,[195] but we do not know whether such reactions are of importance in vivo.

Adrenals. — Adrenalectomy causes some atrophy of the heart and blood-vessels. The functional cardiovascular responses of adrenalectomized animals during the G-A-S have been studied mainly in connection with the counter-

[188] Henriques et al. B24140/48, B26250/49.
[189] Hay and Séguin B1220/46.
[190] Selye **94572/49.**
[191] Hueper 91730/44.
[192] Ruskin B4754/47.
[193] Mills et al. A36678/49.
[194] Selye 94572/49.
[195] Croxatto et al. B23945/48.

shock manifestations which are due to adrenaline liberation. It was found that after adrenalectomy — or even after mere denervation of the adrenals — the usual vasopressor responses and the tachycardia no longer occur. The very mild reactions of this type which are occasionally still demonstrable after adrenal deprivation, may well result from sympathin liberation. If adrenalectomized animals are exposed to comparatively severe alarming stimuli, they not only fail to respond with a rise in blood-pressure, but develop severe and often fatal hypotension. The failure to develop an immediate pressor response is probably due to adrenaline deficiency, the severe hypotension to lack of corticoids.[196]

Adrenaline elicits only a temporary rise in the resting blood-pressure of adrenalectomized animals, and their tendency to develop severe hypotension during stress can not be effectively combatted by this hormone. In fact, after an adrenalectomized animal has developed hypotension as a result of exposure to a severe stressor, the administration of adrenaline may further aggravate the decline in blood-pressure.[197]

The vasoconstrictor action of adrenaline in the mesenteric territory of the rat likewise declines progressively after adrenalectomy. This has been ascribed to an impairment of VEM formation by the kidney, which in turn would be induced by the hypocorticoidism.[198]

Traces of nor-adrenaline allegedly restore the abnormal vascular response to adrenaline in adrenalectomized dogs. Hence, perhaps both adrenergic hormones must be discharged from the medulla during stress to permit a normal pressor response.[199]

Be this as it may, all these observations suggest that it is not because of an adrenaline deficiency alone that adrenalectomized animals tend to respond to stress by pronounced hypotension.

Corticoids are highly effective in maintaining the resting blood-pressure of adrenalectomized animals at about the normal level; at the same time, they counteract the tendency to develop severe hypotension upon exposure to systemic stress. Cortical extracts, gluco-corticoids and mineralo-corticoids are all effective in this respect, although the relative potency of individual steroids have not yet been systematically studied from this point of view.[200]

The hypertensive effect of DCA-overdosage (cf. p. 523) is not, or only slightly, increased by adrenalectomy in the rat,[201] or dog; [202] yet the production of cardiovascular hyalinosis by DCA is markedly enhanced in rats deprived of their adrenals,[203] presumably because they lack the antagonistic gluco-corticoids.

The experimental hypertension produced by various *kidney-lesions* is all but abolished by adrenalectomy and is difficult to re-establish by substitution therapy with NaCl, cortical extracts or DCA.[204] However, this is merely a matter of dosage, since large amounts of DCA or cortical extracts restore the pressure to the pre-adrenalectomy hypertensive level in the rat,[205] and if the

[196] Selye **94572/49**, B1204/46.
[197] Selye **94572/49**.
[198] Zweifach et al. 98747/47.
[199] Meier and Bein B38951/48.
[200] Gaudino 85570/44,
Leathem and Drill A94493/44,
Selye B1204/46, **94572/49**.
[201] Friedman et al. B37244/49,
Green and Glover B17840/48.
[202] Swingle et al. A37859/41.
[203] Pirozynski and Akert B38484/49.
[204] Dexter **91416/46**.
[205] Lewis and Page B4664/47,
Gaudino 85570/44.

general condition of the adrenalectomized animals is well maintained by adequate corticoid treatment, then renal interventions do produce their usual pressor effect.[206] Significantly, in rats whose renal-hypertension has been abolished by adrenalectomy, the original high blood-pressure levels are reëstablished by desoxocortisone or (to a lesser degree) DCA, much better than by cortical extracts.[207] Presumably, in the intact animal, interference with the renal circulation does not raise the blood-pressure through its effect upon the adrenals; yet renal (like most other) pressor substances, fail to maintain a high blood-pressure level in animals suffering from cortical insufficiency. If the hypocorticoidism is treated with mineralo-corticoids, which have a marked pressor effect of their own, the blood-pressure rise will be more pronounced than if gluco-corticoids are used for this purpose. Evidently much more than a maintenance dose of corticoids is required to permit survival with a persistent, severe hypertension, after interference with the renal circulation.

It is not clear why, after experimental renal interventions, cortisone raises the blood-pressure more markedly in adrenalectomized than in intact rats.[207a] Incidental renal trauma, increased salt appetite, a defect in the detoxification of cortisone, or elimination of some anticortisone compound may have to be considered.

In rats bearing an "endocrine kidney" and receiving adequate substitution therapy (NaCl plus cortical extract), adrenalectomy diminished, but failed to prevent, the development of hypertension and hyalinosis.[208]

Observations on cats in *tourniquet shock* showed that after adrenalectomy the usual arterial and arteriolar constriction still occurs in an essentially normal manner. This was taken to indicate that the above vasopressor responses are not solely mediated by adrenal hormones.

Studies on the effect of *anoxia* in vagotomized dogs, led to the conclusion "that the adrenal gland plays little part in the production of the hypoxemic pressor response, but plays a major rôle in the production of the arterial pressor response after re-aeration".[210]

After adrenalectomy, the hypertension normally produced by prolonged *auditory stimulation* is replaced by hypotension. Replacement therapy with cortical extract and salt resulted in a return to normal systolic pressures, but hypertension was not restored. It was suggested that the elevation of blood-pressure caused by prolonged auditory stimulation is due to the production of more than maintenance amounts of corticoids. Emotional excitement usually causes some increase in muscular activity, but this was never very pronounced in these experiments. It was concluded that "...it seems improbable that exercise was the alarming stimulus in our experiments, but fear has been considered a potent alarming stimulus and may have been the initiating factor here".[211]

It has been claimed that *partial constriction of the adrenal arteries* can cause permanent hypertension.[212] However, the results of this intervention are extremely variable [212a] and the pressor effect may well be due to an

[206] Corcoran B44416/49, Dexter **91416/46**,
Goldblatt **B29301/48**,
Page and Corcoran **B18005/48**,
Zweifach and Shorr B32854/49.
[207] Gaudino B179/44.
[207a] Gaudino B179/44,
Knowlton et al. B44790/49.
[208] Selye and Stone B44270/ND.
[209] Page and Abell 84114/43.
[210] Van Loo et al. B29395/48.
[211] McCann et al. B29451/48, B31793/48.
[212] Victor A95818/45.
[212a] Ogden et al. B36780/48.

increased elimination of adrenaline caused by the resulting adrenal ischemia.[213] In any event, this effect is never very pronounced and hardly plays a major rôle in the cardiovascular reactions during the G-A-S.

The intravenous injection of *VEM* causes progressively less marked pressor responses in adrenalectomized rats maintained on salt. From this it was concluded "that the reactivity of the peripheral blood-vessels is dependent upon the adrenal cortex".[214]

The atherosclerosis, normally produced by *cholesterol* feeding, is not prevented by adrenalectomy in rabbits receiving maintenance doses of DCA.[214a]

Adrenaline administered in moderate doses, raises the blood-pressure and strengthens the heart beat of the intact animal. At the same time the pulse rate is slowed, due to a vagal reflex through the pressoreceptors of the carotid sinus and the aortic nerves. This bradycardia is elicited only if the blood-pressure rises, not if it is kept low by bleeding. If the vagi are previously transected, or eliminated by atropinization, adrenaline increases both the rate and the strength of the heart beat. In man, adrenaline quickens the heart rate, even without atropinization, when it is given subcutaneously in small doses.[215]

Approximately physiologic doses of adrenaline influence the various vascular territories unequally. The arterioles and capillaries of the mucous membranes, skin and splanchnic viscera (except the intestinal vessels), are constricted; simultaneously, the coronary vessels as well as those of the skeletal muscles and intestines are actively dilated. At these dose levels the vasoconstrictor effect predominates over the vasodilator action and hence the blood-pressure rises. In coronary sclerosis, the dilatation of the cardiac arteries (if it occurs) is overshadowed by the other effects and angina results. The arteries of the brain are passively distended through the general rise in blood-pressure. The lung vessels are not particularly affected unless large doses are given; these constrict them. As a result of such changes, there is a redistribution of the blood, so that more becomes available to the skeletal and cardiac muscles, at the expense of the splanchnic area and skin. Curiously, very small doses of adrenaline may cause a fall in blood-pressure, presumably because the vasodilatation in the muscles overbalances the vasoconstriction in the skin and abdominal organs.[216] Patients with essential hypertension often exhibit such "paradoxical" (hypotensive, or at least biphasic) responses to adrenaline.[217]

When very large doses of adrenaline are administered, the blood-pressure falls rapidly after an initial increase and death in shock with hypotension ensues. It has been claimed that here the constriction of the smaller arteries, caused by adrenaline, produces shock somewhat like a tourniquet does, by interfering with the nutrition of the tissues.[218]

Long continued administration of adrenaline leads to arteriosclerotic changes, for instance in the rabbit, but most other species are singularly resistant to this effect.[219] Much has been written about the fact that the arteriosclerotic lesions caused by adrenaline are usually accompanied by considerable calcification of the vessel walls. However, most of the pertinent work was performed in

[213] Dumont B24763/47.
[214] Zweifach discussion remarks to Walkerlin et al. B27070/48.
[214a] Kellner and Correll B47288/50.
[215] Bovet and Bovet-Nitti **B28233/48.**
[216] Binet and Burstein B38194/48, Bovet and Bovet-Nitti B28233/48, Selye **94572/49.**
[217] Del Dotto B19365/46.
[218] Freeman B314/39.
[219] Hueper **91730/45.**

the rabbit, and this species tends to respond with vessel calcification, even when arterial changes are produced by other means (cf. Burns, p. 501).

DCA-pretreatment augments the pressor effect of adrenaline in man,[220] hence it is reasonable to suspect some synergism between the pressor action of the endogenous adrenergic and mineralo-corticoid hormones produced during the G-A-S.

Various inactive tissue extracts can sensitize vessels to the constrictor action of adrenaline. Thus perfusion experiments on the rabbit's ear have shown that vaso-inactive extracts of the kidney [221] and of other organs [222] cause vasoconstriction when the perfusion fluid (Ringer-Locke) is supplemented by subthreshold doses of adrenaline. Apparently, normal plasma contains sufficient amounts of adrenaline (or related compounds) to effect such an activation of (in themselves inactive) organ extracts.[223]

The sensitization to the vasoconstrictor action of (in itself inactive) *VEM*, by subthreshold doses of adrenaline — as estimated in the rat mesoappendix test (cf. p. 234) — is so striking that it serves as the basis for the routine bioassay of VEM preparations. It is uncertain whether the above-mentioned tissue extracts and VEM act through the same mechanism. In the interpretation of vasopressor responses during the G-A-S, it is important to remember, however, that several organ extracts increase sensitivity to the vasopressor action of adrenaline. Furthermore, *destruction of the sympathetic nerves* [224] or treatment with *"T.E.A."* (tetraethylammonium) chloride [225] similarly sensitize the vascular system to adrenaline. Since T.E.A. also sensitizes to the vasopressor action of renin and hypertensin,[226] it has been suggested that this, and perhaps also other sensitizing compounds, act by blocking amine-oxidases.

Conversely, numerous *adrenolytic substances* inhibit the vasopressor action of adrenaline. Since not all of these can prevent the vasopressor effects of sympathetic stimulation, "adrenolytic" and "sympatholytic" actions must be different.[227] Yet, it is possible that all these substances act through the same mechanism; perhaps only the sympatholytics can penetrate readily to the sympathetic nerve endings where they must reach in order to be effective.

The often marked potentiation of the pressor action of adrenaline by various *adrenaline-derivatives,* may well be due to competition for the same amino-oxidase system.[228]

The vasopressor action of *"urosympathin"* — which is probably a mixture of *hydroxytyramine, arterenol* and *adrenaline* — has been subjected to careful study, since allegedly large amounts of it appear in the urine of patients with essential hypertension. Indeed, the possibility has even been envisaged that such vasopressor amines are used as raw materials in the synthesis of hypertensinogen, from which renin liberates active hypertensin.[229]

In patients with *essential hypertension* there must be "an upward shift in the base line from which the homeostatic mechanisms are operative" since the pressor effect of adrenaline is about the same as in normal individuals.[230]

[220] Bricaire et al. B37547/48.
[221] Mylon et al. B4337/47.
[222] Mylon et al. B4338/47, B4337/47.
[223] Mylon and Heller B18584/47.
[224] Doupe B23475/43, Elliott 48059/05, Freeman et al. 19772/34.
[225] Page and Taylor B24841/47.
[226] Page and Taylor 98843/47.
[227] Bovet and Bovet-Nitti **B28233/48,** Heymans B23142/48.
[228] Heim B38195/48.
[229] Holtz and Credner B18863/47, Holtz et al. B18862/47.
[230] Green et al. B38675/48.

Although pertinent data are somewhat contradictory, the bulk of evidence suggests that *experimental renal hypertension* increases sensitivity to adrenaline and other pressor amines.[231] Furthermore in experiments on dogs, in which hypertension was produced by partial constriction of the renal artery, it was noted that the renal blood-flow became extremely susceptible to the vasoconstrictor action of small doses of adrenaline; the flow may actually cease for considerable periods of time if large doses are administered. Even partial constriction of one renal artery results in pronounced arterial hypertension if subthreshold doses of adrenaline are simultaneously given.[232] Yet, threshold doses of some pressor amines (related to adrenaline) can actually diminish the blood-pressure in animals with experimental renal hypertension.[233] This was tentatively ascribed to a stimulation of the pressor-amine-destroying enzyme system. Such findings may furnish an explanation for many contradictory data in the literature. Perhaps in renal hypertension the production of pressor amines is increased and their enzymatic destruction decreased. It could thus depend upon experimental circumstances (e.g., the kind of compound and the dose used) whether the injected pressor substance raises or diminishes the blood-pressure. It would cause an unusually pronounced pressor response, under experimental circumstances which interfere particularly with its normal detoxification in the kidney; yet it would actually decrease the previously high blood-pressure level whenever it stimulates the enzymatic destruction of (endogenous) pressor amines more than is necessary to detoxify the injected (exogenous) compound itself. This effect, if confirmed, would agree with the view (cf. p. 530) that an impairment of the renal detoxification of pressor compounds plays a rôle in the pathogenesis of those types of hypertension which result from kidney damage (e.g., renal vessel compression, LAP, DCA, desoxocortisone).

During severe *traumatic shock,* the vasopressor action of adrenaline becomes increasingly weaker and finally disappears completely as shown, for instance, in extensive experiments on the dog.[234] Essentially the same is true of *hemorrhagic shock,* yet adrenaline and many of its derivatives can raise the low blood-pressure in these conditions, as long as shock is not too severe.[235]

It is also of interest that adrenoxyl allegedly diminishes the capillary fragility and cutaneous purpura normally produced by severe *x-irradiation* in mice.[235a]

All these observations illustrate the manifold complex ways in which adrenaline and allied compounds can participate in the vascular reactions of the G-A-S. It may be well to summarize the salient, well established facts: (1) Adrenaline influences the various parts of the vascular tree unevenly, causing constriction in some, dilatation in other regions. (2) Its vasotropic effects can be augmented, inhibited, or reversed by the simultaneous presence of many conditioning substances. (3) Adrenaline and related compounds can be produced by various tissues, e.g., adrenal medulla, extra-adrenal chromaffin cells, sympathetic nerve endings, and — at least under conditions of disturbed blood-supply — perhaps even by the kidney and other tissues. (4) Finally, adrenaline and similar pressor amines can be transformed during metabolism into

[231] Dexter **91416/46.** Katz et al. 98546/47.
[232] Schroeder and Steele B3108/40.
[233] Ohler and Wakerlin 97565/47, Wastl 88328/46.
[234] Hermann et al. B31460/43.
[235] Huggins et al. B37231/49.
[235a] Herve and Lecomte B46855/49.

inert or even depressor compounds. Because of these numerous complicating factors it is difficult to assess precisely the rôle of adrenaline-like compounds in the cardiovascular responses to stress. Yet undoubtedly such compounds are discharged during the A-R, at least from the adrenal-medulla, at sympathetic nerve endings and perhaps also from other cells.

The cardiovascular actions of **corticoids** probably play a very important rôle during the G-A-S and its diseases. Early experiments with **adrenal transplants** gave inconclusive results [236] as this technique does not lend itself to the production of hypercorticoidism. The excess adrenal tissue, if it takes at all, involutes due to "compensatory atrophy" in the presence of the hosts' adrenals: on the other hand, if many grafts are implanted (with the view of producing hypercorticoidism from absorption of the hormones they contain), allergic foreign-protein reactions of the vascular system develop much before any detectable hormone intoxication.

The first observations showing that organic cardiovascular lesions can be regularly produced by experimental hypercorticoidism were made with **DCA.** Experiments on intact rats receiving a normal Na intake, had already suggested that some slight cardiac and renal hypertrophy,[237] as well as hypertension,[238] can be produced by chronic overdosage with DCA, but most mammals are quite insensitive to the toxic action of this compound unless they are specially prepared (cf. below).

For the evaluation of the mechanism through which DCA produces hypertension and cardiovascular lesions, it is probably rather important that comparatively high doses have to be administered over a long time before marked changes are observed. In other words the effects of the hormone are definitely cumulative. This suggests that the mineralo-corticoids do not act through a direct constrictor effect upon the blood-vessels, as the other pressor subsances (e.g., adrenaline, vasopressin, hypertensin) do, but presumably through a more complicated mechanism, perhaps through the intermediary of another organ (e.g., the kidney). It is also significant that among the many steroids so far examined, only mineralo-corticoids proved to be consistently effective in producing hypertensive diseases.[239]

In the light of these observations, it is difficult to evaluate the claim that folliculoids, testoids and luteoids cause an almost immediate rise in blood-pressure and that similar effects are more easily produced by small (0.5 mg. per day) than by "large" doses (1 mg. per day) of DCA. Since this work was done on large (180-250 gm. body weight) intact rats, not sensitized in any way to the pressor action of this hormone, it would appear in view of subsequent observations that all these doses were near or below the threshold level. It is especially surprizing to note that 0.5 mg. of DCA per day sufficed to raise the blood-pressure by 20 mm. Hg. in one day and by 40 mm. Hg. in nine days, while half this dose of estradiol caused a rise of almost 50 mm. Hg. within a week, stilbestrol allegedly producing a rise of essentially similar magnitude.[240] It is possible that these pressor responses were due to chance. but since they represent an early and much quoted contribution to the field, they deserve to be given adequate attention.

[236] Leriche **99671/45,** Morone **B36781/47.** Green and Glover B17840/48.
[237] Selye A31129/40.
[238] Friedman and Friedman B18266/48, Friedman et al. B18570/48,
[239] Prado **B47405/50.** Selye **B1204/46.** B43385/50.
[240] Grollman et al. A33735/40.

The comparative resistance of most laboratory mammals to the hypertensive and vasotoxic actions of mineralo-corticoids greatly delayed progress in the elucidation of their possible rôle in clinical hypertensive disease. Fortunately, however, a very useful test object was subsequently provided, by the observation that young *chicks* are extraordinarily sensitive to this effect. In them, even small doses of DCA sufficed to produce heart failure with tissue edema, ascites, cardiac enlargement, pericardial fluid accumulation, hypertension and nephrosclerosis.[241] Numerous other steroids — including high doses of an active adrenal-cortical extract — failed to produce similar overdosage manifestations, although in the highly sensitive chick (apart from DCA), acetoxy-pregnenolone and progesterone also proved to be effective in this respect.[242] It will be noted that these steroids are all devoid of oxygen at C_{11} and all possess at least a slight mineralo-corticoid effect.

Among the animal species so far examined, the fowl and rat were most sensitive to the hyalinosis-producing effect. Yet, DCA also causes hypertension in the dog; this may even persist for a long time after DCA-treatment is discontinued.[243] After suitable sensitization (by unilateral nephrectomy and Na-supplements, cf. below), even vascular hyalinosis has occasionally been found to occur in the *dog, guinea-pig, hamster, monkey, mouse* and *cat* following heavy overdosage with this compound.[244] However, some of these species are very resistant. In one experiment in two dogs on a high NaCl intake, even 2 gm. of DCA failed to cause hypertension or even edema, paralysis or loss of weight! Autopsy findings were not reported.[245] This degree of insensitivity is certainly exceptional, but it illustrates the truly astonishing efficacy of desensitizing mechanisms, a better understanding of which may well be of great therapeutic value. It is noteworthy in this connection that adult dogs [245a] are much more resistant to DCA than young ones.[245b]

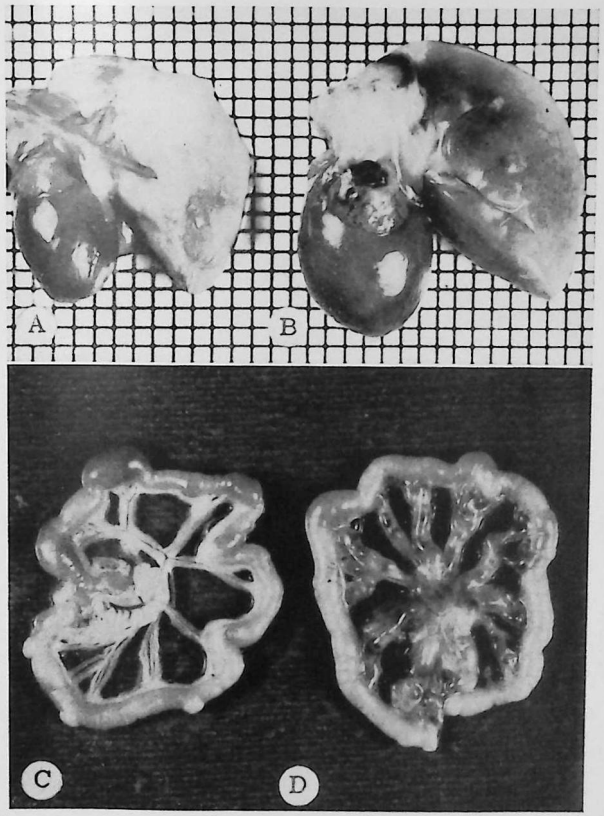
The blood-pressure — and even more constantly the pulse-pressure — of normal *man* also becomes elevated following treatment with DCA and NaCl, but only after a long period of time.[246] Intravenous injection of DCA (5 mg. in propylene-glycol solution) caused little or no immediate rise in the blood-pressure of normal human beings.[247] (Cf. Effect of DCA in Addisonian and hypertensive patients, p. 533.)

We shall now discuss the sensitization by *Na and by partial nephrectomy* conjointly, as both these agents appear to act similarly; perhaps because they favor Na-retention, which in turn impedes the detoxication of R.P.S. by the remaining kidney tissue. The first pertinent observation was that NaCl increases the nephrosclerotic action of DCA in the chick. Curiously, unlike in mammals, substitution of a 0.9% NaCl solution for the ordinary drinking water in itself sufficed to cause nephrosclerosis and other manifestations of hyalinosis in chicks, but ingestion of more dilute (0.2%) NaCl solutions did not produce such lesions unless the birds were simultaneously treated with mineralo-

[241] Selye A55847/42, A56426/43.
[242] Selye A56607/43, Selye and Stone A56585/43.
[243] Rodbard and Freed A37639/42.
[244] Hall **B18146/46**, Selye 35935/ND, **B1204/46, 94572/49**, Selye and Hall A56583/43.
[245] Summers B23925/48.
[245a] Masson et al. B47635/50.
[245b] Selye and Hall A56583/43, Selye 35935/ND.
[246] Decourt et al. 99536/46, B2529/44, Luft and Sjögren B43391/49, Perera and Blood B4520/47, 98220/46.
[247] Sposito A63750/42. Goldman and Schroeder B26544/48. B29754/48.

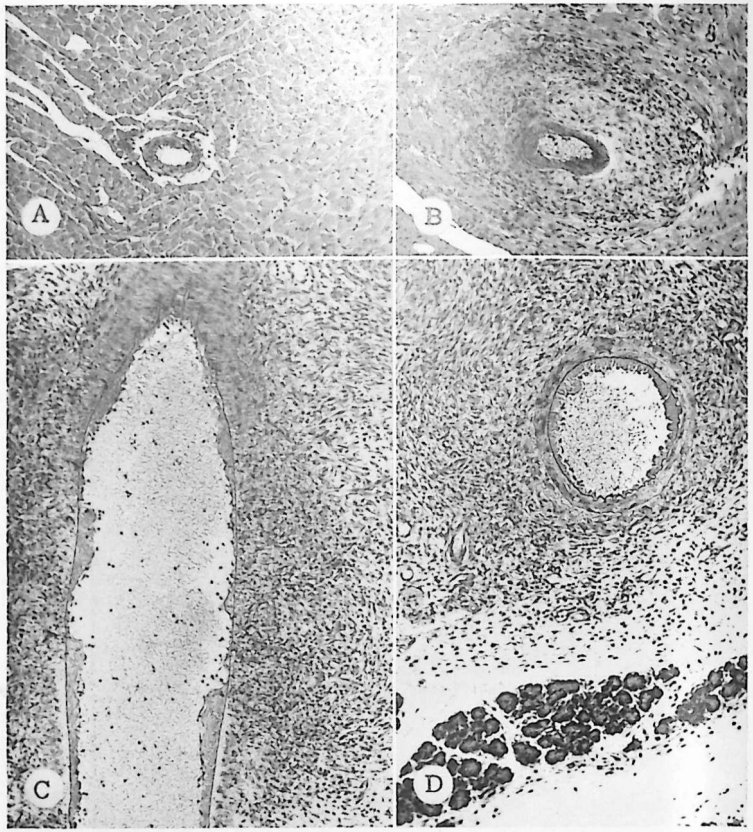
corticoids, such as DCA. The fact that in the fowl, a high NaCl intake imitates DCA overdosage, has repeatedly been confirmed.[248] All these observations led to the assumption that the mineralo-corticoids exert their toxic effect upon the cardiovascular system through their action upon Na metabolism.[249]

Subsequent experiments showed that if DCA-treated rats receive 1% NaCl to drink they — like the chicks — develop cardiovascular hyalinosis with

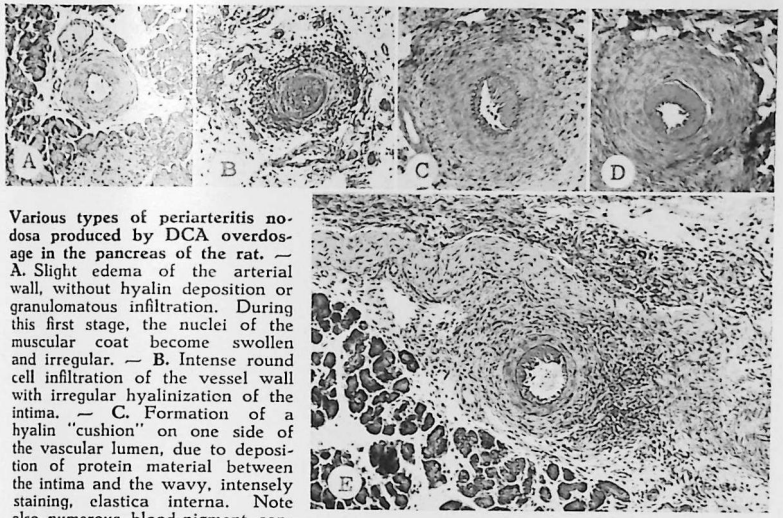


Effect of DCA upon the cardiovascular system of the rat. All animals in these experiments were sensitized to the mineralo-corticoid actions by unilateral nephrectomy and the administration of 1% NaCl as drinking fluid. DCA was given in the form of two 20 mg. pellets subcutaneously. — **A.** Heart and pulmonary lobe of a normal control. — **B.** Corresponding organs of DCA-treated animal, showing marked enlargement of the heart with rounding of its apex characteristic of hypertension. Note also pronounced edema of the lung which is a common cause of death in DCA-overdosed animals. — **C.** Mesenteric vessels of normal rat (seen as dark lines in the white mesenteric fat). — **D.** Intense periarteritis nodosa throughout the vascular tree of a DCA-treated rat. (Selye 35935/ND.)

[248] Krakower and Goetsch 93408/45, Selye A56426/43.
[249] Selye A56607/43, Selye and Stone A56585/43.



Effect of desoxocortisone upon the blood-vessels of the rat. All animals in this experiment have been unilaterally nephrectomized and given 1% NaCl as drinking fluid. — **A.** Arteriole in the myocardium of a normal control rat. — **B.** Arteriole in the myocardium of a desoxocortisone treated rat. There is a heavy dark layer of hyalin material underneath the intima, and the outer walls are greatly thickened by a granuloma. — **C.** Section through a mesenteric artery of a desoxocortisone treated rat. Irregular hyalin deposits underneath dark line which corresponds to intima; endothelium is loosened and in some places the intima is in direct contact with circulating blood. The outer coats of this artery completely lost their normal structure because of the proliferating granuloma tissue. — **D.** Periarteritis nodosa in a pancreatic vessel with normal pancreatic acini on the left. Similar changes were seen throughout the pancreatic arterial tree. Edema and connective tissue proliferation were evident even at a distance from the vessels between the pancreatic acini. The large black dots in the granuloma tissue correspond to blood pigment containing macrophages. Note great similarity between these lesions and those produced by DCA. (After Selye B43385/50.)

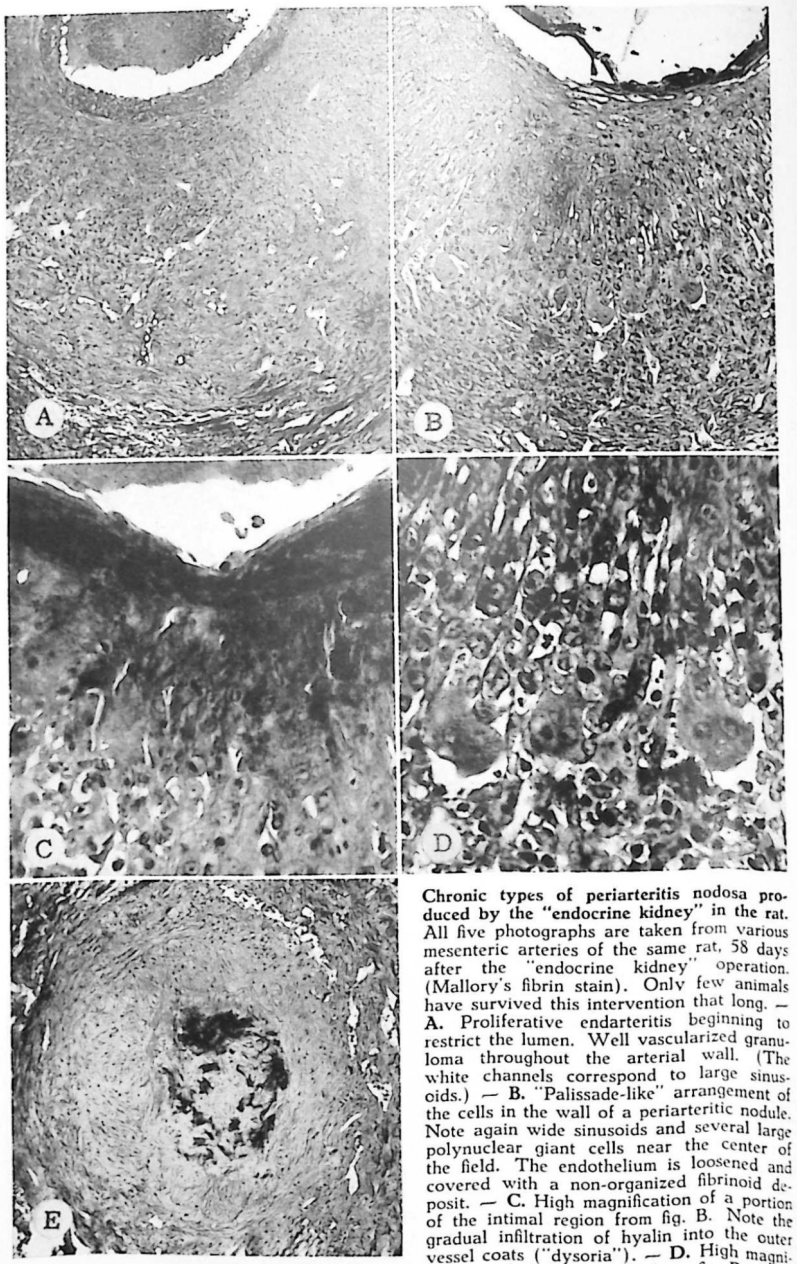


Various types of periarteritis nodosa produced by DCA overdosage in the pancreas of the rat. — **A.** Slight edema of the arterial wall, without hyalin deposition or granulomatous infiltration. During this first stage, the nuclei of the muscular coat become swollen and irregular. — **B.** Intense round cell infiltration of the vessel wall with irregular hyalinization of the intima. — **C.** Formation of a hyalin "cushion" on one side of the vascular lumen, due to deposition of protein material between the intima and the wavy, intensely staining, elastica interna. Note also numerous blood-pigment containing phagocytes in the adventitia, which appear here in the form of large black dots. — **D.** Concentric hyalin deposit which distends the elastica interna, so that the latter is no longer wavy. Note also swelling of muscular cells in the media and dark blood-pigment containing macrophages in the adventitia. — **E.** Hyalin deposit underneath the intima and intense granulomatous proliferation throughout the adventitia. The connective tissue and round-cell containing granuloma also envelops a small nerve, which traverses this field near the upper border. (Selye 35935/ND.)

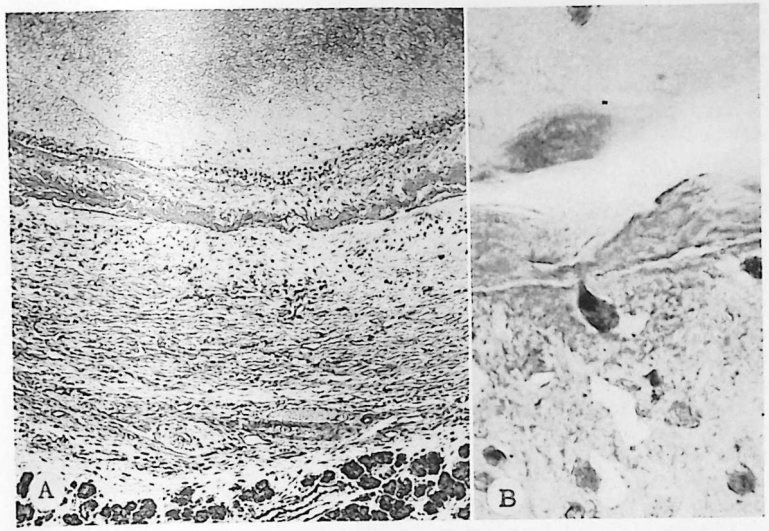
nephrosclerosis and hypertension more readily than on tap water, and that their sensitivity to all these toxic effects is further raised by unilateral nephrectomy,[250] as well as by the nephritis induced by "anti-kidney serum".[251] Later systematic studies in the rat revealed that "the sensitization by NaCl is not due to the Cl ion, but to the Na ion, as indicated by the fact that other chlorides are ineffective in this respect, while other Na salts share this action of NaCl".[252] The sensitization to these toxic actions of DCA by NaCl has repeatedly been confirmed both in intact rats and those with renal damage.[253]

Conversely, rats maintained on a completely *Na-free diet* appear to be entirely resistant to the hypertensive, nephrosclerotic and arteriosclerotic actions of DCA (even after unilateral nephrectomy), although treatment with this steroid continues to produce the usual adrenal-cortical and pituitary atrophy.[254] Incidentally, the life-maintaining action of DCA in the adrenalectomized rat is not prevented by the sodium loss induced with ammonium chloride.[255] All this suggests that Na is mainly necessary for the renal and cardiovascular toxicity of DCA overdosage, not for its other actions.

[250] Selye et al. B235/45, A58748/43, Selye and Hall A56583/43, Selye and Pentz A59789/43.
[251] Knowlton et al. B3053/47, 91205/46.
[252] Selye et al. B235/45.
[253] Briskin et al. A56871/43, Friedman and Friedman B18266/48, Friedman et al. B25983/48, B18570/48, Green B28239/48, Green et al. B29398/48, Knowlton et al. B3053/47, Landis and Abrams B4356/47, Skahen and Green B29995/48.
[254] Selye et al. B19413/49.
[255] Selye and Stone A96818/45.



Chronic types of periarteritis nodosa produced by the "endocrine kidney" in the rat. All five photographs are taken from various mesenteric arteries of the same rat, 58 days after the "endocrine kidney" operation. (Mallory's fibrin stain). Only few animals have survived this intervention that long. — **A.** Proliferative endarteritis beginning to restrict the lumen. Well vascularized granuloma throughout the arterial wall. (The white channels correspond to large sinusoids.) — **B.** "Palissade-like" arrangement of the cells in the wall of a periarteritic nodule. Note again wide sinusoids and several large polynuclear giant cells near the center of the field. The endothelium is loosened and covered with a non-organized fibrinoid deposit. — **C.** High magnification of a portion of the intimal region from fig. B. Note the gradual infiltration of hyalin into the outer vessel coats ("dysoria"). — **D.** High magnification of the giant cells from fig. B. — **E.** Complete obliteration of a mesenteric vessel with substitution of its layers by scar tissue. The dark masses in the region of the former lumen stain like hyalin. (Selye 35935/ND.)



Periarteritis nodosa produced by DCA overdosage in the pancreas of the rat. — **A.** Numerous leucocytes of the circulating blood (top) become adherent to the endothelium. Underneath the latter, there is a now partially organized hyalin deposit. The adventitia is infiltrated with many pigment containing macrophages. — **B.** High magnification of A. Note thick hyalin deposit (top) on the inner surface of the intima. The latter appears to be perforated by a pear-shaped chromatin structure, presumably the nucleus of a mesenchymal cell. Dysoria often commences in this manner, the perforations apparently opening the way for hyalin infiltration of the sub-intimal layers. (Selye 35935/ND.)

It is tempting to seek, in the sensitization by Na, an explanation for the empirically established beneficial effect of low-sodium diets which has been noted in many cases of clinical hypertension.[256]

Small doses of an aqueous cortical extract were without effect in *renal hypertensive dogs*,[257] but a lipo-cortical extract (rich in gluco-corticoids) allegedly diminishes the blood-pressure of rats with renal hypertension.[258] This is surprising since even cortisone aggravates experimental renal hypertension in the rat.[259]

DCA further raises the blood-pressure of renal-hypertensive dogs and may cause fatal lung edema.[260] In rats with various types of mild renal hypertension, DCA also causes a more pronounced pressor response than in normal controls.[261] The occasional negative findings[262] may have been due to the use of subthreshold doses of DCA or the production of an already maximal renal hypertension which cannot be further aggravated by corticoids.

The findings concerning the effect of *complete nephrectomy* upon the above-mentioned toxic actions of DCA, are somewhat contradictory. If rats

[256] Allen and Sherrill 40804/22, Ambard and Beaujard B36273/04, Grollman et al. B777/45.
[257] Wakerlin and Gaines A34993/40.
[258] Corcoran B29330/48.
[259] Knowlton et al. B44790/49.
[260] Rodbard and Freed A37639/42.
[261] Knowlton et al. B3053/47, 91205/46, B43547/49, Landis and Abrams B4356/47.
[262] Davis et al. B36546/48, Gold B1316/46.

are pretreated with DCA until they just begin to develop hypertension but no hyalinosis, the progress of the hypertensive disease is apparently interrupted by bilateral nephrectomy. Here the animals were maintained in comparatively good condition after nephrectomy, for about 10 days, by peritoneal lavage. Under exactly comparable conditions, intact rats developed marked hypertension and fairly pronounced vascular hyalinosis.[263]

On the other hand, short term experiments on completely nephrectomized rats (in which peritoneal dialysis was unnecessary), led to the conclusion "that the pressor action of DCA was present in the absence of both kidneys. The evidence thus supports the suggestion that the kidney is concerned in the excretion and possible inactivation of the steroid".[264] Indeed in the DCA-treated rat the blood-pressure may continue to rise after bilateral nephrectomy.[265] Yet, there is no actual evidence showing that kidney tissue can detoxify DCA, while we have ample experimental material to prove that R.P.S. is detoxified by the kidney. Thus, it is perhaps more compatible with all known observations to postulate that DCA interferes in some way with the normal detoxification of R.P.S. by the kidney and, at the same time, it may also increase their production.[266] Occasionally, DCA does seem to cause some rise in blood-pressure after complete nephrectomy. However, this is not incompatible with the above assumption if we accept, as some authors do, that pressor principles (similar to adrenaline or to those normally produced in the kidney) can, to a lesser extent, also be manufactured elsewhere in the body. Indeed some actual colorimetric assays suggest that DCA (or non-specific stress) increases the concentration of "adrenaline like" substances in various tissues.[267] If this be true, DCA could continue to increase the production of pressor substances after nephrectomy. These would be particularly effective in the completely nephrectomized animal, since here they could not be detoxified. Furthermore, complete nephrectomy in itself tends to raise the blood-pressure temporarily by increasing the blood-volume (cf. p. 538).

In intact, and even more so in partially nephrectomized animals, DCA might thus raise the blood-pressure through three mechanisms, namely: (1) by increasing renal and extra-renal pressor substance production, (2) by interfering with the normal detoxification of renal and extra-renal pressor substances in the kidney, (3) by increasing the blood-volume.

The second possibility received strong support from experiments on the rat, which showed that DCA-pretreatment increases the intensity and duration of the hypertensive response to the injection of *hypertensin* almost as much as complete nephrectomy. It was concluded that the renal detoxification of endogenous R.P.S. is probably similarly impeded by DCA.[267a] More recently, it was reported that DCA-pretreatment does not increase significantly the pressor response to hypertensin, *renin* or *adrenaline;* this was taken to mean that DCA-hypertension cannot be ascribed to vascular hypersensitivity.[267b] However, even the latter report emphasizes that the responses to all three pressor agents "were slightly greater in DCA-treated than in control rats"; perhaps the lack of consistent results was due to the fact that here only single

[263] vanden Bossche B26871/48. B40085/49.
[264] Friedman and Friedman B33003/49.
[265] Hall and Hall B39069/49.
[266] Selye 94572/49.
[267] Raab A36730/41.
[267a] Guillemin and Selye B46944/50.
[267b] Masson et al. B47635/50.

blood-pressure measurements were done and the duration of the pressor response (which is most markedly affected) has not been determined.

In view of the frequent co-existence of hypertension and diabetes, in man, it is interesting that *partial pancreatectomy* (95%) increases the pressor effect of DCA in the rat.[267c]

The toxic effects of *cardiac glucosides* are diminished by DCA-administration in the rat; conversely, the cardiac hypertrophy, ascites and anasarca, occasioned by high doses of DCA (in rats sensitized with thyroid and NaCl), was ameliorated by the intravenous injection of such glucosides.[267d]

Potassium administration does not influence the hypertension and hyalinosis produced by DCA in the chick,[268] the mouse,[269] or the rat.[270] This is true even if enough potassium is given to prevent the usual hypokalemia.

The *sex hormones* apparently also have some influence upon the development of these lesions. Hyalinosis and hypertension is more readily obtained in female or castrate male rats than in intact males,[271] while simultaneous treatment with testoids (e.g., methyl-testosterone) counteracts these toxic effects of DCA.[272] The mechanism of this inhibitory action has not yet been adequately analyzed. Since testoids cause adreno-cortical involution, they could act, at least partly, by repressing the endogenous mineralo-corticoid production. It is more probable, however, that their beneficial effect is due to their reno-trophic action which augments the active tubular mass and thus produces the reverse of what is accomplished by unilateral nephrectomy. It is well known that healthy kidney tissue inactivates the vasotoxic R.P.S., such as may be produced under the influence of DCA. In any case the above-mentioned sex difference is never very marked, and in some colonies of rats the males are more sensitive to the hypertensive action of DCA than the females.[273]

The cardiovascular toxicity of DCA is more effectively inhibited in the rat by *"acidifying salts"* such as ammonium chloride,[274] ammonium sulfate, ammonium nitrate and calcium chloride.[275] Presumably all these compounds act by depleting the Na-reserves of the body.

Since many of the manifestations of hyalinosis resemble the changes characteristic of acute rheumatic fever, attempts have been made to prevent the toxicity of DCA with *salicylates,* but the results were inconclusive.[276]

Preliminary experiments on rats (sensitized by unilateral nephrectomy and NaCl) suggested that forced administration by stomach tube of a *25% dextrose* solution, diminishes the hyalinosis and cardiac hypertrophy normally produced by DCA.[277] However, this is hardly a specific carbohydrate effect. Subsequent systematic experiments with diets containing different proportions of carbohydrate and protein revealed that "while the hypertension and nephrosclerosis produced in the rat by anterior-pituitary preparations are prevented by low protein diets the otherwise similar lesions induced by desoxy-

[267c] Braun-Menendez Martinez B46378/49.
[267d] Kupperman and De Graff B47267/50.
[268] Selye A56607/43. Selye and Stone A56585/43.
[269] Masson and Beland A72916/43.
[270] Knowlton et al. B3053/47. Selye et al. B235/45.
[271] Selye and Pentz A59789/43. Selye et al. A58748/43, A72284/44.
[272] Selve and Rowley A72302/44, A72287/44.
[273] Green and Glover B17840/48.
[274] Selye and Stone A96818/45. Selye et al. A94329/45, B235/45.
[275] Selye et al. B235/45.
[276] Selye et al. B235/45.
[277] Berman et al. 86716/45.

corticosterone overdosage are largely independent of the dietary protein intake".[278] Perhaps the forced administration of the dextrose solution through the stomach tube acted merely by washing out sodium, somewhat like the acidifying salts do.

If DCA-treated rats are kept on diets rich in *phosphates,* the hyalinosis and especially the nephrosclerosis is particularly severe. Histologic examination of the kidneys reveals, however, that here numerous calcified casts are formed in the tubules (presumably due to precipitation of calcium phosphates) so that considerable destruction of renal tissue results. Probably the phosphates do not specifically sensitize to the vasotoxic action of DCA, but act merely by aggravating the renal insufficiency, just as partial nephrectomy does.[279]

A few subsequent investigators failed to produce hypertension, hyalinosis or nephrosclerosis with any regularity in rats treated with DCA.[280] Perhaps they used insufficient doses of steroid for the degree of sensitization (if any) which they employed.[281]

Although no breed of rat has as yet been shown to be entirely resistant to this action of DCA, some are considerably more sensitive than others; [282] disregard of such *genetic* factors may also explain some negative findings.

In intact dogs, pretreatment with DCA gave some protection against the hypotension normally caused by *trauma* [283] or *carbon arc irradiation.*[284] Allegedly similar protection was obtained with an adreno-cortical extract against *tourniquet* shock in the dog.[285] However, the pressor effect of corticoids is rarely pronounced in such acute experiments.

It has been claimed that even single, small, intramuscular injections of DCA can cause hypertension in the rat and that this is ameliorated by the ingestion of *histidine* and *ascorbic acid,* while the anti-histaminic substance *"antistine"* tends to prevent this inhibition. It was concluded that "these findings would indicate that histamine is a factor in ameliorating experimental hypertension induced by DCA".[286] These observations have not yet been confirmed and, as they are contrary to common opinion, they must be evaluated with care. We have recently observed that an antihistaminic, *phenergan,* prevents the hypertension and hyalinosis (including the nephrosclerosis) normally produced by DCA in unilaterally nephrectomized, NaCl-sensitized rats.[286a]

A recent review of this subject mentions many observations suggesting, on the basis of more or less indirect evidence, that the increased capillary permeability caused by *histamine, bacterial toxins, excessive muscular exercise,* etc. is counteracted by various cortical preparations.[287] However, most of the work referred to, was performed with comparatively impure extracts or DCA and requires confirmation. One investigator states that the arteriosclerotic changes produced by *nicotine* in experimental animals are accentuated by DCA,[288] but gives no details concerning the experimental procedure upon which this conclusion was based.

[278] Prado et al. B1777/47.
[279] Friedman et al. B25983/48.
Selye et al. B235/45.
[280] Bechgaard and Bergstrand B32335/49.
Braun-Menendez and Foglia B182/44,
Gaudino B179/44, 85570/44,
Gold B1316/46, Harrison B3033/46,
Knowlton et al. 91205/46.
[281] Selye 91825/46.
[282] Friedman B23327/48.
[283] Lambret et al. A55080/41.
[284] Graham A61343/43.
[285] Bourque et al. 84560/44.
[286] Allardyce et al. B29416/48.
[286a] Guillemin and Selye B46944/50.
[287] Eppinger **B37085/49.**
[288] Hueper 91722/43.

Anti-kidney serum in doses causing mild hypertensive nephritis in the rat, greatly increases the vasopressor and nephrotoxic actions of DCA.[289] However, an *anti-rat-placenta serum* also increased these toxic effects of DCA,[290] hence the action of the anti-kidney serum is not entirely specific.

The fact that the low blood-pressure of *Addisonian patients* is significantly and consistently increased by DCA is so well known that it hardly deserves to be mentioned. If the patient simultaneously receives large doses of NaCl, serious cardiovascular disturbances may result. The cardiac x-ray shadow increases rapidly because the blood-volume rises. At the same time, there is a tendency towards the retention of extracellular fluid and especially of sodium.[291] Sometimes an "œdematous pericarditis" or "myopericardial œdema", with cardiac insufficiency and lung edema has been noted at the autopsy of such DCA-overdosed Addisonians.[292]

If, under the influence of chronic overdosage with DCA and NaCl, hypertension develops in an Addisonian patient, it is usually accompanied by edema.[293] Especially marked, and sometimes "dry" hypertension (i.e., without water retention) ensues in patients who previously suffered from renal damage and/or slight hypertension.[294] These clinical observations have been compared with the sensitization to the hypertension or hyalinosis-producing effect of DCA which we induced by renal lesions in the rat. It was concluded that probably, both in animals and in man, renal insufficiency, or a preëxistent hypertensive tendency, predispose to the pressor action of corticoids; hence the latter may well play a prominent rôle at least in certain types of essential and renal hypertension.

In *postural hypotension,* combined treatment with DCA and NaCl also actively raises the blood-pressure, although with the doses used, no actual hypertension ensued. Here, this hormone is actually of therapeutic value.[295]

In patients with preëxistent, uncomplicated *hypertension,* DCA (e.g., 5 mg. subcutaneously, twice daily) causes a definite rise in blood-pressure within a few days, but this effect is pronounced only if the diet contains adequate amounts of sodium.[296] In hypertensive patients, even a single, intravenous injection of DCA (5 mg. dissolved in propylene glycol) caused an almost immediate elevation of the blood-pressure, while no such effect was noted after similar administration of various other steroids or of a cortical extract.[297] Indeed "the continued administration of an adrenal cortical extract for one month to four subjects with uncomplicated hypertensive vascular disease on a constant regimen, was associated with a decrease in 'resting' blood-pressure in three instances, only in one case was there a small rise".[298] Similarly the rise in blood-pressure occasioned by DCA in patients with mild hypertensive disease is prevented by cortical extract.[299] This apparently beneficial effect

[289] Knowlton et al. B43547/49.
[290] Loeb et al. B41168/49.
[291] Selye **94572/49.**
[292] Sarradon B33935/47.
[293] Henri B24200/47.
[294] Bricaire et al. B37547/48,
De Gennes et al. B26540/47, B1912/47,
Laureau B27061/47,
Loeb et al. A97728/39,
Luft and Sjögren B39101/49.
Mathieu de Fossey B31703/49,
Perera B778/45,
Perera et al. **93511/44.**
[295] Gregory B28037/45,
Luft et al. B24895/48.
[296] Bricaire et al. B37547/48,
Luft et al. B43391/49,
Perera B19865/48,
Perera and Blood B4532/47, B4520/47,
B3996/47.
[297] Goldman and Schroeder B29754/48,
B17676/48, B26544/48.
[298] Pines et al. B26422/48.
[299] Perera and Pines B37746/49.

of the extract may well be due to its high gluco-corticoid content; gluco-corticoids depress the mineralo-corticoid production of the adrenal and in some respects, even antagonize their peripheral actions upon the vascular system. Cortisone likewise depresses the blood-pressure in hypertensive patients.[300]

The *various vascular territories* are not equally sensitive to the hyalinosis-producing action of DCA. Experiments on the rat revealed that the medium-sized and small arteries and arterioles of the heart, pancreas, kidney, mesentery and brain are the most sensitive, approximately in the order mentioned. Other arterial vessels, and especially the veins, are much more resistant.[301] Capillaries are almost never selectively affected, except in the renal glomeruli, where the blood-pressure is high. There appears to be a direct correlation between the height of the blood-pressure and the hyalinosis in the various vascular territories of DCA-treated rats. A similar relationship is obtained in animals with experimental renal hypertension as we shall see below. — Further pertinent data will be found in connection with our description of the lesions produced in the various individual organs (cf. below).

At least under certain conditions, DCA increases *capillary permeability*. This may play a rôle in the production of edema by this compound. It will be recalled that in certain species, for instance, in the chick [302] and in man [303] DCA treatment in itself can cause pronounced edema and fluid accumulation in the serous cavities of the body. In the rat, this effect is rarely pronounced, although after large doses, peritoneal fluid accumulations do occur.[304] However, even in the rat, pronounced subcutaneous water accumulations can be produced by DCA if some irritating substance is injected simultaneously (though not necessarily at the same place). Thus it was found that subcutaneous injection of formaldehyde causes excessive accumulations of edema in rats given toxic doses of DCA.[305]

On the other hand, the increase in capillary permeability produced by peptone injections in the rabbit skin is allegedly counteracted by cortical extracts.[306] Similarly, Ungar claims that his "splenin-A", which increases capillary resistance is "discharged under the influence of the hypophysis and the suprarenal cortex and plays a rôle in the general-adaptation-syndrome where it acts by accelerating the neutralization of the proteases, which are activated under the influence of various stresses. Thus it protects the capillary endothelium".[307]

Our previously mentioned experiments concerning the effect of corticoids upon "formalin arthritis" had shown that DCA aggravates, while cortisone inhibits the formation of local edema after the injection of formalin into the joint region. This suggested that the mineralo-corticoids and gluco-corticoids mutually antagonize each other's actions upon capillary permeability — or at least edema formation — under these conditions.[308] It is rather difficult to reconcile these observations with other findings made on rabbits in which capillary permeability was studied after intravenous injection of trypan blue. Here it was found that intramuscular injection of either DCA or a cortical extract (the latter is mainly gluco-corticoid) inhibit the increase in capillary permeability occasioned by carbon arc irradiation.[309] The interpretation of these

[300] Perera et al. B36595/49.
[301] Selye and Pentz A59789/43, Selye et al. A71886/44. A58748/43.
[302] Selye A55847/42, A56607/43.
[303] Selye **94572/49.**
[304] Selye and Friedman A33118/40.
[305] Selye et al. A32768/40.
[306] Shleser and Freed **88841/42.**
[307] Ungar B4968/47.
[308] Selye B39702/49.
[309] Graham A63324/43.

latter experiments is all the more difficult since both cortical preparations were injected immediately before, during or even after the irradiation and in our experience, corticoids do not markedly affect capillary permeability so rapidly.

It is assumed by several investigators that corticoids exert an important effect upon *intercellular cement substances* and that it is due to this action that they influence capillary permeability. However, a detailed review [310] discloses so many contradictions in the pertinent literature that a uniform interpretation is not yet possible.

As judged by in vivo observations on the rat mesoappendix, corticoids (like hypertensin) stimulate the *motility of the terminal arterioles* [311] The contractility of the mesenteric arteries and veins is greatly increased in rats chronically pretreated with DCA.[312] It remains to be shown whether there is a relationship between these actions and the hypertensive effect of the mineralo-corticoids.

Many investigators doubted that the experimental lesions produced by DCA could be related to spontaneous diseases, because only traces of desoxycorticosterone occur in the normal adrenal.[313] Some workers suspect that even the small amounts that have allegedly been prepared from the gland may be artefacts, due to a reduction of the C_{11}-OH group caused by post-mortal autolysis or the chemical procedure used for extraction. We have previously mentioned that other steroids such as **acetoxypregnenolone** and **progesterone** also cause hyalinosis at least in the highly sensitive chick.[314] However, the hypertensive and hyalinosis-producing action of these steroids is very slight and there is little evidence of their increased production by the adrenal during stress. It is therefore of special importance that **desoxocortisone** likewise produces hypertension, cardiovascular hyalinosis and nephrosclerosis in the rat. Large quantities of this steroid undoubtedly occur in the normal adrenal cortex, hence there is no reason to doubt that similar hyalin changes may arise during stress, as "diseases of adaptation", if excesses of natural mineralo-corticoids are produced.[315] In the few experiments in which desoxocortisone failed to cause hypertension and hyalinosis, insufficient doses were given.[316]

Considerable attention has been given to the persistence of hypertensive changes following **withdrawal of mineralo-corticoid treatment.** In dogs rendered hypertensive by DCA, the blood-pressure may remain high for weeks after discontinuation of this treatment.[317] Similar experiments in the rat also revealed that after a certain time DCA-induced hypertension becomes "self-sustaining".[318] However, it appears to depend largely upon the intensity and duration of the DCA treatment whether the resulting hypertension becomes permanent. After short pretreatment periods — just sufficient to raise the blood-pressure significantly — the hypertension vanishes sooner or later after discontinuation of steroid administration in the dog [319] and rat.[320]

The cardiovascular actions of gluco-corticoids have not yet been examined in detail since adequate amounts of such compounds have only quite recently

[310] Chambers and Zweifach **B26122/47.**
[311] Chambers B19253/48.
[312] Selye B38909/49.
[313] Corcoran B44416/49.
[314] Selye A56607/43, Selye and Stone A56585/43.
[315] Selye B43385/50, B41762/49.
[316] Corcoran B44416/49.
[317] Rodbard and Freed A37639/42.
[318] Friedman and Friedman B39686/49, B43537/49.
[319] Davis et al. B36546/48.
[320] Knowlton et al. B43547/49, Prado B47392/50, Selye 35935/ND.

become available. It is already evident, however, that even typical gluco-corticoids such as **cortisone** can cause hypertension in suitably sensitized (unilateral nephrectomy and excess sodium) rats. Even some myocardial nodules and renal changes (especially marked glomerular hyperemia and occasional cast formation) have been noted in these experiments. Apparently the slight mineralo-corticoid potency present in all gluco-corticoids suffices to produce such effects after adequate "conditioning". Conversely — especially in rats not particularly sensitized to the mineralo-corticoid effect — cortisone actually inhibits many of the toxic cardiovascular actions of DCA. For instance it can depress the hypertensive action, as well as the production of periarteritis nodosa in most organs. Curiously, these arteritic changes are not readily depressed by cortisone within the coronary circulation and the renal damage caused by DCA may even be aggravated by cortisone. The antagonism between mineralo- and gluco-corticoids thus appears to play an important rôle in the pathogenesis of the diseases of adaptation.[321] It is in agreement with this view that cortical extracts also counteract the production of periarteritic and myocarditic lesions by DCA in the rat.[321a]

Numerous experiments are now in progress at our Institute to elucidate the mechanism of this hormone interplay but unfortunately, these have not yet progressed far enough to permit a more detailed discussion of this rather crucial point.

In man, cortisone does not affect the normal blood-pressure consistently. In rare instances, it has been claimed to precipitate cardiac failure, if given in very large doses, to highly sensitive patients.[321b]

Kidney. — The kidney undoubtedly exerts a very important influence upon the cardiovascular system in general and the blood-pressure in particular. Yet bilateral nephrectomy does not cause any immediate drastic changes in blood-pressure or in the morphologic appearance of the cardiovascular system. Therefore some investigators doubt that the renal pressor mechanism participates in the homeostasis of blood-pressure under normal conditions, although certain kidney lesions undoubtedly do cause cardiovascular changes.

We should like to emphasize at the outset of this discussion that such a view is not justified. The maintenance of the blood-pressure, like that of so many other vitally important functions, is assured by several alternative regulating mechanisms; destruction of one among these does not necessarily result in any immediately manifest change. Many well established observations force us to assume that the kidney plays a very prominent rôle both in the maintenance of the blood-pressure during the G-A-S and in the pathogenesis of the cardiovascular "diseases of adaptation". Because of the great complexity of this field and the enormity of the pertinent literature, we must limit ourselves here to a few especially pertinent observations. Some additional data concerning individual, more or less well defined, renal-pressor-substances (R.P.S.) and their antagonists will be found elsewhere in this book (cf. p. 228, Metabolism), but the reader especially interested in renal hypertension is advised to consult monographs specifically concerned with this subject. Several such

[321] Selye B41762/49.
[321a] Woodbury et al. B47201/50.
[321b] Baehr B46308/50.

books have recently been compiled in different languages by prominent specialists in this field.[322]

The various techniques **used for the production of experimental renal hypertension** produce essentially similar functional and morphologic alterations in the cardiovascular system; they are all based on an interference with the renal blood supply.

Whatever procedure is used to impede renal circulation, the technique must be applied to both kidneys or, if the operation is performed on one side only, the other (healthy) kidney must be removed in order to assure the consistent production of permanent hypertension. This is apparently true of all common laboratory animals except the rat and rabbit [323] in which unilateral operations of this types suffice. Perhaps in these species the normal kidney tissue is singularly ineffective in destroying R.P.S.

Only the salient features of the most commonly employed techniques will be sketched below.

Chronologically the first, and certainly one of the most useful, procedures permitting the consistent production of severe renal hypertension was that devised by Goldblatt et al.[324] It is based on the *partial compression of the renal artery* by means of a metal clamp. Instead of the "Goldblatt-clamp", nylon or silk threads, wire loops, etc., may be used, as long as the filament is not too irritating (which would cause inflammatory granuloma formation) or too thin (which might cause it to cut into the vessel wall or elicit the formation of a dissecting aneurysm).

Another useful technique consists in wrapping the kidney in permeable cellophane, silk or other material which provoke a diffuse chronic *perinephritis*.[325]. This results in the formation of a fibrous tissue shell around the kidney, leaving the hilum intact. The perinephritis acts by compressing the kidney and thus interferes with renal circulation essentially in the same manner as the Goldblatt clamp does. Recently some investigators recommended the perirenal application of elastic rubber or plastic capsules which also act in a similar manner.[326] These techniques are claimed to give more predictable results than the Goldblatt clamp, but we feel that results largely depend upon the personal experience of the operator. The danger of the perinephritis procedures is that they sometimes tend to result in suppuration with more or less complete destruction of the kidney.

Rather consistent hypertension and associated morphologic changes in the cardiovascular system have also been obtained (especially in rats) by applying a *"figure of eight ligature"* to the kidney. Such a ligature describes two loops which leave the hilum intact and cross each other on the opposite (convex) surface of the kidney. Experiments with this technique led to the conclusion "... that neither damage of renal tissue nor ischemia nor intra-renal vascular changes are primary prerequisites for the induction of hypertension, but that

[322] Braun-Menendez **A96122/43**,
Corcoran **B29330/48**, Dexter **91416/46**,
Dumont **91513/46**, Goldblatt **B29301/48**,
Goldblatt et al. **B27066/48**,
Goldring et al. **96566/46**,
Page and Corcoran **B2081/45**, **B18005/48**,
Tarantino **B28538/48**,
Trueta et al. **99193/47**.
[323] Flasher and Drury B39034/49,
Flasher et al. B39033/49.
[324] B36287/34, Dexter **91416/46**.
[325] Page B36288/39.
[326] Flasher et al. B39033/49,
Rau B46351/50.

it is the reduction of the total number of functioning nephrons which initiates the disorder."[327] In our opinion, it is equally compatible with the observed facts to assume that the ligature compressed the kidney and thus induced a hemodynamic change very similar to that obtained with the Goldblatt clamp, the perinephritis procedures, or the "endocrine kidney technique" (cf. p. 540). In this sense the rise in blood-pressure would not be due to the destruction of functional nephrons, but to an increase in their endocrine function at the expense of their excretory activity with which the compressing ligature interferes.

Partial nephrectomy is not a very effective procedure to induce persistent hypertension in any species. In the rat, unilateral nephrectomy tends to cause an at least temporary (very rarely persistent) hypertension, while more extensive nephrectomies (up to 5/6th of the total kidney mass) consistently raise the blood-pressure and induce hyalinosis in this species.[328] However, in all other laboratory animals so far examined (e.g., dog, cat, monkey), removal of any amount of renal tissue, compatible with the maintenance of life, results in little or no permanent pressor effect.[329]

Complete bilateral nephrectomy causes death from uremia within two to five days in most species of laboratory animals. It is usually followed by hypotension due to shock or by no change in blood-pressure. If great care is taken to prevent surgical shock, hypotension can be avoided. This shows that the kidney is not indispensable for the maintenance of the resting blood-pressure level. Occasionally, there is even a transient rise in the blood-pressure of nephrectomized animals, but this has been ascribed to a nervous reflex mechanism or to a rise in blood-volume.[330]

If completely nephrectomized animals (e.g., rat, dog) are maintained in good condition by an "artificial kidney" or "peritoneal lavage" procedure, moderate rises in blood-pressure have also repeatedly been observed; here again the results were inconsistent.[331] Yet in some dogs, in which survival was much prolonged by the use of an "artificial kidney", allegedly the rise in blood-pressure was even accompanied by morphologic lesions characteristic of malignant hypertension.[332] Such observations tend to support the view (cf. p. 238, Metabolism), that pressor substances similar to those produced by the kidney can also be elaborated, to some extent at least, by other tissues. Furthermore the kidney is probably capable of detoxifying both renal and extra-renal pressor compounds (cf. also "hind-quarter transplantation" experiments, p. 539). Even if extra-renal tissues produced only minimal amounts of such pressor principles, their effect would become manifest in the nephrectomized animal because of the complete elimination of this renal detoxification. It is of the greatest importance, however, in all pertinent experiments to follow the blood-volume variations. After complete nephrectomy the rise in the circulating fluid volume may be of sufficient magnitude to cause a purely mechanically induced hypertension.[333] Adrenalectomy or Na-deprivation prevents this hypertension.[333a]

[327] Halpert and Grollman B4222/47.
[328] Dexter **91416/46.**
Grollman and Halpert B37739/49.
[329] Dexter 91416/46.
Ogden et al. B32800/49.
[330] Dexter **91416/46.**
[331] Braun-Menéndez and Covian B31716/48,
Braun-Menéndez and
von Euler B25671/47,
Grollman B27069/48,
Grollman et al. B33415/49,
Oppenheimer et al. B32306/48.
[332] Grollman et al. B33415/49, B36852/49,
Muirhead et al. B46098/49.
[333] vanden Bossche B40085/49,
Guillemin **B44418/49.**
[333a] Tobian B47902/50.

Transplantation of a kidney upon a donor animal by vascular anastomosis, has been used especially in acute experiments on the pathogenesis of renal hypertension.[334] Here partial constriction of the transplanted kidney's artery leads to marked hypertension in the recipient animal, but only if the kidneys of the latter have been previously removed. This further supports the view that the normal kidney can detoxify R.P.S.[335]

With the use of this technique, it has also been shown that the excess production of R.P.S. by a clamped kidney is only a transitory phenomenon. In one such experiment on a dog, hypertension was produced by constriction of the renal arteries. At the end of three years the blood-pressure still remained very high, but transplantation of this dog's kidney to another, completely nephrectomized dog produced no elevation of blood-pressure in the latter. It was concluded that at the end of three years the clamped kidney no longer produced any excess of R.P.S. Yet further constriction of the transplant's renal artery considerably raised the blood-pressure of the recipient, thus demonstrating that even after three years, the clamped kidney did not lose its power to produce pressor substances.[336] Hypersensitivity to normal amounts of renin, or the initiation of a secondary "neurogenic" hypertension, have been considered to be responsible for the persistent hypertension of the donor dog, whose kidney has thus been proven no longer to produce an excess of renin. An exhaustion of the kidney's pressor-substance detoxifying power may result in the maintenance of a high blood-pressure despite normal R.P.S. production in such experiments. This same defect could also explain why removal of a clamped kidney in the chronic hypertensive rat often fails to cure a hypertension of long standing even if the structure of the remaining kidney is not grossly abnormal. Perhaps DCA also acts partly by such interference with the renal detoxification of pressor substances,[337] as outlined above.

Transplantation by vascular anastomosis of the hind-quarters (containing neither kidneys nor adrenals) of one dog unto the neck-vessels of another dog, led to very interesting results concerning the pathogenesis of renal hypertension. Constriction of the arteries of such a hind-quarter produced hypertension in the recipient dog. The kidneys of the recipient can detoxify this extra-renal pressor substance (just as they inactivate R.P.S.), since nephrectomized recipients proved much more sensitive than intact dogs. It is especially important that functional excitation (pretreatment with thyroxine, or stimulation of the motor nerves) of such hind-quarters increased the liberation of pressor substances, as judged by the hypertension induced in a nephrectomized recipient. Such functional excitation of the transplanted hind-quarters produced particularly pronounced pressor responses if the arteries of the transplant were partially constricted, but even without such constriction, nervous excitation of the musculature in the transplant sufficed to raise the blood-pressure in the recipient. It was concluded that in thyroxine-pretreated tissues, as in muscles during intense contractions, a condition of "relative ischemia" exists (since the oxygen want is above normal) and that under these conditions, extrarenal pressor substances are produced. In every respect, these substances behaved like renin and were supposed to be identical with this renal enzyme.[338]

[334] Dexter **91416/46.**
[335] Dexter **91416/46.**
[336] Dumont B24764/48.
[337] Selye 94572/49.
[338] Brull B23116/47,
Dumont B26778/43, B26794/43,
91513/46.

These observations are of the greatest importance in the interpretation of vascular responses during the G-A-S. They suggest that non-specific stressors can liberate pressor substances from extra-renal tissues. Whether the substance in question is renin (and leads to the formation of hypertensin) or not, the fact is clear that — like hypertensin — it is inactivated by the normal kidney. The occasional rise in blood-pressure noted in completely nephrectomized animals (cf. p. 538) may well be caused by this same principle. Our investigations along these lines have not yet led to definite conclusions, but, in view of the great theoretic importance of this point, it should be kept in mind that DCA could perhaps also augment the formation (or impede the detoxification) of such extra-renal pressor substances.

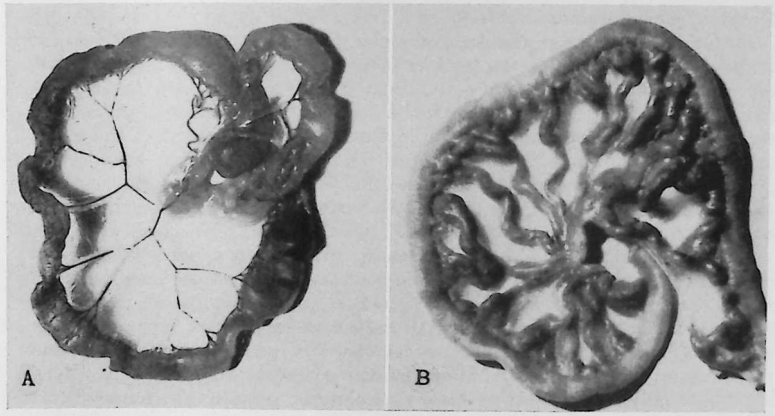
Recently we have developed a technique which permits the complete transformation of the kidney into a structure exhibiting the structural characteristics of a typical endocrine organ. This preparation has been referred to as the *"endocrine kidney"*. Our technique is based upon the fact that in order to permit filtration, the hydrostatic pressure in the glomerular capillaries of the kidney must be much higher than in other capillary territories. Indeed, it is indispensable for urine formation that the hydrostatic pressure in the glomerular tufts be greater than the colloid-osmotic pressure of the blood. To stop filtration we reduce the hydrostatic pressure in the glomeruli to the level of the colloid-osmotic pressure of the blood. By placing the style of a hypodermic needle parallel with the aorta and tying a nylon thread around both aorta and style, an accurately gauged degree of partial constriction can be obtained, which decreases the lumen of the aorta approximately to the width of the style. The latter is subsequently removed and hence circulation re-establishes itself, but if the constriction is placed between the origins of the two renal arteries, it decreases the pressure in the left (lower) renal artery. By choosing styles commensurate with the size of the rat, it is possible to decrease the pressure exactly to the level at which urine formation ceases, while the nutrition of the renal parenchyme does not suffer.

The precise gauging of the degree of constriction is difficult, but a greater safety margin can be introduced by simultaneously occluding the left ureter by transection between two ligatures. Thus, if the aorta constriction is not quite sufficient, a slight hydronephrosis develops which nullifies the effects of any remaining filtration pressure.

The adequacy of the operation is readily determined, at autopsy, by naked-eye inspection; if the vascular constriction is too great, the left kidney becomes partially (or even completely) necrotic, while if it is insufficient, an excessive hydronephrosis is formed.

A few days after this operation, the entire renal parenchyme transforms itself. The glomeruli tend to disappear completely or are transformed into inconspicuous, poorly vascularized scars. The tubular lumina disappear and the nephrons undergo severe involution. The proximal convoluted tubules lose their brush-border and their eosinophilia. Yet the so-called "spiral segments" — that is, the distal portions of the proximal convoluted tubules — exhibit intense proliferative changes. Its cells become enlarged and numerous mitotic figures indicate that in addition to hypertrophy, there is also actual hyperplasia in these segments. The lining cells grow into what was the luminar space, in the form of papillomatous excrescences. These processes eventually lead to the complete transformation of the tubule into solid, rather irregular, cords of

epithelial cells. The juxtaglomerular apparatus tends to disappear together with the other elements of the renal corpuscles. Only occasionally (especially in kidneys in which some infarction has occurred because the ligature on the aorta was too tight) have we noted any proliferative changes in the epithelioid cells of the juxtaglomerular apparatus. There was no manifest relationship between the development of this apparatus and the resulting hypertension or hyalinosis, while there was a fairly close parallelism between the proliferative changes in the spiral segment and the above-mentioned hypertensive lesions. From this it was concluded that probably the cells of the spiral segment are the source of the R.P.S. However, as we have said above, a diminished capacity of the kidney to detoxify R.P.S. may also play a rôle in this as in all other types of experimental renal hypertension and perhaps even in the hypertensive changes produced by LAP, mineralo-corticoids or non-specific stressors.[339]



Periarteritis nodosa caused by the "Endocrine kidney." — **A.** A loop of small intestine in a normal control rat showing the normal aspect of the mesenteric vessels. — **B.** Pronounced thickening of all mesenteric vessels, which showed the histologic characteristics of periarteritis nodosa. In this rat a partially-constricting ligature had been placed, 38 days previously, on the aorta between the origins of the two renal arteries. It caused complete endocrine transformation of the left kidney, accompanied by marked hypertensive disease.

The above-mentioned proliferative changes had already indicated that the cells of the spiral segment were not suffering from any severe lack of nutrition. This was further illustrated by the observation that treatment with renotrophic steroids (e.g., testosterone) or anterior-pituitary extracts, continues to stimulate the morphologic development of these segments in spite of the change in renal hemodynamics.[340] This may perhaps be explained by the "renal shunt" which appears to be maximally opened almost immediately after the endocrine kidney operation; the renal medulla becomes intensely hyperemic, the cortex anemic. Even macroscopic inspection of the kidney shows the extent of this vascular

[339] Dunihue B27067/48, Selye 91824/46, B3142/47, Selye and Stone 94202/46, Stone B23867/49.

[340] Selye 91824/46, Selye and Stone 94202/46, 96099/47.

response; on a section the intense redness of the medulla and the pallor of the cortex clearly indicate that the blood supply is shunted from the latter to the former. This re-arrangement of the renal circulation may assure an adequate blood supply to the juxtamedullary region which (at least in the rat in which these experiments have been performed) contains almost all the spiral segments.

Microdissection of the individual nephrons in the "endocrine kidney" led Oliver [341] to the following conclusions: "In the kidney below the ligature there is a marked atrophy of the proximal convolutions with relatively lesser changes in other portions of the nephron. The total volume of the average proximal convolutions was found to be 30% of normal. This atrophy does not, however, affect all portions of the proximal convolutions equally. The periglomerular portion, which lies in the cortex, was reduced to one-tenth of its normal volume whereas the terminal portion of the proximal convolution, which lies in the medulla (juxta-cortical zone), still maintained 80% of its normal volume. The bizarre hyperplasia described by Doctor Selye was limited to this less atrophied medullary portion.

In the normal nephron, the periglomerular (cortical) portion of the proximal convolution represents two-thirds of its total volume, while the terminal portion represents one-third. This ratio is almost exactly reversed in the endocrine kidney. The change would seem to be related to the change in blood-flow through the kidney, since a reduction in flow would be greatest in the terminal small cortical vessels at the periphery of the vascular tree and would be best maintained by means of the juxtamedullary glomeruli and their efferents (Daniel-Trueta) which supply the medullary terminal one-third of the proximal convolutions".[342]

It is surprizing that, although so many investigators used various types of renal blood-vessel clamps, this "endocrine transformation of nephrons" had never been recognized. Goldblatt [343] had regarded similar changes in his renal hypertensive dogs "as merely an indication of tubular degeneration and atrophy (followed by repair) that occurred as a result of the deprivation of the organ of blood." Such an interpretation is understandable if it is kept in mind that only the "endocrine kidney" technique permits the massive transformation of the whole renal parenchyme into a structure resembling an endocrine gland. In patients with malignant hypertension, as well as in animals bearing the Goldblatt clamp, the filtration pressure is never completely abolished in all glomeruli; only occasional renal corpuscles fail to secrete and hence only their nephrons undergo this transformation. However, after the possibility of this metamorphosis was clearly demonstrated by the "endocrine kidney" experiments, it became possible to recognize the existence of individual "endocrine nephrons" within the renal parenchyme of experimental animals and man suffering from renal hypertension. Re-examination of the clamped kidneys of dogs with chronic renal hypertension did in fact lead to the conclusion that: "In some of these small kidneys there is little or no interstitial fibrosis, and the reduced size of the organ is due mainly to disappearance of glomeruli and of cortical tubules as well as shrinkage of tubules which have no distinct lumen and which are lined by greatly altered epithelium in which signs of regeneration (mitoses and hyperchromatic nuclei) are common in the lining epithelial cells. This is the so-called endocrine kidney which Selye

[341] B36308/48.
[342] Oliver B36308/48.
[343] B27066/48.

has produced in the left kidney of rats by constriction of the aorta between the origin of both main renal arteries".[344]

The endocrine kidney procedure has proved to be useful in the study of various problems concerned with renal hypertension, for instance, to show that ferritin is ineffective in reducing the blood-pressure in rats in which a standard degree of hypertension is produced by this procedure.[345] However, the main value of the technique lies in the fact that it permits the complete transformation of one kidney into an endocrine organ and thus yields a tissue in which endocrine and excretory activities are not co-existent.

In this sense, it is of especial interest that "in endocrine kidneys there is a marked, indeed almost complete, disappearance of both arginase and alkaline phosphatase. On the other hand, the acid phosphatase decreases in total amount but not in concentration". Presumably the acid phosphatase is necessary for the integrity of the cell and perhaps its endocrine function, while the alkaline phosphatase and arginase are necessary only in connection with urine formation.[346]

It will be recalled, furthermore, that the malignant phase of experimental renal hypertension (during which it leads to hyalin arterial necrosis and a rapidly fatal progress of the disease) was attributed to the superimposition on hypertension of renal excretory insufficiency.[347] This theory appeared to be well founded. With most methods used for the production of renal hypertension the malignant phase does develop only when the lesion is severe enough to cause some degree of uremia. With the "endocrine kidney" technique, however, all nephrons of one kidney are suddenly transformed into endocrine units and the resulting hypertension is immediately malignant. It causes marked vascular hyalinosis and even death, within one to three weeks, much before there is any manifest uremia. Excretory insufficiency does not appear to play a rôle here, since the contralateral kidney suffices to prevent uremia. Perhaps the sudden and intense overproduction of R.P.S. by the endocrine kidney rapidly exhausts the power of the contralateral kidney to detoxify such pressor-substances, and thus, causes malignant hypertension.[348]

Using this technique, it has also been possible to show that marked hypochloremic alkalosis ensues almost immediately after the endocrine transformation of one kidney, while the blood-potassium level remains essentially normal.[349] This suggests that metabolic changes conducive to hypochloremic alkalosis can be occasioned by the endocrine products of the kidney. This metabolic derangement may play a part in the pathogenesis of malignant renal hypertension, while the hypokalemia (so characteristic of the hypertension produced by DCA) is obviously not involved here.

Treatment with *"nephrotoxic sera"* results in glomerulonephritis, generalized vascular hyalinosis and hypertension in various species. Such sera are prepared by the repeated injection of renal extracts of one species into animals of another species. This results in the formation of organ-specific anti-kidney antibodies which destroy the renal tissue of the recipient.[350] Using antibodies

[344] Goldblatt B29301/48.
[345] Corcoran et al. B32725/49.
[346] Kochakian and Dontigny B3631/48.
[347] Goldblatt and Kahn 91178/40.
[348] Selye and Stone 94202/46.
[349] Schaffenburg and Selye B3478/48, Selye B3142/47.
[350] Dexter 91416/46. Knowlton et al. 91205/46.

tagged by radioactive tracers it has been noted that nephrotoxic sera have a selective affinity for renal glomeruli.[351]

The question has repeatedly been raised whether such a nephrotoxic nephritis could play a rôle in the pathogenesis of clinical hypertension. The possibility has been envisaged that allergy to endogenous renin or hypertensin may cause hyalinosis through some similar mechanism of sensitization.[352] It will be remembered that increased formation of renin and hypertensin is demonstrable, by actual bioassay of the blood, only during the first stages of experimental hypertension; yet the blood-pressure often continues to remain high. These facts led to a somewhat similar conclusion, namely that hypersensitivity to R.P.S. had been created (cf. above).

It has been claimed, furthermore, that incubation of streptococci with kidney tissue leads to the formation of particularly nephrotoxic substances.[353] If this observation were confirmed, it might explain the specific tendency of certain microörganisms such as the streptococcus, to cause nephritis and rheumatic changes characterized by hyalinosis.

Various *nephrotoxic drugs, bacterial toxins* (e.g., uranium salts,, oxalates, derivatives of mercury, bismuth, lead, diphtheria toxin, streptococcus toxin) and especially the injection of irritating substances (e.g., trypsin) into the renal artery itself, tend to cause nephritis, nephrosclerosis and occasionally hypertension, but the results are extremely irregular; [354] hence such techniques have not been routinely used on a large scale.

Various *other traumatic interventions on the kidney* such as injection of sclerosis-producing irritants into the renal parenchyme,[335] complete ligature of the renal artery or of its branches, partial or complete ligature of the renal vein, the production of arteriovenous anastomoses, complete or partial ligature of the ureter, the artificial production of renal embolisms, have all been used to produce experimental hypertension in animals.[356] Some of these investigations yielded interesting results concerning specific problems in the pathogenesis of renal hypertension, but the pressor responses obtained are too irregular for routine use.

The **cardiovascular changes produced by the various techniques used for the production of renal hypertension** are remarkably similar. They simulate the "hyalinosis syndrome" which we have previously described as also being characteristic of chronic exposure to stress, or treatment with LAP, DCA or desoxocortisone. This is clearly demonstrated by numerous histologic studies on dogs with a Goldblatt clamp [357] and on rats,[358] with a "figure of eight ligature",[359] perinephritis [360] or an "endocrine kidney".[361]

From a histogenetic point of view apparently the basic change in all these cases is an increased membrane permeability — a "dysoria" [362] — which allows plasma to penetrate into the vessel-walls and the surrounding tissues. There it leads to the formation of the abnormal proteinaceous material known as

[351] Pressman B36683/49.
[352] Schloss B26355/48.
[353] Cavelti B4227/47, B4336/47, B18572/46, B38103/48, Cavelti and Cavelti 88849/45, 88869/45, 88850/45.
[354] Dexter **91416/46.**
[355] Rindone B37591/48.
[356] Dexter **91416/46.**
[357] Dexter **91416/46.** Goldblatt B29301/48.
[358] Schloss B26355/48.
[359] Halpert and Grollman B4222/47.
[360] Jablons 98539/47.
[361] Selye and Stone 94202/46.
[362] Schloss B26355/48.

"hyalin", which in turn stimulates granuloma formation. Hyalinosis does not occur in the clamped kidney, or anywhere else distal from a partially constricting ligature (e.g., in mesenteric arteries); this is true even in animals exhibiting most intense hyalinosis in other parts of their vascular treè. Presumably a high blood-pressure is indispensible for the hyalin infiltration. Since, on the other hand, hypertension (e.g., neurogenic) in itself does not suffice to produce hyalinosis, it was concluded that both high blood-pressure and a humoral factor are involved in its pathogenesis. The humoral substance is mainly, but perhaps not exclusively, of renal origin.[363]

Removal of the clamped kidney does not abolish a well established hypertension if it is performed late (e.g., one or more months after the establishment of a high blood-pressure level). Conversely, early removal of such a kidney (e.g., during the first few weeks after the operation) usually elicits at least a temporary normalization of the blood-pressure, if the contralateral kidney is still in good condition.[364] As we have stated before, the increase in the renin content of the blood is also demonstrable only during the initial phases of renal hypertension. Hence it was thought that removal of the clamped kidney helps only during that phase of the hypertensive disease during which the increased production of R.P.S. is the principal cause of the derangement, while later the hypertension may become neurogenic.[365] Yet, as we shall see below, the response of the blood-pressure to autonomic drugs (e.g., TEA, benadryl) failed to demonstrate a late neurogenic phase in renal-hypertensive animals.[366] Furthermore, extensive experiments on rats with perinephritis showed that even early removal of the directly damaged kidney rarely, if ever, brings about a true permanent cure. In most animals, after an initial blood-pressure drop, the blood-pressure gradually rises again and eventually (sometimes only after many months) fatal hypertensive disease ensues. This was found to be true even if the damaged kidney was removed before any visible change had time to develop on the other side.[367]

Such observations are difficult to explain; perhaps, under these conditions, the ability of the contralateral kidney to inactive R.P.S. is permanently impaired. After removal of the perinephritic kidney, the remaining detoxifying power of the contralateral kidney may temporarily suffice to cope with the (now diminished) circulating R.P.S. Yet this inactivation may be performed by the damaged kidney under considerable stress and hence lead to the eventual exhaustion of the residual detoxifying power. This process is reminiscent of the so-called "Sandmeyer type" of diabetes, induced by partial pancreatectomy. Here the remaining glandular (pancreatic) tissue temporarily succeeds in compensating for the lack of insulin and the blood-sugar level remains constant for weeks or even months, but eventually the Langerhans islets are exhausted and fatal diabetes ensues.

In agreement with this interpretation, it has been shown that if one renal artery is constricted with a clamp and the contralateral kidney is simultaneously removed, the resulting hypertension and cardiac hypertrophy subside after **removal of the clamp** from the remaining kidney. It was concluded that the

[363] Selye 35935/ND, Selye and Stone 94202/46.
[364] Dexter **91416/46.** Flasher and Drury B39034/49, Ogden **B29650/47.**
[365] Ogden B29650/47.
[366] Page and Taylor B36674/49.
[367] Flasher and Drury B32741/49, Gaudino 85570/44.

residual hypertension which persists in rats with a second kidney, even after the contralateral clamped kidney is removed, is due to renal damage caused largely, if not entirely, by the hypertension itself.[367a] It will be remembered that the arterial clamp protects the kidney against the direct effects of an increased blood-pressure.

Certain **kidney extracts** are highly effective in diminishing the blood-pressure level in animals with renal hypertension.[368] This also suggests that the kidney exerts important antihypertensive actions. Renin-containing kidney extracts proved particularly efficient in depressing the blood-pressure of chronically hypertensive animals; hence it was thought that some "anti-renin" substances may be involved.[369] These extracts also protect against the arteriolonecrotic lesions which normally accompany renal hypertension, for instance, in the dog. Some recent observations intimate that these arteriolonecrotic (hyalinosis) changes are due to a separate "renal necrotizing substance" which is not renin.[370] Indeed, on precipitation with acetone, it has been possible to separate a non-dialyzable fraction of acid kidney-extract, which was devoid of either vasopressor or depressor activity. It proved to be a protein-like material containing phosphorus. "When injected into nephrectomized dogs, it was found to be associated with widespread arteriolar necrosis".[371]

Hepatic damage caused by carbon tetrachloride, prevents the establishment of renal hypertension, although it does not impede the rise in blood-pressure following destruction of the depressor nerves in the rabbit. This was ascribed to a deficiency in hypertensinogen, which is normally elaborated in the liver.[371a]

Partial pancreatectomy (95%) increases the hypertension caused by experimental perinephritis in the rat.[371b] This may have some bearing upon the well known predisposition of diabetics to develop hypertension.

In connection with the possible participation of the kidney in the vascular manifestations of the G-A-S, it is interesting that, for instance in cats, the usual arterial and arteriolar constriction following **traumatic injury** (tourniquet) to a limb occurs even in the complete absence of kidney tissue.[372] Of course, this merely shows that the kidney is dispensable for such a response, but not that renal vasoconstrictors fail to participate in it under ordinary circumstances. Perhaps, in the absence of the kidney, alternate homeostatic mechanisms fully compensate for the loss.

In experiments on dogs, the blood consistently showed pressor activity after **hemorrhage.** "Many of the responses were renin-like, persisting 10 to 30 minutes; others of equivalent magnitude approached the duration of reactions to angiotonin". The renal origin of these pressor substances was demonstrated by their absence in adrenalectomized-nephrectomized dogs submitted to equally severe hemorrhage. In the same study it was also shown that nephrectomy impairs the ability of the dog to maintain its blood-pressure after hemorrhage.[373] Nephrectomized rats likewise exhibit more severe hypotension, and

[367a] Byrom and Dodson B44515/48.
[368] Dexter **91416/46.**
[369] Burns et al. B32715/49.
Kiely et al. B47154/50.
Marshall et al. B33109/48.
De Sutö-Nagy and Waters B32945/49.
Wakerlin et al. B32845/49.
[370] Burns et al. B32715/49.
[371] De Sutö-Nagy and Waters B32945/49.
[371a] Capone-Braga B46753/49.
[371b] Braun-Menendez and Martinez B46378/49.
[372] Page and Abell 84114/43.
[373] Collins and Hamilton 81946/42.

die after removal of smaller amounts of blood, than sham-nephrectomized controls.[374] However, pertinent data are somewhat contradictory since in other experiments on dogs, bilateral nephrectomy — even if accompanied by hepatectomy — allegedly failed to influence the hypotensive action of hemorrhage.[375] Presumably, the relative participation of the kidney in blood-pressure homeostasis depends largely upon experimental conditions.

Experiments on nephrectomized rats showed that their resistance to *burns* is subnormal, but this was ascribed principally to excretory insufficiency since ureter ligation caused a similar diminution in resistance.[376] Yet ureter-ligation — with the consequent kidney compression by hydronephrosis — might have interfered also with the incretory activity of the kidney.

Production of an abscess (tissue implantation or intramuscular injection of CCl_4) leads to a fall in the blood-pressure of renal hypertensive dogs. There is also an increase in the renal blood-flow, but this is not always synchronous with the fall in blood-pressure; hence it was concluded that, under such conditions, the latter is not necessarily a consequence of the former.[377] Allegedly, here again, the antihypertensive effect of tissue injury is mediated through the A-R mechanism.[377a]

Various intercurrent systemic **diseases** tend to reduce the blood-pressure in renal-hypertensive animals. In dogs distemper is notoriously effective in this respect.[378] Perhaps this — as well as the beneficial action of various **non-specific organ extracts, bacterial toxins and drugs**[379] — are merely the result of the systemic stress which these agents cause. (For theory of such non-specific therapeusis, cf. p. 106.)

In summary, it may be said that available data neither prove nor exclude the participation of the renal-pressor-mechanism in the vascular responses to non-specific systemic stress. There is no doubt, however, that an A-R diminishes the blood-pressure in experimental renal hypertension.

In renal hypertensive dogs, neither **folliculoid** nor **testoid** hormones exerted any significant effect upon the blood-pressure.[380] Similarly, in rats bearing an "endocrine kidney", even large doses of testosterone failed to influence the blood-pressure or the morphologic manifestations of hyalinosis, although a definite renotrophic effect was manifest, both in the intact and in the non-secretory kidney.[381]

Data concerning the influence of **pregnancy** upon the development of renal hypertension are somewhat contradictory. However, most investigators agree that, at least just prior to delivery, the blood-pressure tends to fall, while after delivery it returns to the previous high level.[382]

Parabiosis experiments yielded interesting information concerning the pathogenesis of renal hypertension. If three of the four kidneys in a pair of parabiotic rats are removed, hypertension develops, but only in the unilaterally nephrectomized twin.[383] If only the two kidneys of one twin are removed, the blood-pressure rises in the nephrectomized animal, but not in its twin.[384]

[374] Bahnson A71310/43.
[375] Reinhard et al. B17738/48, B29448/48.
[376] Hechter et al. B2007/45.
[377] Stamler et al. B32834/49.
[377a] Stamler et al. B46212/50.
[378] Wakerlin and Gaines A34993/40.
[379] Dexter **91416/46.**
[380] Wakerlin and Gaines A34993/40.
[381] Selye and Stone B19379/49.
[382] Dexter **91416/46.**
Gorizontov and Andreeva B27319/48.
[383] Jeffers et al. A34192/40.
[384] Grollman B4352/47.
Grollman and Rule A57773/43.

This was subsequently confirmed, but since the results were not quite consistent, a bilaterally nephrectomized rat was joined in parabiosis with two normal rats (one on each side), whereby its general condition was improved and survival prolonged. Arterial hypertension was then consistently observed in the nephrectomized animals of such "triplets", but only occasionally did a moderate rise in pressure occur in one or both of the normal parabionts. It was thought that probably "the normal kidney inactivates some extrarenal factor producing hypertension".[385] However, in the course of further studies "an increase in blood-volume and in the volume of extra-cellular fluid was found in parabiosed nephrectomized animals. It is supposed that this may be an important factor in the observed hypertension" in the nephrectomized animals of parabiotic triplets.[386] In experiments concerning the "antihypertensive action" of normal kidney tissue, this factor is often disregarded. Even in experimental arrangements not involving parabiosis, it would be rewarding to examine to what extent the antihypertensive action of normal renal tissue is dependent upon the ability of the kidney to regulate the blood-volume.

Conversely, the parabiotic union of a normal rat with one in which hypertension had been produced by unilateral perinephritis, led to the normalization of the blood-pressure in the former. Surgical separation of the two parabionts was followed by the rapid return of the hypertension in the perinephritic animal. No change in the blood-pressure of a hypertensive rat is produced by parabiotic union with another hypertensive or with a nephrectomized rat. Unfortunately in these experiments no attempt was made to determine the relative rôle played by the detoxification of R.P.S. and the regulation of blood-volume by the intact kidney tissue.[387]

Some investigators claimed that diets poor in **sodium** diminish the blood-pressure and prolong the survival time of rats,[388] and dogs [389] with various types of experimental renal-hypertension. It has also been stated that both in the rat [390] and in the dog [391] this type of hypertension runs paralled with the **protein** content of the food. The rice and fruit juice diet advocated by Kempner,[392] which is deficient both in protein and in sodium, was claimed to be particularly effective in reducing the blood-pressure of rats suffering from renal hypertension.[393] Others, however, obtained inconclusive results with either protein or sodium deficient rations.[394] Subsequent observations suggested that while on high-protein diets sodium restriction has no effect upon renal-hypertension in the rat, protein deficiency is beneficial and sodium restriction "prolongs still further the lives of animals on low-protein diets".[395]

Our studies in rats bearing an "endocrine kidney",[396] as well as those of others in dogs with experimental perinephritis,[397] failed to show any relation-

[385] Braun-Menéndez and von Euler B25671/47.
[386] von Euler and Braun-Menéndez B27865/48.
[387] Braun-Menéndez and von Euler B27864/48.
[388] Grollman 89543/45, Grollman and Harrison B1104/45, Grollman et al. B777/45, Handler and Bernheim B46213/50.
[389] Hantschmann 99721/31, Verney and Vogt 98709/38.
[390] Braun-Menendez and Martinez B46378/49, Handler and Bernheim B17889/48, B46213/50,
[391] Verney and Vogt 98709/38.
[392] B740/45.
[393] Grollman and Harrison B1104/45.
[394] Guerrant et al. A64074/43, MacLachlan and Taylor B33786/40, Philipsborn et al. A55887/41.
[395] Handler and Bernheim B36354/49.
[396] Selye and Stone B18527/48, B19379/49.
[397] Page and Lewis B36675/49.

ship between the dietary sodium or protein intake and the resulting hypertensive disease. The "endocrine kidney" experiments were performed both on low- and on high-protein diets, both with and without sodium restriction; under no circumstances, was there any significant influence upon the course of the hypertensive disease due to a variation in the dietary concentration of these food constituents.[398] In this respect, primarily renal hypertension differs sharply from that produced by corticoids (inhibited by sodium deficiency), or LAP (inhibited by protein deficiency). Perhaps the occasional positive findings of earlier investigators may find their explanation in that they used experimental procedures causing less complete and less rapid "endocrine transformation" of the kidney. Presumably, the peripheral action of R.P.S. itself is uninfluenced by the diet. Apparently the beneficial effect of protein deficiency is merely due to a decreased ACTH production, while sodium deficiency acts by inhibiting the effect of mineralo-corticoids upon the kidney, thus it impedes "endocrine transformation" of nephrons and the concomitant rise in R.P.S. Perhaps it also prevents the normal inactivation of pressor-compounds and the compensatory regulation of the blood-volume by the kidney. In the case of the "endocrine kidney" procedure or any other type of intervention which causes very rapid and almost maximal "endocrine transformation" due to a direct peripheral action upon the kidney itself, such dietary measures would therefore be ineffective.

Administration of excess **potassium** to rats rendered hypertensive by the silk-perinephritis method, occasioned no change in the blood-pressure level. In the publication describing these data, it is stated that they differ from our observations concerning the sensitization of the rat to DCA hypertension by "potassium".[399] It will be recalled, however, that we found sodium to exert such a sensitizing effect and we learn from a personal communication of the authors that their reference to potassium was merely due to a typographic error.

Restriction of food consumption allegedly lowers the blood-pressure of rats with renal hypertension on any diet, but has least effect on low-protein, high-sodium rations.[400] Even this measure exerts little, if any, influence upon the rapidly fatal course of the hypertensive disease in rats bearing an endocrine kidney.[401]

Nevertheless, many observations suggest that, under certain circumstances, the diet can change the course of renal hypertension. For instance, it was shown that in dogs, a specified high-**fat** diet, causes no cardiovascular lesion in itself. However, if the kidneys are removed, or damaged in one of several ways, after the dogs have been kept on this diet for two months or longer, intense periarteritis nodosa or rheumatic arteritis-like lesions become evident. The development of these lesions can be prevented or at least retarded by **vitamin-E, cholesterol** or by merely omitting the excessive fat-supplement for four weeks or longer.[402] "From these experimental studies, the suspicion has grown that a disturbance of fatty-acid metabolism is fundamental in the genesis of arterial lesions and that the kidney plays an important rôle in this disturbance". ..."In some species, and possibly in all, cholesterol may be

[398] Selye and Stone B18527/48, B19379/49, A57456/43, B4333/47, 98688/47.
[399] Jarpa and Croxatto B33754/48, 84081/43,
[400] Handler and Bernheim B36354/49. Holman and Swanton 94958/46.
[401] Selye and Stone B44270/ND. Holman et al. B47287/50.
[402] Holman A97133/43, A97132/43,

primarily protective and only secondarily alterative".[403] Damage to tissues other than the kidney (prolonged chloroform anesthesia, abscess formation due to injection of turpentine, bacterial infections, etc.) does not elicit such necrotizing arteritis in dogs pretreated with the same high-fat diet. Indirect evidence led to the suggestion that perhaps "...the proximal convoluted tubules elaborate a substance that is necessary for the proper utilization of certain lipid substances".[404]

Apparently, it depends largely upon the conditions of the experiment whether cholesterol has a pathogenic or curative effect in animals with renal damage. In rabbits and dogs fed a high-cholesterol diet until marked hypercholesterolemia developed, subsequent acute renal damage (caused by uranium or nephrotoxic serum) produced marked aortic atheromatosis within a few days or weeks; the same diet elicited only a very low incidence of such atheromas in controls without renal damage.[405] Yet, as we shall see below, at least in some species, prolonged overdosage with cholesterol in itself suffices to cause severe lesions in the cardiovascular system.

During recent years, considerable attention has been given to the effects of **autonomic drugs** upon the vascular system in renal hypertension. It has been stated that during the early weeks of renal hypertension, nembutal, yohimbine or F883 exert no effect upon the high blood-pressure level, but animals which had been hypertensive for several months, usually show a lowering of their blood-pressure in response to these drugs. This, and many related observations have been cited in support of the view that in the later stages — unlike in early renal hypertension — the maintenance of a high blood-pressure level is effected through the nervous system, particularly the sympathetic.[406] However, subsequent work does not appear to support this view. For instance, dibenamine produces a greater decline in the blood-pressure of renal hypertensive than of normotensive rats. This effect was ascribed to the adrenergic blocking action but since dibenamine is at least as effective in the acute as in the chronic renal hypertension, it was concluded that the observations "do not support the contention that a greater neurogenic factor is involved in late than in early renal hypertension".[407] Extensive experiments on renal hypertensive dogs led to essentially similar conclusions: "neither early nor late after eliciting renal hypertension does the vascular reactivity to adrenaline, nicotine, histamine, barium chloride, angiotonine, renin or tetraethyl ammonium chloride change in a characteristic fashion, so as to suggest the dominance of either the nervous system or a humoral mechanism in the production or maintenance of hypertension".[408]

In this connection it is also noteworthy that immediately following pretreatment with TEA the pressor responses normally elicited in the dog by renin or hypertensin [as well as that caused by adrenaline (cf. p. 521)] are enormously increased. The mechanism of this sensitization has not yet been elucidated, but it has been compared to the sensitization to adrenaline induced by denervation, although the latter takes much longer to become manifest.[409]

[403] Holman B28165/48.
[404] McCormick and Holman B32953/49, B43581/49.
[405] Moses et al. B32794/49.
[406] Ogden **B29650/47.**
[407] Nickerson and Goodman B25559/48, Nickerson et al. **B23904/48.**
[408] Page and Taylor B36674/49.
[409] Page and Taylor B24841/47.

Available data do not permit us to outline clearly the extent to which the **nervous system** participates in the pathogenesis of renal hypertension. Although the blood-pressure of renal hypertensive rabbits is markedly diminished by pithing,[410] it can be raised again by the subsequent administration of renin.[411] Furthermore, extensive sympathectomies failed to reduce the blood-pressure to normal in various species of animals in which hypertension had been induced by interventions on the kidney. Of course isolated denervation of the clamped kidney itself is likewise ineffective.[412] Hence R.P.S. does not appear to act through the nervous system, although its effect upon the vessels is undoubtedly modified by the condition of the latter. There is also ample evidence to suggest that nervous stimuli can increase the production of R.P.S. through their effect upon renal circulation (cf. p. 553).

Other hormones. — In addition to the humoral substances produced by the hypophysis-adrenal-kidney axis, several other hormones have been shown to influence the cardiovascular responses during the G-A-S. As a pertinent example let us mention the important rôle of the **pancreas** in clinical diabetes, where the incidence of hypertension and arteriosclerosis is notoriously high.[413] (Cf. also Kimmelstiel-Wilson syndrome, below.) The participation of the pancreas in the production of hyalinosis has been brought out particularly well by experiments on partially pancreatectomized rats. These develop typical hyalinosis of the renal glomeruli and arterioles, similar to that seen in clinical diabetes, several months after markedly elevated blood-sugar levels have established themselves.[414] Contrary to anticipation, however, alloxan-diabetic rabbits are singularly resistant to the production of atherosclerosis by cholesterol feeding.[415] Here, the possible part played by the exocrine pancreas (fat absorption, lipotropic factors) may deserve more attention than it has hitherto received.

In guinea-pigs, the tendency of a focal hemolytic streptococcus infection to cause non-purulent carditis is greatly increased by heavy overdosage with insulin. Allegedly the "susceptibility of the cardiac damage during infection is probably associated with the altered metabolic activity incident to insulin treatment".[416]

The **thyroid** undoubtedly also plays an important rôle in modifying cardiovascular responses during the G-A-S. It is needless to review here the well-known changes in pulse rate and pulse pressure which are characteristic of clinical hypo- and hyperthyroidism respectively. Available data do not permit us to appraise the possible relationship between the intercellular protein accumulations characteristic of the "myxedema of the heart" and those seen in the hyalinosis syndrome.[417] Under some experimental conditions it is apparently possible to produce arteriosclerosis and myocarditic lesions in animals by thyroxine overdosage, but this is not regularly the case,[418] and we do not know upon what conditioning factors it depends.

A relationship with the G-A-S is particularly suggested by the observation that thyroxine induces non-purulent carditis in guinea-pigs or rabbits infected

[410] Dock B36727/40, B36726/40.
[411] Dock B36727/40, B36726/40.
[412] Dexter 91416/46, Ogden **B29650/47.**
[413] Selye **94572/49.**
[414] Foglia et al. B31714/48, Mann and Goddard B33426/49.
[415] McGill et al. B32954/49.
[416] Schultz and Rose B31347/39.
[417] Selye **94572/49.**
[418] Hueper **91730/45**, Marino B36630/45.

with a hemolytic streptococcus.[419] It has already been mentioned in other connections that the production of hyalinosis and myocarditis by stress, LAP and DCA are facilitated by thyroxine administration.[420]

Thyroidectomy, or functional inactivation of the thyroid by thioureas, causes bradycardia and involution of the heart muscle.[421] Thiouracil facilitates the production of arterial lesions "similar in distribution and morphologic characteristics to human arteriosclerosis" by cholesterol feeding in dogs, although given separately, neither cholesterol nor thiouracil causes any significant incidence of such changes under otherwise comparable circumstances.[422] In the chick, thyroid feeding tends to inhibit cholesterol atherosclerosis.[422a]

In the fowl, **folliculoids** such as stilbestrol do not inhibit the production of cholesterol atheromatosis but may modify the distribution of the lesions in the vascular territories.[423]

Certain alcoholic **urine extracts** raise the blood-pressure after an initial decrease.[424] This type of effect is shared by a number of toxic substances which, after an initial (hypotensive) shock phase cause secondary (hypertensive) counter-shock phenomena; hence it is highly problematic whether such changes should be ascribed to some specific humoral compound eliminated through the urine.

The alleged participation of **"splenic hormones"** in the pathogenesis of cardiovascular changes during the G-A-S [425] has already been mentioned.

Nervous stimuli. — In several earlier passages of this book we touched upon the participation of the nervous system in the cardiovascular responses during the G-A-S. We mentioned that nervous stimuli can act as systemic stressors eliciting a G-A-S (cf. page 504) and both autonomic drugs (cf. page 550) and surgical interventions on the nervous system (cf. page 551) can influence the course of primarily renal hypertension.

The mechanism of the persistent and intense blood-pressure rise which ensues following transection of the **depressor ("modulator") nerves,** has been studied particularly by Heymans and his co-workers.[426] From these investigations it is obvious that proprioceptive nervous reflexes — arising in the carotid sinus, the arch of the aorta, the heart and several other vascular regions — help to maintain a steady blood-pressure level. An increase in pressure within these vascular territories stimulates the depressor nerves and thus tends to restore the blood-pressure towards normal. "In fact the endovascular pressure itself regulates and adapts automatically the cardiac output, the circulating blood-volume and the peripheral vascular resistance so well that the arterial pressure is maintained within normal limits. This automatic and proprioceptive regulation is effected mainly by the intermediation of the pressoreceptor innervation of different arterial and venous vascular areas".[427] Such reflexes must obviously play an important rôle during the G-A-S.

"Complete removal of the paravertebral sympathetic chains prevented the elevation of blood-pressure that ordinarily follows section of the modulator

[419] Schultz B36729/38.
[420] Selye B1204/46.
[421] Leblond and Hoff A97859/44. Selye **94572/49.**
[422] Steiner et al. B28166/48.
[422a] Dauber et al. B46189/49.
[423] Chaikoff et al. B36779/48.
[424] Simon B38192/48.
[425] Ungar B4934/47.
[426] Charlier B23221/48, B23223/48, Heymans 75530/38, Heymans and Casier B23147/48, Heymans and Pannier B23146/48, B23145/48, Heymans et al. **A2429/33.**
[427] Heymans 75530/38.

nerves, provided that these nerves were cut before the onset of the incomplete vasomotor recovery which ordinarily follows complete sympathectomy in dogs. Similarly, total paravertebral sympathectomy reduced the blood-pressure of neurogenic hypertensive animals to or below normal for a time (4 to 6 weeks)", although later, some degree of blood-pressure rise did occur.[428] Isolated denervation of the kidneys and removal of various other parts of the sympathetic nervous system, leaving the splanchnics intact, did not prevent such neurogenic hypertension. "Hypertension, apparently of renal origin, was observed to follow division of the modulator nerves in dogs completely sympathectomized except for the splanchnic nerve distribution to the adrenal glands and kidneys. This was markedly reduced by subsequent denervation of the kidneys. Late elevations of pressure, apparently parallel to those observed in totally sympathectomized dogs, were seen in some of these animals".[429]

Conversely, it was demonstrated that persistent and intense arterial hypertension can be produced by selective overstimulation of the **renal nerves** alone.[430] This has especially clearly been shown in nephrectomized dogs in which a pair of kidneys is transplanted (by vascular anastomosis) to the neck vessels. Here electric stimulation of the vasomotor nerves of the transplanted kidneys led to a manifest increase in the R.P.S. production of the transplant coinciding with a visible renal vasoconstriction.[431] Conversely, in rabbits with neurogenic hypertension, the vasopressor activity of blood taken from the renal vein fell suddenly after transection of the kidney nerves.[432]

All these observations are compatible with the view that, in the experimental neurogenic hypertension induced by transection of the depressor nerves, the blood-pressure rises as a result of increased sympathin, adrenaline and R.P.S. production. The latter response is presumably induced through the sympathetic nerves of the kidney which can cause renal vasoconstriction with consequent hemodynamic changes in the kidney similar to those induced by arterial clamps. As long as any one of these pressor mechanisms remains intact, the blood-pressure can rise in response to depressor-nerve transection, but after complete elimination of the sympathetic nervous system, significant neurogenic pressor responses of this type are no longer possible.

Cardiovascular derangements may also result in man owing to abnormal sensitivity of the pressoreceptor areas. This is illustrated by the **"hypersensitive carotid sinus syndrome".**[433] In man suffering from this syndrome, stimulation of the sinuses by pressure caused bradycardia, hypotension and syncope. The bradycardia has been ascribed to increased vagal tonus and the hypotension to a vasodilatation of sympathetic origin. In this patient, *atropine,* through its effect upon the vagus, blocked the parasympathetic but did not influence the sympathetic component; *TEA,* which paralyzes both parasympathetic and sympathetic ganglia, prevented both responses.[434] Surgical denervation of the carotid sinus causes marked hypertension in man, especially if the operation is performed on both sides.[435]

Extensive destruction of the **spinal cord** usually causes hypotension due to vasomotor paralysis. In patients with localized high spinal-cord lesions, however, paroxysmal spells of hypertension may be elicited by almost any cutaneous

[428] Grimson B33775/41.
[429] Grimson B33775/41.
[430] Heymans and Bouckaert 89592/39.
[431] Coppée and Dumont B24049/46.
[432] Kin A32185/39.
[433] Weiss and Baker B36751/33.
[434] Taylor et al. B24844/47.
[435] Penfield and McEachren B38671/47.

or proprioceptive stimulus. This is usually accompanied by intense sweating, flushing of the face, pilomotor erection, congestion of the nasal passages, convulsions and loss of consciousness. The syndrome is effectively controlled by *TEA* and has been ascribed to a reflex "mass sympathetic discharge" in response to non-specific stimuli.[436]

The participation of the nervous system in the cardiovascular responses to acute systemic stress is of particular interest in connection with the G-A-S. Here we can not discuss all the many nervous reflex mechanisms which are called into play to preserve the homeostasis of blood-pressure. Let us merely re-emphasize the importance of the principal neuro-humoral mechanisms.

The tachycardia induced by *hemorrhage* in cats whose heart had been previously denervated (and thus sensitized to adrenaline), is due to an increase in the endocrine secretion of the adrenal medulla. This, in turn, depends upon the integrity of the splanchnics; it is prevented by splanchnicotomy.[437] Obviously here, both the sensitivity of the target organ (heart), and the production of the pressor substance itself (adrenaline) are dependent upon nervous stimuli. The splanchnics can effect an adrenaline discharge while the normal tonus of the cardiac nerves exerts a continuous inhibitory influence upon the responsiveness of the heart to the circulating adrenaline. The general vasoconstriction caused by hemorrhage is also largely dependent upon the integrity of the sympathetic nervous system. Thus, in normal dogs, hemorrhage causes a less pronounced vasoconstriction in the heart and brain than in other organs. In sympathectomized dogs, such "preferential treatment" of the vital centers is lost and all vascular territories react in essentially the same manner. Consequently, resistance to stress is greatly reduced because of the tendency to develop cardiac and cerebral anemia.[438]

An essentially similar difference between the intact and sympathectomized animals is seen during *traumatic shock*.[439] Application of a tourniquet to the hind legs of the dog produces pronounced renal vasoconstriction and may thus increase the production of R.P.S. Dogs in which afferent stimuli from the hind legs were blocked by section of the spinal cord do not exhibit this renal vasoconstriction. Consequently, it was concluded that this vascular response is neurogenic and arises at the site of tourniquet-application. Yet, mere denervation of the kidneys does not prevent renal vasoconstriction following application of the tourniquet; hence, presumably, the ultimate effector mechanism is still humoral.[440]

In agreement with expectations, the hypotensive action of various *shock-producing drugs*, such as peptone, histamine or acetylcholine is greatly augmented by sympathectomy.[441]

Various *cinchona alkaloids* proved very effective in decreasing the blood-pressure of dogs with neurogenic hypertension. Indirect evidence suggests, however, that at least part of this beneficial effect is due to renal hyperemia.[442]

Drugs and Diet. — Among the many publications concerning the influence of various drugs and dietary constituents upon the cardiovascular system, only a few have a direct bearing upon the G-A-S and its diseases. Some of these

[436] Thompson and Witham B26325/48.
[437] Cannon B14905/39, Freeman A32609/35.
[438] Freeman et al. B27052/38.
[439] Freeman B314/39.
[440] Taylor and Page B32838/49.
[441] Bennati and Bacq B23242/47.
[442] Hiatt B29449/48.

have been discussed in a previous section conjointly with other stressors which produce organ changes possibly related to the G-A-S. Here we shall merely consider a few special instances in which such compounds act primarily as stimuli influencing the course of a G-A-S elicited by other stressors.

We have repeatedly mentioned the important rôle played by **sodium** in the production of hypertension and hyalinosis by LAP and corticoids. Only in neurogenic and in particularly acute and intense renal hypertension (e.g., endocrine kidney) does sodium fail to affect the development of the hypertensive disease (cf. p. 548). In the rat, as in most laboratory animals, high-sodium diets, in themselves, do not cause hypertension or cardiovascular lesions, but rats exposed to systemic stress (for instance, cold) develop such changes much more readily on high than on low-sodium diets.[443] Curiously, cold is much more effective in this respect than most other stressors, except parenterally administered foreign proteins.[444a]

Unlike the other species so far examined, the chick develops hypertension, nephrosclerosis and arteriosclerosis on high-sodium diets even without any additional treatment.[445]

We have also previously mentioned that wherever sodium aggravates hyalinosis and hypertension, **ammonium chloride** and other "acidifying salts" exert an opposite effect. In view of these findings NH_4Cl was administered to rabbits in which an allergic reaction of the periarteritis nodosa type was produced by horse serum. "There was a decreased incidence of arteritis in the group of animals receiving horse serum and ammonium chloride, and it is suggested that this trend might become significant by a more effective use of ammonium chloride". Under the conditions of this experiment the serum Na/Cl ratio was not significantly altered until after the 24th day of treatment, when it began to fall. Nevertheless, the authors conclude that "these results clearly indicate that the development of foreign protein arteritis is not mediated through alterations of the serum Na/Cl ratio and therefore, if such an alteration is essential to the development of DCA-induced arteritis, as suggested by Selye, then the pathogenesis of these two varieties of arteritis must be different".[446] In the pathogenesis of the hyalinosis produced by mineralo-corticoids, Na presumably acts in the receptor cells themselves, not in the circulating blood. A rise of the Na/Cl ratio of the serum is merely an index of some derangement in Na metabolism. Allergic arteritis probably results from much more complex changes than the mere liberation of mineralo-corticoids, yet we feel that the above experiments tend to suggest that this hormonal response may also be involved and would well deserve to be repeated under more suitable experimental conditions of NH_4Cl administration.

For the manifold cardiovascular actions of **autonomic drugs**, the reader is referred to pertinent monographs.[447] In view of the frequent use of *TEA*, it is noteworthy, however, that in the dog, this compound suppresses the carotid sinus reflexes and causes pronounced hypotension. This is due partly to peripheral vasodilatation and partly to paralysis of the ganglionic synapses.[448]

[443] Leblond and Dugal A72918/43, Selye A62756/43.
[444] Selye A62756/43.
[444a] Selye 35935/ND.
[445] Anonymous B32007/49, Lenel et al. B19871/48, Selye A56631/43.
[446] McLean and More B39074/49.
[447] Bovet and Bovet-Nitti B28233/48, Tardieu and Tardieu B19961/48.
[448] Boelaert B23230/48.

DFP (di-isopropylfluorophosphate) inactivates the pseudo- and true- cholinesterases of blood and tissues. This causes no manifestations of cholinergic stimulation, although sensitivity to injected acetylcholine is enormously increased.[449]

Nu-683, in doses inducing selective inactivation of "pseudo-cholinesterase", sensitizes the chemo-receptors of the carotid body to acetylcholine and thus increases the vasopressor reflex responses due to chemoceptive stimulation by acetylcholine.[450]

Various *adrenergic blocking agents* may interfere with the normal vasopressor responses to systemic stress. For instance, they block the carotid reflex and reverse the blood-pressure rise normally caused by exposure to such stresses as reduced oxygen tension. On the other hand, these drugs do not interfere with the pressor responses elicited by vasopressin or ergot alkaloids.[451] In dogs pretreated with *dibenamine,* irreversible hemorrhagic shock, due to prolonged sympathogenic vasoconstriction, can be prevented because the drug blocks the vasopressor mechanisms.[452] Both *benadryl* and *BAL* (as well as many non-specific stresses) cause "vascular refractoriness" to various stimuli. This is, at least partly, due to a direct action because benadryl inhibits vasoconstriction even in vitro, as shown by experiments on the isolated rabbit's ear. In dogs, such systemic stressors as severe skin burns, have essentially the same paralyzing effect upon the blood-vessels, and simultaneous administration of benadryl further augments the vascular refractoriness. In the case of intense and simultaneous overdosage with benadryl and BAL, vascular refractoriness becomes almost complete. Such treatment decreases the survival time of subsequently scalded animals, apparently because there is vascular paralysis, vasodilatation and perhaps also increased vascular permeability.[453]

The production of myocardial nodules and generalized hyalinosis by sterile horse serum in the rabbit is not influenced by benadryl or other antihistaminic drugs.[454]

Since **salicylates** proved so useful in acute rheumatic fever, it is interesting that, in rabbits, allergic arterial lesions can be prevented by pretreatment with sodium salicylate. Circulating antibodies are demonstrable in spite of the salicylate treatment, but: "It is believed that the lesions fail to develop because there is no antigen-antibody reaction, and that this reaction cannot take place because salicylate has prevented antigen from uniting with the tissue cells".[455]

It is perhaps also pertinent that **aminopyrine** allegedly inhibits the capillary leakage and "serous inflammation" otherwise caused by histamine.[456]

Changes in tissue **hyaluronidase** activity have often been suspected to play a rôle in the development of rheumatoid and other inflammatory lesions. Yet intravenously-administered hyaluronidase has little or no visible effect upon the capillary wall. Some sticking of leucocytes in the collecting venules and a slight dilatation of the arterioles were the only changes detectable in the frog mesentery or rat mesoappendix. On the other hand, if topically applied on the surface of the mesentery, petechial hemorrhages appeared, especially in venules and capillaries.[457] It has not yet been definitely proven that hyaluronidase plays

[449] Heymans and Casier B23147/48.
[450] Mazzella and Migliaro B39656/49.
[451] Biörck **B29350/47.** Nickerson and Goodman **B25559/48.**
[452] Wiggers et al. B23362/48.
[453] Page and Green B36673/49.
[454] Kyser et al. B24814/47.
[455] Sullivan et al. B27058/48.
[456] Eppinger **B37085/49.**
[457] Zweifach B33039/49.

a part in the pathogenesis of cardiovascular "diseases of adaptation" and whether there is any relationship between an inhibition of this enzyme and the therapeutic efficacy of salicylates.

Data concerning the effect of flavonoids of the vitamin-P group upon the hemorrhagic syndrome caused by x-irradiation, are conflicting (cf. **ionizing radiations,** above).

The hypotensive effect of various **non-specific therapeutic agents** (e.g., bacterial toxins, colloidal metals, foreign proteins, trypsin) is demonstrable even in normal individuals, but is much more pronounced in patients suffering from hypertension.[458] Some observations indicate that this is due to a decreased vascular responsiveness, but perhaps increased detoxification or decreased production of R.P.S. as well as a diminution of the blood-volume may also be involved. It remains to be shown whether some of the so-called *"antihypertensive drugs"* (e.g., thiocyanates, marine oils, more or less toxic tissue extracts) exert their effects, at least partly, through a similar mechanism.[459]

The "hyperergic myo-endocarditis" which can be produced in rabbits by horse serum is allegedly prevented by *artificially produced fever.*[460] Periodic intravenous administration of *nitrogen mustard* suppresses not only antibody formation but also the production of periarteritis nodosa in rabbits treated with horse serum.[461] These observations are somewhat reminiscent of non-specific therapy.

Various **lipotropic hydrocarbons** (e.g., chloroform, toluene, xylene, petroleum ether, gasoline) sensitize the mammalian ventricle to adrenaline so that extra systoles, tachycardia and fibrillation may result after administration of small doses of the hormone. A number of observations suggest "that intrinsic epinephrine, if liberated in sufficient quantity through emotional stress, could present a serious hazard through its effect on the ventricular complex sensitized to various lipotrophic hydrocarbons.[462]

Since **morphine** is extensively used in post-traumatic and hemorrhagic hypotension to relieve pain and emotional tension, the effect of this drug has been carefully examined in dogs subjected to hemorrhagic shock. It was found that, in the later stages of shock, morphine lowers the blood-pressure, depresses the peripheral circulation and is therefore definitely contra-indicated.[463]

Other factors. — Among the many additional stimuli which influence cardiovascular responses during the G-A-S, the age of the individual is especially noteworthy. It is well known that, in man, the incidence of cardiovascular disease and especially of arteriosclerosis increases with age. This is in agreement with the concept that the above are diseases of adaptation, since these would become more frequent in individuals who have been exposed to many stressors during the course of a long life. In the rat the usual forms of arteriosclerosis as we know them in clinical medicine are rare, but periarteritis tends to develop spontaneously with increasing age.[464] Significantly, in this species, stress, LAP, mineralo-corticoids or surgical interventions on the kidney which cause hypertension, also elicit periarteritis nodosa rather than atheromatosis or calcification of the vessels.

[458] Corcoran **B29330/48,** Del Dotto B19365/46, Dexter **91416/46.**
[459] Dexter **91416/46,** Goldblatt **B29301/48,** Page and Corcoran **B2081/45.**
[460] Lucherini and Pala B33489/48.
[461] Bukantz et al. B43575/49.
[462] Trimble B39518/48.
[463] Lee and Zweifach B37246/49.
[464] Willens and Sproul B33783/38.

Bilateral enucleation of the eye significantly raises the blood-pressure in the rat. Although this experiment was initially performed in order to study the effect of removing an important source of hyaluronidase, it was admittedly not considered to be significant in this connection. It was pointed out, however, that the hypertension so produced is unaccompanied by detectable changes. The authors state that "it seems evident that a hypertension has been produced which is neither renal nor neurogenic in origin".[465] However, the rise in blood-pressure was very slight (on the average 14 mm. Hg.) and the possibility of a nervous factor should perhaps not be entirely discounted in these blinded animals.

Cardiovascular Diseases of Adaptation

It is our belief that a number of cardiovascular diseases currently considered to be more or less independent clinical entities, are closely related to each other in that they all represent derailments of the G-A-S.[466] Among these, we shall discuss various diseases of the heart and vessels (e.g., hypertension, arteriosclerosis, periarteritis nodosa, endarteritis obliterans, thrombo-angiitis obliterans) as well as some mesenchymal derangements (such as diffuse collagen disease, rheumatic diseases) which in our opinion, are closely related to the former.

The arthritic manifestations of rheumatic (or rheumatoid) conditions (p. 386), the allergic vascular manifestations (cf. chapter: "Serology") and certain related skin diseases (chapter: "Skin") are discussed separately. Additional pertinent data will also be found in the chapters devoted to the various organs (e.g., kidney, pancreas, nervous system) since in these, vessel lesions are considered in conjunction with the other local structural changes.

Let us emphasize here at the outset that this whole group of the cardiovascular and other mesenchymal diseases of adaptation is closely related to the phenomenon of "serous inflammation". The "serous myocarditis", the "serous arteritis", the "serous imbibition" with subsequent inflammatory changes which occur in the collagenous connective tissue in rheumatic disorders, all commence with a derangement of the selective permeability of capillary membranes. This is followed by the transudation of plasma into the interstitial spaces and a consequent granuloma formation. In such diseases, salicylic acid and aminopyrine derivatives have long been recommended with a view of decreasing the permeability of the capillaries and other membrane surfaces.[467] — It has been one of our major objectives to show that the organism itself tends to combat such diseases by producing corticoids. These normally regulate the permeability of membranes and hence a more natural, etiologic therapy of such maladies could be based on helping the body in this task by supplying exogenous supplements of corticoids whenever required. In the following pages we shall discuss the cardiovascular diseases of adaptation particularly from this point of view.

Hypertension. — Many of the data discussed in the preceding pages of this section suggest that hypertension can develop as a result of exposure to systemic stress. However, hypertension is a symptom and not a disease.

[465] Friedman and Friedman B36913/47.
[466] Selye A75044/44.
[467] Eppinger **B37085/49.**

Obviously, the blood-pressure can be raised by a variety of different mechanisms. Especially important among these are: (1) nervous stimuli (e.g., emotional stress, increased intracranial pressure, severance of the depressor nerves), which increase peripheral resistance through widespread vasoconstriction, (2) excessive production of directly or indirectly vasoconstrictor substances such as adrenaline, nor-adrenaline, corticoids, R.P.S. or vasopressin, (3) arteriosclerosis or coarctation of the aorta, which increase peripheral resistance due to an organic blood-vessel-lesion, (4) an increase in blood-volume and (5) combinations of several among the above-mentioned factors. It is not permissible, therefore, to interpret hypertension as a single disease entity and the extensive efforts to discover "the etiology of hypertension" were a priori doomed to failure.

The homeostasis of the blood-pressure is extremely important for the maintenance of life; hence it is safe-guarded by several alternative mechanisms in order to insure its stability even if one or the other of the regulators should fail. A necessary corollary of this multiple regulation is that the blood-pressure may also be adversely affected through many channels. One of the greatest dangers during exposure to severe systemic stress is "shock" and hypotension. Presumably it is to defend the body against this danger that nature has foreseen so many alternative pathways through which the blood-pressure can be raised. When a homeostatic mechanism is so intensely stimulated that its excessive function is in itself the principle derangement, we may well speak of a "Disease of Adaptation". Curiously, in this sense, most cases of clinical hypertension fall within the confines of this group, irrespective of their diverse pathogenic mechanisms.

In the case of hypertension — as with many other diseases of adaptation — it is very important, however, to distinguish clearly between primary and secondary disorders of the adaptive mechanisms. When the blood-pressure rises because of a primary change in one of the blood-pressure-regulators themselves, we speak of a *primary disease of adaptation.* Compression of the renal artery by a tumor or scar, stimulation of the vasopressor nerve-centers by local disease foci, destruction of the depressor nerves, primary hyperfunctional tumors of the anterior-pituitary, adrenal-cortex or adrenal-medulla, could be cited as pertinent examples. In none of these cases does the blood-pressure rise as a defensive measure. It is true that any of the above derangements can secondarily cause systemic stress and elicit a G-A-S, but here the systemic defense-reaction is not the cause, but the consequence of the principal derangement.

Much more frequently, hypertension presents itself as a *secondary disease of adaptation;* that is to say, the blood-pressure rises because one or more of the pressor mechanisms became unduly overactive in response to a systemic stressor. We have seen that hypertension can thus be produced through many, very diverse, mechanisms. It is especially noteworthy therefore that the final link in the chain of events always appears to be either an adrenergic stimulus (adrenaline or nor-adrenaline formation by the adrenal medulla and sympathetic nerve-endings), or an excess of RPS (increased production, decreased destruction). Some investigators believe that the renal-pressor-substances are closely related to the adrenergic pressor amines, hence, the final pathway of the various pressor systems may be even more uniform than has been hitherto suspected.

During systemic stress, *adrenergic stimulation* can be effected through purely nervous pathways, such as stimulation of the sympathetic vasomotors and/or inhibition of the antagonistic (depressor) cholinergic nerves. A similar effect is achieved through neuro-humoral pathways when a stressor discharges adrenaline and nor-adrenaline from the adrenal medulla through stimulation of its secretory nerves, the splanchnics.

The *renal-pressor-system* can be activated, during systemic stress, through the hypophysis-adrenal-kidney chain. There is increased ACTH production, this augments the elaboration of corticoids and these, in turn, influence the kidney so that more RPS is formed and less is detoxified. All these pressor mechanisms are activated during the G-A-S, though not always proportionately and to the same extent. Adrenergic stimulation is more prominent in acute emergencies, while RPS appears to be called upon particularly during continued stress. In any event, the resulting rise in blood-pressure is transitory and normally does not long outlast the period of exposure; here we are dealing with a physiologic adaptive reaction, the G-A-S. Only when health is impaired by a derailment of this response and persistent hypertension ensues, can we speak of a disease of adaptation.[467a]

We know comparatively little about the participation of *vasopressin* in either physiologic or pathologic elevations of blood-pressure and the chemical structure of this posterior-lobe principle has not been fully elucidated. Hence it is impossible at present to assess the rôle of the posterior-pituitary in the pressor responses to stress. Since vasopressin causes especially pronounced renal vasoconstriction, it could increase the production of RPS, somewhat like a mechanical clamp does, when it constricts the renal artery. It also causes systemic vasoconstriction due to a direct effect upon the blood-vessels, like RPS and the adrenergic compounds. This makes us think of a possible chemical resemblance between part of the relatively large vasopressin molecule and the other pressor agents mentioned, but there is no actual evidence to suggest this. In any case, we have no definite reason to believe that vasopressin plays any important rôle in physiologic or pathologic pressor responses during systemic stress.

The following are the principal **experimental data** which appear to suggest that hypertension is a disease of adaptation. During exposure to systemic stress, *adrenergic substances* (adrenaline and nor-adrenaline) are demonstrably discharged from the adrenal-medulla and at sympathetic nerve endings. The resulting pressor responses can be diminished or abolished if this discharge is prevented by sympathectomy or adrenergic blocking agents.

Certain data suggest that an excess of nor-adrenaline is the principal factor in this type of hypertension. Indeed at the comparatively low blood-levels at which such adrenergic compounds are likely to circulate, adrenaline appears to diminish the pressor action of nor-adrenaline, presumably because at a low dose-range the former has a vasodilator, the latter a vasoconstrictor effect. These findings suggested "that a disturbed balance between both 'sympathetic transmitters' could be concerned in the production of hypertension".[468] This is rather reminiscent of the derangement in the gluco-corticoid:mineralocorticoid ratio which may also cause hypertension.

[467a] Capone-Braga B46754/49, Selye **B1204/46.**

[468] Goldenberg et al. B38368/48.

There is ample evidence to prove that systemic stress also causes a discharge of *ACTH* from the anterior-lobe. This increases the production by the adrenal-cortex of *corticoids*, some of which (e.g., desoxocortisone) can cause hypertension in animals and man.

Since emotional stress plays an important rôle in the pathogenesis of clinical hypertension, it is especially interesting that the experimental hypertension produced by nervous (e.g., audiogenic) stimuli is apparently also dependent upon the adrenal-cortex. The pressor response to corticoids is perhaps mediated by the kidney, since it is accompanied by characteristic changes in the renal parenchyme and is probably abolished by complete nephrectomy. Indirect evidence suggests that mineralo-corticoids can both increase the production and diminish the detoxification of RPS, but this latter point has not yet been fully proven.

The pressor effect of DCA is most pronounced in patients who previously suffered from some degree of renal damage and hypertension. Correspondingly, partial nephrectomy considerably augments the hypertensive action of DCA in animals. This enhancement of the pressor response to DCA by renal impairment may merely be due to a concentration of its toxic effect upon the renal remnant, with a further increase in RPS production. However it may also be ascribed to a diminution of the RPS-detoxifying power of the kidney. Such an action would naturally raise the pressor potency of DCA, especially in those individuals whose RPS production is elevated as a result of a pre-existent renal damage.

Some experimental observations intimated that certain stressor agents also increase the production of *vasopressin* by the posterior-lobe. It is not known, however, whether this response is common to all alarming stimuli and whether it ever participates in the production of hypertension.

Several investigators reviewed the pertinent **clinical data.**[469] It was pointed out that hypertension tends to occur with particular frequency among people subjected to intense and long-lasting *emotional stress* so that the disease frequently presents itself in the form of a psychosomatic disorder.[470] The often rather persistent hypertension which develops in soldiers repeatedly exposed to the intense stress of battle,[471] illustrates this point with special clarity. The "blast hypertension" which may persist for weeks in people who were in the vicinity of a single major explosion is probably a related phenomenon.[472]

However, less intense emotional experiences may eventually also produce the same result. It might be best to illustrate current opinion concerning this important point by a few direct quotations from those who specialize in the study of this field. "The tendency to exhibit transient hypertension in response to mental or other stimuli, may be taken to indicate a physiological make-up which is likely to express itself in daily life by abnormally strong and frequent blood-pressure elevations. The balance of evidence suggests that such elevations, if sufficiently frequent or prolonged, predispose the subjects towards the development, later, of essential hypertension".[473]

[469] Mosenthal et al. **B38282/49,** Page **B40242/49.**

[470] Ayman B36447/48, Gressel et al. B48058/49, Groen and Reisel B44804/48. Halliday B44599/43, B46202/48. Menninger B44420/38. Wolf et al. B43405/48.

[471] Graham B2425/45.

[472] Ruskin et al. B43758/48.

[473] Smirk B36283/49.

The kidney may perhaps also eventually participate in the neurogenic type of hypertension. "Possibly certain abnormal cerebral activity in man results in persistent or recurrent renal cortical ischemia, and this mechanism may lie at the basis of essential hypertension".[474]

Of course, hereditary factors likewise play an important rôle in psychogenic hypertension,[475] not all individuals react to the same situation with equal intensity. Indeed, "essential hypertension is considered a psychosomatic disease because of the important rôle personality factors appear to play in it." ..."The individual appears frequently to be caught between his inability to roll with the punch and take life's onslaughts passively or to express his aggression and hostility and attempt to end them by a frontal attack. An insoluble life situation is often the result"; this may lead to abnormal adaptive reactions with a rise in blood-pressure.[476] Somewhat in the same vein, it has been said of hypertension that "it is the price the millionaire pays for his directorships and the clerk for his failure".[477]

It is well-known of course that *organic lesions in the central nervous system* (e.g., brain tumors which raise the intracranial pressure) may also raise the blood-pressure. Lesions to the diencephalic centers appear to play an important rôle, for instance in the "hypertensive diencephalic syndrome of Page".[478]

In connection with our approach to this problem it is especially noteworthy that not only emotional, but various other stressors can probably produce hypertension, at least in predisposed individuals. That this is so in experimental animals has been discussed in the preceding pages. Let us merely add here that in clinical medicine *focal infections* are often claimed to act in this manner.[479] After various *systemic infections* a persistent rise in blood-pressure is claimed to be sufficiently common to justify the term "postinfectious hypertension".[480] Yet it is remarkable that the continuous and severe systemic stress of organic disease does not lead to hypertension more often in clinical medicine. Apparently the organism is much better prepared to make the necessary metabolic adjustments required for adaptation to physical or chemical damage, than to nervous and emotional stimuli.

We have repeatedly had occasion to point out in this volume that adaptation itself is normally not conducive to disease; pathologic derangements, including hypertension, ensue only when the adaptive reactions are excessive or abnormal. A common cause for such derailments is the excessive defensive production of certain hormones (e.g., mineralo-corticoids), without the necessary compensatory readjustment of metabolism, which makes it possible to withstand the resulting hormone-excess without damage. Experimental work has taught us that the production of hypertension by stress, LAP or corticoids is largely dependent upon the abundant availability of sodium and protein; it is further facilitated by pre-existing renal damage. This illustrates the importance of conditioning factors. Perhaps emotional stress produces hypertension more readily than does organic damage because the latter is more effective in initiating those compensatory adjustments (e.g., changes in intermediate metabolism) which can protect the body against the toxic side-effects of its own adaptive response.

[474] Hoff et al. B32772/49.
[475] Platt **B38113/47.**
[476] Daniels B24034/48.
[477] Ogilvie B36284/49.
[478] van Buchem B43406/48.
[479] Goia B25571/46.
[480] Arnold B41249/49.

It is customary to distinguish between essential and malignant hypertension. It is the great merit of Volhard[481] to have delimited the so-called *red (essential)* from the *pale (malignant) hypertension.* Patients with red hypertension are apparently in excellent health, their face is usually flushed and they do not lose weight; conversely, the pale hypertensive exhibits generalized vasoconstriction, loses weight and is manifestly ill. Volhard believes that only the latter type of hypertension is of renal origin and caused by a strictly humoral derangement. Concerning essential hypertension he states that "increased wear on the arterial system occurs under the influence of endocrine, nervous, psychologic and hereditary factors and leads to great variations of blood-pressure, as the first stage of hypertension, due to increased minute volume." He admits, however, that this form may gradually assume the malignant type "in which case the neuro-regulatory mechanism of red hypertension changes into the humoral mechanism of pale hypertension."[481a]

We are inclined to think, however, that certain types of clinical hypertension do not fit readily into either of these categories. Among these are the cases due to mere sympathetic overactivity or the excessive production of adrenergic substances by the adrenal medulla (chromaffinoma). The classical example of the red or sthenic hypertensive is the patient with Cushing's disease due to a basophilic adenoma of the anterior-lobe, adreno-cortical hyperplasia or a primary adreno-cortical tumor. The typical pale or asthenic hypertensive is the patient who suffers from "idiopathic" nephrosclerosis or some other primary renal disease. There are many transitional forms, but it may be expedient to distinguish the following three main types of clinical hypertension:

(1) *Adrenergic hypertension* (including adrenergic stimulation by sympathetic nerves, chromaffinomas or adreno-medullary hyperplasia).

(2) *Sthenic or red hypertension* (exemplified by Cushing's disease, and some of the "Cushingoid" forms, e.g., those of the menopause or pregnancy; certain types of neurogenic hypertension also belong to the sthenic variety).

(3) *Asthenic or pale hypertension* (chiefly of renal origin, e.g., nephrosclerosis).

The first two types are usually "benign" at first, while the third is frequently malignant from the onset. It is most probable, however, that in predisposed individuals, any continuous severe hypertension gradually tends to affect the kidney and to become "malignant". It is mainly due to this progression that transitional forms occur. The disease can progress directly from type 1 or 2 to type 3, it could also develop from type 1 through type 2 to type 3. In other instances, it remains in the same category from its inception to the end. Retrograde development from type 3 to type 2, or from type 2 to type 1, does not appear to occur.

It should incidentally be mentioned that the "redness' of patients in the second category is not always due to neurovascular reactions (e.g., flushes) alone, but may partly result from polycythemia and an increased blood-volume. These changes as well as the pyknic aspect of such patients are reminiscent of Cushing's disease. They may well be due to excess production of anabolic anterior-lobe principles.

[481] **B29452**, B45266/48, B46392/49.
[481a] Volhard B29452/48.

The endocrine origin of hypertension has repeatedly been postulated on the basis of purely clinical evidence,[482] and by comparing clinical with experimental data, several investigators came to the conclusion that stimulation of the adrenal-cortex through the anterior-lobe is of special pathogenic importance.[483]

In connection with the interpretation of hypertension as a disease of adaptation, particularly valuable data were also obtained by studies concerning the metabolic derangements and the efficacy of certain therapeutic procedures in such cases.

Several investigators expressed the opinion that, in certain hypertensive patients, there is a derangement in the **metabolism** of *sodium*. Quite frequently, the blood-Na is high in proportion to the blood-Cl so that the Na/Cl ratio rises; simultaneously we note an increase in the CO_2-combining power of the blood.[484] It was pointed out that these changes are similar to those seen in DCA-treated animals during the development of experimental nephrosclerosis and hypertension.[485] They also resemble the "hypochloremic alkalosis" of Cushing's disease.[486] Furthermore, hypertensive patients, unlike normals, do not tend to lose weight or fluid when deprived of sodium. It has been emphasized that this "inability of hypertensive patients to lose weight and fluid in response to sodium restriction is consistent with the view that the adrenal cortex may be implicated...".[487]

In the "pseudo-Cushing" type of hypertension, the elimination of Na through the sweat is diminished; this has again been ascribed to hypercorticoidism.[487a]

There are important changes in *fibrinogen* metabolism during the G-A-S (cf. p. 166 ff.). It is noteworthy therefore that one group of workers found no obvious correlation between the level of arterial pressure and the blood-fibrinogen concentration,[488] but others report the blood-fibrinogen to be rather consistently elevated, especially in the malignant form of hypertension.[489]

In view of the theory that the anterior-pituitary and the adrenal-cortex may be involved in the pathogenesis of hypertension, insulin-tolerance curves have been performed. It was found that, in patients with essential hypertension, the *blood-sugar* concentration returns very slowly to the pre-injection level. This was taken to indicate that there is no increase in the contra-insulin factors (gluco-corticoids) in these patients. Indeed the observations appeared to suggest an actual decrease.[490] This is of especial interest in view of the fact that gluco-corticoids exert a depressor effect in certain hypertensives, perhaps because they antagonize the vascular actions of mineralo-corticoids.

On the other hand many patients with malignant hypertension tend to be highly resistant to insulin.[491] The same is true of patients with hypertension due to Cushing's disease with a marked increase in gluco-corticoid formation.

[482] Shulga B31592/46.
[483] Bugoslavskaya B30331/46, Davis B29881/48, Friedman et al. B18570/48, De Gennes et al. B1912/47, Hall and Luetscher B24712/48, Hase B19303/48, Miller de Paiva 94159/46, Milliez et al. B26870/48, Pedersen B25933/48, Selye et al. A58748/43, Shorr B30644/48.
[484] Selye B4535/47.
[485] Selye et al. A94329/45.
[486] Selye **94572/49.**
[487] Perera and Blood 98220/46.
[487a] Davies and Clark B45925/49.
[488] Gayet-Hallion et al. B37497/42.
[489] Goreckzy and Berencsi B37496/39, Lewis and Page B4181/47.
[490] Mirsky et al. B33429/49.
[491] Nuetzel and Olsen B32799/49, De Takats and Lasner B44657/49.

Here both insulin resistance and the blood-pressure level are diminished by subtotal adrenalectomy.[492] These apparently contradictory findings may well be due to the fact that gluco-corticoids can raise or depress the blood-pressure depending upon conditioning factors (cf. above). In any case these observations tend to support the adreno-cortical theory of hypertension, in the sense that they suggest an abnormal elaboration of corticoids.

Observations concerning derangements in the hormone metabolism of hypertensives yielded particularly interesting data. Several observers claim to have demonstrated a rise in the *ACTH* content of the blood in hypertensive patients.[493] Although the blood of normotensive individuals was used for comparison, the interpretation of these findings is rendered somewhat difficult because the assays were performed on intact, not on hypophysectomized, test animals. Repetition of this work with more specific bioassay methods would therefore be desirable. Yet, the data are interesting especially since in patients with hypertension due to Cushing's disease, a marked increase in the urinary elimination of corticotrophin has repeatedly been observed with unassailable bioassay technics.[494]

We have mentioned data suggesting that *vasopressin* (presumably identical with the "anti-diuretic hormone") is discharged during systemic stress. In this connection it is noteworthy that in a series of 15 hypertensive patients "the excretion of the anti-diuretic principle was increased in 11 and within the normal range in the remaining 4".[495] The blood of hypertensive patients also frequently contains large amounts of an anti-diuretic substance (presumably vasopressin).[496]

Although in certain types of hypertension the *corticoid* content of the urine is increased, it appears to be within the normal range in most patients with essential hypertension (formaldehyde-cleavage method).[497] The blood of patients suffering from essential hypertension also fails to exhibit any detectable increase in "formaldehydogenic" corticoids. However, using other criteria of cortical hyperfunction (eosinopenia, plasma CO_2-combining power, plasma CO_2/Cl ratios) it was noted that "32% of the hypertensive group have ratios higher than anyone in the normotensive group". Yet the differences were not statistically significant, and it has been concluded that "although it is possible that there might be a slight adrenal hypersecretion in essential hypertension, the above data indicate that a marked adrenal hypersecretion is quite unlikely".[498] In one case with hypertension and marked anxiety, the initially very high (177 glycogenic units/24 hrs.) corticoid excretion fell to low (36 glycogenic units/24 hrs.) values after sympathectomy, while the blood-pressure became normal.[498a]

It must be kept in mind that the experimental data which led to the assumption of an interrelationship between clinical hypertension and cortical hyperactivity were based on the production by corticoids of malignant, not of essential, hypertension. Hence, it would be interesting to extend such studies to the latter condition. As we have repeatedly emphasized in other connections, it is quite improbable that hypercorticoidism in itself is responsible for any

[492] Selye 94572/49.
[493] Miller de Paiva B18845/47, Sievert A99491/38.
[494] Selye **94572/49.**
[495] Ellis B45767/48, Ellis and Grollman B36428/49.
[496] Pendergrass et al. B37689/41, B2467/47.
[497] Tobian B36322/49.
[498] Tobian and Joseph B35958/49.
[498a] Browne and Venning B46928/49.

common type of clinical hypertension. We believe that it may became pathogenic, however, in conjunction with other sensitizing factors (Na-retention, derangements in protein metabolism, renal damage). Therefore, pertinent clinical studies should also be directed to detect the possible co-existence with mild hypercorticoidism of such sensitizing factors. Finally more attention should be given to possible derangements in the gluco-corticoid:mineralo-corticoid ratio, without any change in the total corticoid production.

In a group of hypertensive (type not indicated) women, the urinary elimination of *pregnanediol* and *17-KS* was found to be frequently below normal.[499] Since both these substances are potential metabolites of corticoids, such a diminution might be interpreted as an indication of an abnormal corticoid metabolism. However, such far-fetched conclusions would hardly be justified in view of the rather inconsistent data and the comparatively small number of patients examined.

Since systemic stress characteristically causes a pronounced discharge of *adrenergic substances* from sympathetic nerve-endings and the adrenal-medulla, their participation in clinical hypertension has long been suspected.[500] It has been emphasized, however, that within a near physiologic range, adrenaline acts as a vasodilator and causes hypertension only by increasing cardiac output. If higher doses are administered, adrenaline produces marked hyperglycemia and other manifestations which are not commonly seen in clinical hypertension. Nor-adrenaline, on the other hand, acts as an over-all vasoconstrictor, with no important change in cardiac output and only a slight hyperglycemic effect. It is now well established that both the sympathetic nerve-endings and the adrenal-medulla discharge a mixture of adrenaline and noradrenaline, in varying proportions; it is possible, therefore, that endogenous overproduction of adrenergic compounds could be of etiologic significance in certain types of clinical hypertension.[501]

The adrenaline content of the blood is within the normal range in hypertensive patients at rest,[502] but "urosympathin" (mixture of adrenaline, noradrenaline and hydroxytyramine) elimination in the urine is allegedly high in chronic nephritis and nephrosclerosis,[503] as well as in some cases of essential hypertension.[504]

Allegedly physical exercise causes excessive elevations in the adrenergic compound content of the blood in hypertensives and there are abnormally high concentrations of such compounds in the hearts of patients who had died from hypertensive heart disease. These and many other similar observations led to the conclusion that "exaggerated joint adreno-cortical and adreno-sympathetic co-operation seems to be a decisive pathogenic factor in hypertensive heart disease with or without hypertension".[505]

There is no definite proof that the blood level of *RPS* is significantly elevated in hypertensive patients. Yet several investigators adduced evidence suggesting that under suitable conditions a rise in the *renin*[506] and *hypertensin*[507] concentration is demonstrable, especially in malignant hypertension with nephrosclerosis.

[499] Jayle and Bret B31672/48.
[500] Goldenberg et al. B40862/47, Selye **94572/49.**
[501] Goldenberg et al. B36332/49.
[502] Kobro B34026/46.
[503] Holtz et al. B18862/47.
[504] Holtz and Credner B18863/47.
[505] Raab B23181/48.
[506] Taquini and Fasciolo B46006/47, Zelenka and Eiselt B41924/49.
[507] Bilecki B43404/48.

It has been claimed, furthermore, that an alcohol-soluble pressor substance *"nephrin"* can be extracted from kidney tissue and that this material is not identical with adrenaline, tyramine, hydroxytyramine, vasopressin or renin. Since its concentration is high in the blood and urine of patients with chronic glomerulo-nephritis and other types of renal hypertension "nephrin" was believed to play an important rôle in the pathogenesis of these diseases.[508] Other investigators also state that "it seems reasonable to conclude at the present time that the blood from some hypertensive patients often contains a substance or substances which raise the blood-pressure of rats". In connection with the possible relationship of such compounds to the adrenergic pressor amines it is interesting that — "so far, most of the evidence suggests that these substances are amine-like in nature".[509] The pressor action of this material is greatly potentiated by threshold doses of adrenaline in which it resembles the VEM of Shorr et al. It must be kept in mind, however that the pressor substances, in the blood of hypertensives, are not necessarily related to adrenaline. Although, allegedly, there is a simultaneous rise in blood-amines and pressor-substances, the method used would not determine phenolic amines, such as tyramine and adrenaline.[509a] Yet, here we may be dealing with adrenaline precursors or metabolites. The name *"pherentasin"* (phero = hold up, entasis = pressure) has been proposed to designate this pressor material, which appears in the blood in most types of hypertension".[509b]

Significantly, using the classical meso-appendix test, the blood concentration of *VEM* has also been shown to be unusually high in various types of clinical hypertension. Sometimes, especially in malignant hypertension, VEM manifestly predominates, but much more frequently its effect is masked by a simultaneous rise in the VDM-concentration of the blood. In this event an excess of VEM can only be demonstrated after the depressor effect of the VDM is abolished.[510]

For additional data concerning changes in metabolism, especially hormone metabolism in hypertensive disease, consult also the section: Hormone Metabolism, pp. 214-245.

The **pathologic anatomy** of hypertensive disease furnishes many additional data which suggests that it belongs to the diseases of adaptation. The pertinent literature has already been discussed in the sections concerned with morphologic changes in the adrenals, the kidneys and the cardiovascular system. Let us merely summarize the most important points here.

In the *pituitary*, hyperplasia of the basophils appears to be quite common, though far from constant, in cases of hypertension and renal disease.

In patients who die from hypertension and nephrosclerosis, the *adrenal-cortex* is frequently enlarged and rich in lipids; it often contains multiple small adenomas and foci of lymphocytic infiltration. Similar adrenal changes are also frequently observed in patients who die from other chronic diseases (e.g., neoplasms, chronic infections); hence they can not be considered as typical of hypertension. It is probable, however, that conditioning factors determine whether prolonged adrenal stimulation raises the blood-pressure,

[508] Enger A72764/42, B19358/47, Enger and Jellinghoff A39118/41.
[509] Schroeder et al. B27071/48.
[509a] Stock and Schroeder B46861/50.
[509b] Schroeder and Olsen B47898/50.
[510] Shorr and Zweifach B27646/48, B36357/49, Shorr et al. B17755/48, Zweifach and Shorr B27072/48.

hence adrenal hyperplasia is not necessarily conducive to hypertension. Conversely, an elevation of blood-pressure may result from other causes.

There is some indication that *adrenal-medullary* hyperplasia is more common among hypertensive than among normotensive individuals. This could be interpreted as indicative of an increased adrenergic hormone production in certain cases. Furthermore, the symptomatology of some pheochromocytomas is indistinguishable from that of essential hypertension.[510aa]

Essential hypertension is not accompanied by characteristic morphologic changes (detectable with present day methods) in the *kidney*.[510a] However, in malignant hypertension and in the more chronic forms of Bright's disease, where the kidney is usually affected, the changes are strikingly similar to those produced experimentally with stress, LAP or corticoids. This suggests some correlation between the experimental and the spontaneous disease.

As regards essential hypertension, without manifest renal involvement, it is possible that insufficient attention has been given in the past to the tubular lesions which are so characteristic of early LAP — or corticoid — overdosage. The absence of glomerular or arteriolar hyalinization does certainly not prove that the elevation of blood-pressure is of extra-renal origin. It is a late secondary change in experimental hypertension induced by LAP or corticoids and does not occur at all in the "endocrine kidney", the most active producer of RPS.

Compression of the renal artery by hydronephrosis, scars or tumors is an exceptional cause of hypertension in man. The occasional occurrence of cases in which such changes are of pathogenic importance, proves, however, that interference with the renal circulation can elevate the blood-pressure in man just as it does in experimental animals.[510b] Hyperplasia of the juxtaglomerular apparatus is probably not of pathogenic significance or even of common occurrence in hypertensive patients.[510c]

In *summarizing* the most important pertinent morphologic data, it may be said that we know of no change in the pituitary, adrenal or kidney, which could be regarded as absolutely characteristic and constant in clinical hypertension. On the other hand, it is certain that basophilic adenomas of the anterior-lobe, adrenal-cortical hyperplasia or tumors, adrenal-medullary tumors and renal vessel lesions can produce hypertension in man. Such primary lesions in the anterior-pituitary, the adrenal or the kidney account only for a very small percentage of the hypertensive patients. However, in a large number of them, we find evidence of milder, but qualitatively similar, changes. These also resemble the lesions experimentally produced by stress, LAP, corticoids or the "endocrine kidney". If we accept the tenet that conditioning factors determine whether or not the G-A-S produces a persistent rise in blood-pressure, it may be concluded that morphologic observations in man are generally in agreement with the interpretation of hypertension as a disease of adaptation.

The efficacy of certain **therapeutic** procedures also gives us valuable information concerning the probable pathogenesis of hypertension. We have already spoken of the rôle played by emotional strain and the well-known efficacy of rest-periods gives further support to the view that neurogenic

[510aa] Goldenberg and Aranow B47872/50.
[510a] Castleman and Smithwick B24904/48.
[510b] Pool B34405/46, Sahnan B24541/48.
[510c] Des Prez B30970/48.

systemic stress is of great pathogenic significance.[511] Recently, "progressive relaxation methods" have been especially recommended for this reason.[512]

Several investigators claim to have obtained encouraging results in a large number of hypertensives subjected to x-irradiation of the *hypophysis*. The beneficial effect of this treatment has variously been ascribed to interference with the hormone production of the posterior-[513] or anterior-lobe.[514]

Possibly irradiation of the hypophysis interrupts, at the pituitary level, the chain of events elicited by stress during the G-A-S. However, since these observations have not yet been confirmed on a large scale, discussions concerning their interpretation are perhaps somewhat premature. ACTH-treatment (as Cushing's disease) tends to raise the blood-pressure in man.[514a] This is one of the rare instances where ACTH and cortisone have been claimed to exert opposite effects (cf. below). However, in the rat, cortisone may also raise the blood-pressure and the alleged antagonism between these hormones, in man, requires confirmation, under entirely comparable conditions.

More or less extensive partial *adrenalectomies* have been performed on hypertensive patients, either with the view of diminishing adrenaline production or in order to inhibit an intoxication with excessive amounts of endogenous corticoids. A temporary fall of the blood-pressure has almost invariably been obtained, but this in itself is not of great significance since most major surgical operations are also effective. Prolonged remissions and permanent cures are comparatively rare.[515] Since after partial adrenalectomy, the remnant rapidly regenerates, it would be unwarranted to expect any consistent and lasting therapeutic effects from this operation.

It is especially interesting, on the other hand, that bilateral complete adrenalectomy in a young woman led to a fall of the blood-pressure from 260/140 to 110/80 mm.Hg. within four hours after the operation. Although, previously, the hypertension had been very severe and progressive with transitory episodes of encephalopathy and myocardial failure, in this case the remission persisted. At first it was necessary to give large amounts of cortical extract, but later the daily requirements dropped considerably. It is instructive that elevated pressures were observed after the operation only during brief periods of DCA-overdosage.[516]

It is very significant that, while DCA greatly aggravates a pre-existing hypertension in man,[516a] *cortisone* exerts "a depressor effect on the resting blood-pressure of the hypertensive patients".[517] Cortical extract can also prevent the rise in blood-pressure which would otherwise be produced by DCA in hypertensive men.[518] These findings agree well with observations on rats, in which cortisone was found to antagonize the hypertensive action of DCA under suitable experimental conditions.[519]

Interventions on the *kidney* are rarely justified; yet, occasionally, permanent cures have been obtained in patients who developed hypertension due to uni-

[511] Cecil **A63152/43**, Musser **88056/45.**
[512] Jacobson B29878/48, B33102/48.
[513] Pendergrass et al. A37689/41, B2467/47.
[514] Pedersen B25933/48.
[514a] Perera **B46945/50.** B46972/50.
[515] De Courcy A49777/34.
Friedman and Eisenberg 95128/37.
Guichard and Boulliat B38074/48.
[516] Green et al. B32755/49.
[516a] Luft and Sjögren **B43391/49.**
[517] Perera
et al. B36595/49, B33431/49, B47895/50.
[518] Perera B46972/50. B46945/50,
Perera and Pines B37746/49.
[519] Selye B41762/49.

lateral renal damage (hydronephrosis, atrophy of one kidney, compression of one renal artery by scar tissue, unilateral infections, etc.). Even in these rare cases, the prognosis is favorable only if the diseased kidney is removed at an early date before the other kidney is also implicated.[520] Some surgeons advocate a variety of other interventions, such as decapsulation of the kidneys, attachment of the omentum to the kidney with a view of establishing a new collateral circulation, etc.; none of these proposals has found many followers.[521]

In a few hypertensives, anti-renin-containing *kidney extracts* proved to be beneficial, but this may have been due to a non-specific "foreign-protein effect".[521a]

Especially interesting pertinent observations have been made in connection with the *dietary* treatment of hypertension. It has long been known that overeating aggravates, while under-nutrition improves hypertension in most cases.[522]

Especially favorable results have been obtained with diets poor in *sodium* and *protein*.[523] Although in several series of observations the benefit to the patient was quite striking, it is astonishing how little attention the early reports received, merely because the treatment had no clear-cut rationale. The demonstration that ACTH production is enhanced by protein and the vasotoxic action of corticoids by Na, has supplied an objective reason for the use of these dietary measures and helped further logical experimentation along these lines. At present many types of Na- and protein-restricted diets are in current use, but most investigators insist mainly upon sodium deprivation.[523a]

The much discussed *"rice diet"* of Kempner[524] is poor in total calories, sodium and protein. In the form in which it was originally recommended, this diet may lead to severe losses of body-weight, especially of tissue-protein[525] and may impair renal hemodynamics.[526] As the diet is extremely unpalatable, it has not met with much enthusiasm. However, from a theoretic point of view, it is interesting that such dietary restrictions may produce marked and prolonged remissions in hypertensive patients. Under suitable conditions, spectacular results may be accomplished, even without any loss of body weight, as illustrated by the adjacent pictures.

It is of special interest, in connection with our approach to this problem, that addition of NaCl to the rice diet immediately raises the blood-pressure.[527] This clearly shows the important rôle of Na-restriction. It agrees with our experimental observations on animals in which hypertension was produced by systemic stress, LAP or corticoids since here, the pressor effect also largely

520 Carroll B45583/46, Dossot B44805/48, Goldring and Chasis **B38295/49**, Linder **B46505/49**, Maitland B44656/49, Marcel B45700/48, Moore B46318/48, Ratliff et al. **B43757/47**, Sahnan B24541/48.

521 Lebon et al. B24207/47, Palmer **95299/46**.

521a Porge B46063/49.

522 Adlersberg et al. B36114/46, Cecil A63152/43, de Langen B45435/47, Musser **88056/45**, Palmer **95299/46**, Volhard B46392/49.

523 Allen and Sherrill 40804/22, Bassett B19946/45, Borst B26872/46, Volhard B38001/31, B46392/49.

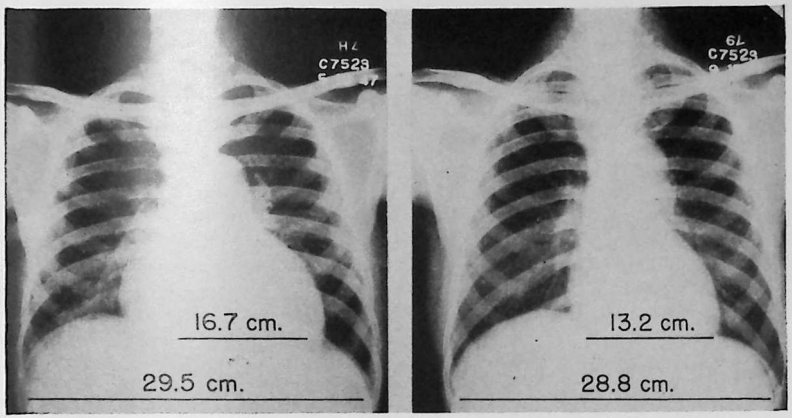
523a Bang et al. B45703/48, Crucilla B44590/47, Lichtwitz B46121/50, Lichtwitz et al. B46123/50, Raab B45766/48, Scott B45292/49, Soloff and Zatuchni B45299/49.

524 Behrendt and Burgess B44381/47, Kempner B38002/44, B740/45, B4216/46, **B45953/49**, Kempner et al. B43408/48, Lichtwitz et al. B46122/50, Rosenberg et al. B43407/48.

525 Schwartz and Merlis B26403/48.

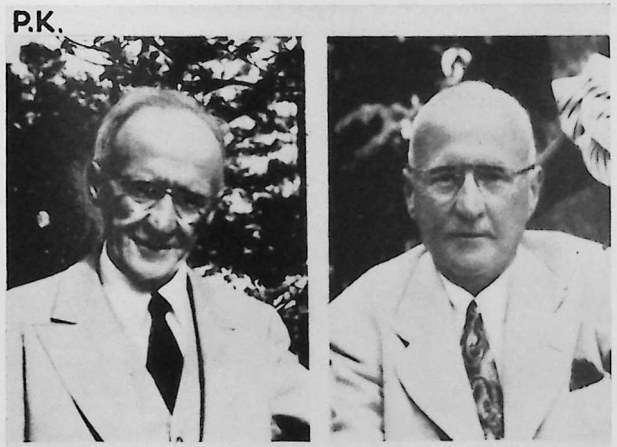
526 Chasis et al. B33406/49.

527 Currens et al. B33408/49.



Effect of rice diet in clinical hypertension. 42-year-old male, who had hypertensive vascular disease of ten years' duration and cardiac failure of six months' duration. Previous treatment: sympathectomy in 1940 and from 1940 to 1946, digitalis, mercurials and sedatives (0.6 gm. sodium amytal daily). — **A.** May 17 to 27, 1947; total PSP-excretion in two hours, 32%; venous pressure 195 mm. of saline. Blood-pressure 220/152; weight 60.3 Kg. Rice diet was started on May 17th and strictly followed for four months. All medication was discontinued on May 17th except digitalis which was discontinued June 9, 1947. — **B.** September 15, 1947; blood-pressure 214/148; weight 57.1 kg. There was a reduction in heart size, with change in transverse diameter of 27%, in spite of persistence of high blood-pressure.

(After Kempner B45471/48.)

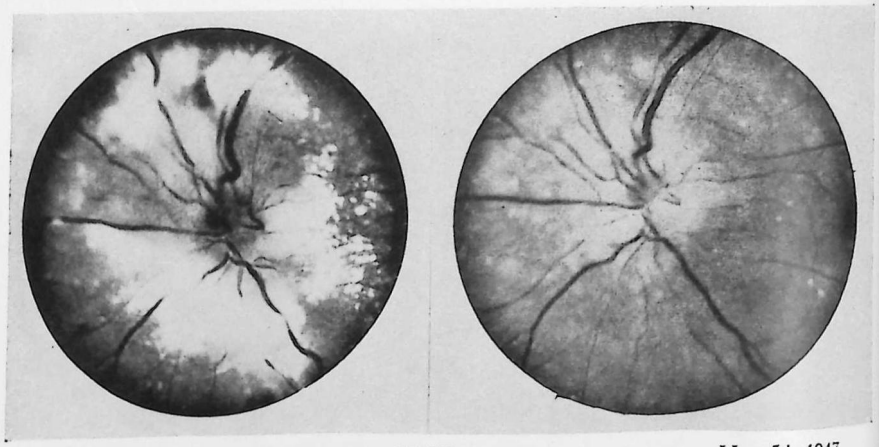


Effect of rice diet in severe hypertensive heart disease. The patient ate one pound of rice (dry weight) and one pound of dextrose daily and gained over 7 kg. during seven months in spite of the loss of edema. There was a great reduction in the transverse diameter of the heart and the patient continued to gain weight on this low-protein intake, during the last two and a half years, in the absence of any other medication. The first photograph shows the characteristic face of a patient with advanced heart disease, drawn, emaciated, prematurely aged, like a victim of starvation. The second photograph shows him well nourished and healthy.

(After Kempner B45053/49.)



Dec. 8th 1945 RIGHT May 5th 1947



Dec. 8th 1945 LEFT May 5th 1947

Effect of rice diet in clinical hypertension. 38-year-old male who had hypertensive vascular disease of at least one year's duration. He was previously treated with sedatives and low-salt diet. December 8 to 20, 1945: blood-pressure, average, 216/132; EKG T_1 inverted; total PSP-excretion in two hours 58%. Rice diet was started, December 13, 1945, but was not strictly followed (28-55 mg. Cl per 100 cc. of urine). May 5 to 8, 1947: blood-pressure, average, 208/123; EKG T_1 upright. Papilledema, hemorrhages, exudates disappeared in spite of persistence of high blood-pressure. (After Kempner B45471/48.)

depended upon the NaCl-intake. Several investigators pointed out that Na-restriction in itself is often beneficial in hypertension.[528]

Extensive studies in which TEA was used to separate the nervous from the humoral component (see below), led to the following conclusions concerning the mechanism of the Na-effect: "(1) That in some patients with essential hypertension and only moderately impaired renal function, the important change during sodium deprivation may be lessening of the humoral contribution to the maintenance of an increased peripheral resistance. (2) That in other patients with malignant hypertension, renal failure, or both, an apparently large humoral component in peripheral resistance may be uninfluenced by an even greater degree of sodium depletion".[529] This would appear to be in agreement with the fact that the RPS-component of hypertension is uninfluenced by sodium depletion as we have said when discussing the blood-pressure elevations caused by the "endocrine kidney".

The use of commercially available *"salt substitutes"* should be strictly supervised since many of them are dangerous. Thus lithium chloride, given instead of NaCl, is definitely toxic, especially on low-sodium diets.[530]

In order *to facilitate sodium depletion* in clinical practice, mercurial diuretics (e.g., mercupurin) have been administered to patients kept on a comparatively low sodium intake.[531] Simultaneous examination of blood-uric-acid, eosinophil and lymphocyte responses as well as 17-KS and corticoid elimination studies suggested: "that the decline in blood-pressure, which follows accelerated sodium depletion, is associated with a temporary alteration of corticoid function".[532] Oral ingestion of cation-exchange-resins is also useful in inducing an accelerated sodium depletion because these substances interfere with the absorption of Na by the intestine.[533] However, this procedure may lead to dangerous electrolyte depletion unless it is very carefully supervised.[534]

Since the nephrosclerosis and hypertension caused by DCA are effectively prevented by ammonium chloride ingestion, this substance was administered to hypertensive patients in the form of enteric-coated pills. The results were generally rather satisfactory, although it would be premature to draw definite conclusions.[535] Unfortunately the coatings of many commercial preparations of this kind are not adequately dissolved in the intestinal tract; this should always be kept in mind when ammonium chloride is used.[536]

Much has been written about the supposedly detrimental effects of various *condiments* (pepper, mustards, ginger, etc.) in hypertensive patients,[537] but this is perhaps debatable. It must be kept in mind that those who indulge in the use of highly spiced food, usually also like to employ a good deal of salt.

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[528] Allen and Sherrill 40804/22, Bryant and Blecha 98920/47, Contratto and Rogers B24713/48, Greenfield B36362/49, Grollman B44382/46, Grollman et al. B777/45, Koenigsberg B24850/48, Landowne B43808/48, Maynard B38287/49, Page et al. B35587/49, Perera B44209/47, Pines and Perera B38292/49, Rosenberg et al. B43407/48.
[529] Stead et al. B29410/48.
[530] Corcoran et al. B40148/49, Waldron B45300/49.
[531] Megibow et al. B31705/48.
[532] Megibow et al. B33427/49.
[533] Crismon B32726/49, Dock B17481/46.
[534] Irwin et al. B43399/49.
[535] Schneider 86581/44, Selye 99184/46, B4535/47.
[536] Anonymous B37555/47, Selye 99184/46.
[537] Blair B23231/48.

An observation which is somewhat difficult to interpret at the present time, is the alleged curative effect of *vitamin-K* in essential hypertension.[538] If confirmed, this finding may throw some light on the pathogenesis of the disease, but up to the present, only few patients have received such treatment.

In some hypertensives capillary fragility is augmented. This may at times be corrected by *"vitamin-P"* (rutin and other flavonols), but without conspicuously diminishing the incidence of cerebral vascular accidents or retinitis[539] and there is no reason to suspect that deficiency in "vitamin-P" plays an important rôle in the pathogenesis of hypertension.

It would not be within the scope of this volume to discuss the extensive literature concerning the results obtained in the treatment of hypertension with the various techniques of more or less complete *sympathectomies*. Suffice it to say that extensive destruction of the sympathetic nervous system often diminishes the blood-pressure level, especially in those hypertensives in whom the disorder is presumably of neurogenic origin.[540] It is much debated to what extent denervation of the kidney (elimination of local vasoconstriction, which could cause a "renal type" of hypertension), the adrenals (elimination of adrenergic hormone discharge from the medulla), and of the peripheral vessels (diminution of peripheral vascular resistance, due to generalized neurogenic vaso-dilatation), participate in the effects obtained. Especially after total or subtotal sympathectomy, the results were often satisfactory. However, these operations considerably impair the functional capacity of the vascular system and can only be performed by skilled surgeons. Hence, this approach to the therapy of hypertension hardly lends itself to use on the large masses of the population who require treatment for this disease.

When the blood-pressure rises as a result of increased intra-cranial pressure, *cerebral decompression* may be useful, but it is not without danger. Hence, denervation of the splanchnic-bed has been recommended to abolish or minimize the orthostatic pressor responses and thus protect the cerebral circulation.[541]

Various *autonomic drugs* have been used to abolish the nervous factor in the pathogenesis of clinical hypertension. Ergot derivatives are among the most intensely studied sympatholytic agents, hence they received special attention in this connection.[542] With dihydroergotamine remarkable results have apparently been obtained in hypertensive patients who did not respond to any other form of therapy.[543] Dihydroergocornine depresses the blood-pressure, both in normal and in hypertensive individuals, but the mechanism of its action has not yet been clarified.[544] In man it diminishes only slightly the effects of adrenaline on blood-pressure and heart rate.[545] These observations have subsequently been confirmed on a series of young hypertensives and it was pointed out that since the drug possesses both "sympathicolytic and adrenolytic actions the above observations indicate that sympathetic nervous system activity may

[538] Rinaldi and Alagna B37532/47.
[539] Bruger B38289/49.
[540] Castleman and Smithwick B24904/48, Fowler and de Takats B46716/49, Grimson et al. B36363/49, Palmer et al. B26327/48, Peet and Isberg B36908/46, B43762/48, Raab B45766/48, Smithwick B6325/44, B43761/48.
[541] Palmer et al. B26327/48.
[542] Freis et al. B41118/48, Kappert et al. B41122/48.
[543] Dreyfus B37528/47.
[544] Bluntschli B41121/48, Bluntschli and Goetz B24720/47, B24787/48, Goetz B43946/49, v. Kappert B45634/49, Wilkins et al. B46071/49.
[545] Fries et al. B43394/49.

contribute to the establishment of early hypertension". The renal clearance test in these patients revealed normal kidney function.[546]

Dibenamine, another sympatholytic and adrenolytic drug, has also been recommended for the therapy of hypertension.[547] A "reduction to normal or below normal levels in resting arterial blood-pressure was observed only in mild or moderately advanced essential hypertension, but not in the malignant phase". The usefulness of dibenamine in evaluating the neurogenic component in hypertension has been especially emphasized.[548]

Since nor-adrenaline as well as adrenaline appear to play a rôle in hypertension — at least in that caused by pheochromocytomas — it is of interest that, in man, benzodioxane (933F) inhibits hypertension due to nor-adrenaline much more than corresponding animal experiments had suggested.[548a]

TEA elicits a marked fall in blood-pressure in certain cases. It has been stated that "in these hypertensives, neurogenic hypertonus may be a significant factor, since it would appear that blocking autonomic pathways with tetraethylammonium produced not only a fall in blood-pressure, but also partial release of the increased renal-arteriolar constriction, which is characteristic of the hypertensive state.[549] TEA appears to act primarily due to its blocking effect upon the autonomic ganglia. It diminishes the tonus of the urinary bladder, the normal gastrointestinal peristalsis as well as gastric, salivary and sweat secretion. These and other toxic effects make it appear impractical to use the drug for the routine treatment of hypertension, but it is interesting from a theoretical point of view, that TEA causes a transient fall in arterial blood-pressure and has relieved many of the complicating symptoms of hypertension. In view of its specific effect upon the autonomic nervous system, it has also been recommended particularly for the estimation of the neurogenic component in individual cases.[550]

Anti-histaminic drugs (e.g., pyribenzamine), allegedly exert a beneficial effect upon the albuminuric hypertension of pregnant women.[550a] This is reminiscent of the inhibition, by anti-histaminics, of some DCA-overdosage effects (cf. p. 532).

Potassium thiocyanate has been widely recommended in the treatment of hypertension. In general, the best results were obtained in the quiescent phase of benign hypertension. Headache and dizziness showed the most conspicuous improvement. Toxic effects were rare, but the response in malignant hypertension is usually poor.[551]

Adenylic nucleotide treatment of hypertension has been recommended, to supply energy to the cardiovascular musculature. The allegedly encouraging results require confirmation.[551b]

Extensive studies concerning the effect of various *pyrogens* (especially those of bacterial origin) suggest "that the malignant phase of hypertension may be reversed by repeated injections" provided renal function is adequate.[552] Since

[546] Kubicek et al. B32780/49.
[547] Simeone and Sarnoff B38984/47.
[548] Haimovici and Medinets B37643/48.
[548a] Goldenberg and Aranow B47255/50.
[549] Hoobler et al. B30647/47.
[550] Hoobler et al. B33419/49, B38299/49, Kowalski et al. B38053/48, Lian et al. B46067/49, Lyons et al. B30650/47, Monto and Keyes B46066/49, Stead et al. B29410/48.
[550a] Hoffman B47750/49.
[551] Guidotti and Puddu B46061/48, Watkinson and Evans **B44380/47.**
[551b] Ruskin B47756/48.
[552] Page and Taylor B40251/49.

all kinds of damaging agents tend to decrease the blood-pressure, especially in hypertensive patients, this may well be a "non-specific therapy" effect.[552a] Further investigations will have to show to what extent, if any, such agents act by normalizing a deranged corticoid production or an abnormal "conditioning" of corticoid actions due to alterations in intermediate metabolism. In an attempt to assess the mechanism through which pyrogens, sterile abscesses, etc., reduce experimental renal hypertension in animals, it has been pointed out that: "tissue injury is known to be a stimulus for an alarm-reaction, eliciting alterations in pituitary adrenocorticotrophic and adrenal corticoid secretion. The resulting effects upon protein, carbohydrate and mineral metabolism, as well as upon vascular reactivity, may be of prime importance in the genesis of the vasodilatation which results in return of the blood-pressure to normal values".[552b]

Hypotension. — The pathogenesis of orthostatic (postural) hypotension is still very incompletely understood. However, the often very pronounced improvement obtained with DCA [552c] suggests that inadequate corticoid-production may play a rôle here.

Cardiac diseases. — It is of course quite impossible to delimit the "cardiac diseases" sharply from the other cardiovascular derangements discussed in this section. Nevertheless, it seemed expedient to discuss some predominantly cardiac derangements, especially the non-specific inflammations of the heart and congestive cardiac failure, under a separate caption.

Ample **experimental** evidence has shown that stress and overdosage with various hormones, which are produced during stress, can cause characteristic morphologic changes in the heart. Thus LAP, mineralo-corticoids and RPS all elicit a type of myocarditis very similar to that seen in acute rheumatic fever or periarteritis nodosa. This is often accompanied by thrombosis of the coronary arteries and the formation of infarcts (cf. above).

It is of special interest that purely nervous stress (e.g., irritation of animals with the electric current) is particularly effective in causing similar cardiac lesions. From this it was concluded that cardiac infarcts, hyalinosis and even angina pectoris should be regarded as diseases of adaptation.[553]

Certain **clinical** observations also suggest that cardiac lesions may be the consequence of a derailed G-A-S.[554] Most of the pertinent publications are based on the study of anatomic lesions such as non-specific carditis (cf. below) but even functional derangements may fall into this category. Thus in patients with chronic *congestive heart failure*, there may develop a clinical picture very similar to that observed in surgical or hemorrhagic shock.[555] While of course here the manifestations of stress are largely secondary to the heart disease, certain components of the resulting G-A-S may in turn aggravate the circulatory derangement. The resemblance of the clinical manifestations of cardiac failure with those of addisonism, lead to the assumption that the former causes a state of relative hypocorticoidism.[555a]

Several investigators expressed the view that the increased incidence of *coronary disease* in modern times is largely due to the stresses and strains inherent in present day life [556] and in particular to derangements of the G-A-S

[552a] Del Dotto B45702/48.
[552b] Stamler et al. B46212/50.
[552c] Luft and Sjögren B44806/48.
[553] Hirsch B33742/49.
[554] Mosinger B30627/48.
[555] Stead and Ebert B26802/42.
[555a] Viciu B45696/48.
[556] Biörck and Pannier 99838/46, McCormick 94819/45.

mechanism. In such instances, it is doubtful whether one should speak of a primarily cardiac disease. "Clinicians have come to think of disease more and more in terms of a disturbance in the total economics of the personality, a temporary overwhelming of the efforts of the organism to maintain a continuous internal and external adaptation to continuously changing relationships, threats, pressures, instinctual needs and reality demands". Many a so-called cardiac disease is in reality due to such maladaptation and the question has been asked "what is the diagnosis in a patient who has coronary symptoms whenever he takes his wife to a party ?".[557]

Various types of *myocarditis*, especially the "rheumatic-allergic" variety have been discussed elsewhere as possibly due to derangements of the G-A-S. From a clinical point of view it is interesting that severe, diffuse myocarditis ensues rather frequently in combination with war-nephritis, under conditons of severe exposure.[557a] The anatomc literature concerning this type of change is reviewed in the immediately following paragraphs.

More objective evidence in favor of the G-A-S concept can be derived from the **pathologic anatomy** of heart disease. It has been emphasized that various types of endocarditis, myocarditis and pericarditis have much in common with the cardiac lesions of acute rheumatic fever and are in essence phenomena of *"serous inflammation"*. They depend largely upon a derangement in membrane permeability which permits the transudation of edema fluid into the intercellular spaces with consequent organization of the transudate into a granuloma.[558]

The hyalinizing myocarditis of *rheumatic fever*, is often accompanied by the formation of granulomatous nodules containing polynuclear Aschoff cells, hyalin deposits and thromboses of the coronary arteries.[559] This picture is especially reminiscent of the lesions produced by mineralo-corticoid overdosage in animals. Significantly, latent rheumatic myocarditis is not an exceptional cause of cardiac decompensation even in older persons.[560]

A variety of infectious diseases (malignant diphtheria, scrub typhus, bacterial endocarditis, meningococcal septicemia, typhoid, peritonitis, croupous pneumonia) and intoxication, particularly with allergenic poisons (e.g., sulfonamides) may produce an anatomically quite similar myocarditis.[561] Although the typical Aschoff nodule, with characteristic polynuclear giant cells, is rather pathognomonic of acute rheumatic fever, there are many transitional stages between the typical rheumatic myocarditis and the so-called *"post-infectious myocarditis"*,[562] the *"allergic myocarditis"* [563] or *"non-specific myocarditis"*.[564] The structural similarity between these myocardial lesions and those experimentally produced in animals by corticoids has repeatedly been emphasized.[565] It is also noteworthy that in various infections and intoxications, the manifestations of myocarditis tend to become evident after the acute period of damage. It will be recalled that following continuous overdosage with LAP, mineralocorticoids or RPS, such myocardial lesions also take several days to be manifest: hence the observed facts are compatible with the assumption that, in clinical

[557] Menninger B44688/48.
[557a] Bohn and Feldmann B46010/47.
[558] Eppinger B37085/49.
[559] De Brux B44344/48.
[560] Rogers and Robbins B29393/47.
[561] Arnold **B41249/49**, Boyer and Weinstein B29392/48, Gore B38112/48, Gore and Saphir B43910/47, Ritter B44513/48, Solomon and Irwin B3982/47.
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[564] Marcuse B4224/47.
[565] Alphonse B18158/47, Selye B1204/46.

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[563] Skrzydlewski B1718/47.
[564] Marcuse B4224/47.
[565] Alphonse B18158/47, Selye B1204/46.

pathology, the development of corresponding changes could be enhanced by excess corticoid production in response to the systemic stress of infections and intoxications. Thus, hyperactivity of the pituitary-adrenal-kidney system may well be that common pathway through which so many different damaging agents produce fundamentally similar cardiac lesions. Significantly, both the clinical and the experimental myocarditis are often accompanied by pronounced morphologic changes in the kidneys.

The often extraordinarily pronounced adrenocortical changes, in patients with *chronic cardiac decompensation*,[565a] also suggest that corticoids may modify the clinical symptomatology rather significantly. Such adrenal changes are not specific for heart disease. However, the fact that they are so prominent here, is in itself strong evidence indicating that the adequacy of an adaptive cortical response probably influences the course of this malady, which depends so much upon target organs (cardiovascular system, kidney, electrolyte and water metabolism) largely controlled by corticoids.

Metabolic studies on patients with heart disease likewise gave some evidence concerning the pathogenic rôle of the G-A-S. In chronic congestive heart failure — especially in the so-called "forward failure" — the derangements in *electrolyte* metabolism are rather reminiscent of those caused by mineralo-corticoid intoxication.[566] The view has been expressed "that sodium retention in heart failure may be as complex as the body mechanisms for sodium conservation in the adaptation of the body to various situations. In fact it appears likely that heart failure may simply result in a prolonged exaggeration of these phenomena which occur in daily life". It appears that the adrenal-cortex may play a rôle in the sodium retention of advanced heart failure.[567] Studies with radio-sodium revealed that the clearance of the tracer element from the blood is considerably delayed in congestive heart failure.[567a] It remains to be seen whether this is actually due to increased mineralo-corticoid activity.

Although in congestive heart failure there is a retention of both NaCl and water, it appears that the retention of water exceeds that of salt "with a resultant dilution of extracellular fluid, suggesting an extra-renal influence on water retention, probably coming from the *posterior pituitary*".[568] In normal individuals artificial congestion of the limbs by blood-pressure cuffs is followed by marked antidiuresis a few minutes after release of the tourniquet. At the same time, renal plasma-flow (PAH), filtration rate (inulin, mannitol) and the excretion of Na, K and Cl are reduced. Similar changes are noted in hypertensive patients both before and after lumbo-sacral sympathectomy, hence it was concluded that a disturbance in renal circulation may play a major rôle in the pathogenesis of congestive myocardial failure. "Since these changes persist after sympathectomy, they are possibly mediated through humoral mechanisms".[569]

The urinary-*corticoid* excretion (survival test and glycogen-deposition test) is increased in patients with congestive heart failure. Since the liver is involved in the detoxification of steroids and most of these patients had enlarged livers, the possibility was considered that failure of hepatic detoxification may be

[565a] Liebegott B45912/44.
[566] Fox et al. B33413/49, Peters **B26232/48**, Warren and Stead **B26801/44.**
[567] Merrill B36365/49.
[567a] Burch et al. B46003/47, Threefoot et al. B44700/49.
[568] Schroeder B36366/49.
[569] Wilkins et al. B33448/49.

involved. It was also pointed out that excess corticoid excretion is characteristic of a G-A-S produced by any stressor including anoxia or hyperventilation both of which are manifest in patients with heart failure. Hence "the increase in corticoids found in this study possibly represents adaptation to these non-specific stimuli".[570] In this sense, the derangement in sodium metabolism would have to be regarded as secondary to increased corticoid production, just as the structural lesions in the heart are supposed to be consequences of excess corticoid secretion.

Bioassays suggest that the heart contains an excessive amount of *adrenergic substances* in cases of angina pectoris and hypertensive or uremic heart disease. This may be accompanied by excessive accumulation of sodium in the heart muscle, due to an increased activity of the adrenal-cortex.[571] It would be most interesting to verify these findings on a large autopsy material as they suggest that both corticoids and adrenergic substances participate in the pathogenesis of these types of cardiac failure.

The *renin* content of the renal venous blood is allegedly increased in patients with chronic heart failure.[572] It has also been claimed that excessive amounts of VEM are present in the renal-vein blood during chronic congestive heart failure and that VDM activity is demonstrable in the hepatic blood of all cardiacs, but almost never in normal controls. This was interpreted as an indication that the *VEM-VDM* mechanism is deranged in these patients.[573]

All these observations imply that vasopressin, adrenal (cortical and medullary) and renal hormones participate in the pathogenesis of cardiac failure. Since these hormones play important rôles in the regulation of the G-A-S mechanism, it is suggestive to assume that cardiac failure is, at least partly, also a disease of adaptation.

Since *cholesterol* feeding tends to produce arteriosclerotic lesions in animals and corticoids exert an important effect upon the blood-cholesterol level, it is interesting that coronary thrombosis in patients under the age of sixty is frequently associated with hypercholesterolemia and other disturbances of cholesterol metabolism.[574] It remains to be shown, however, whether these derangements and the coronary lesions are actually related to the changes in corticoid production. Recent studies, based upon ultra-centrifugal flotation diagrams, suggest that both in the experimental cholesterol atherosclerosis of the rabbit, and in the spontaneous atherosclerosis of man, the cholesterol is transported in the serum via giant lipid- and lipoprotein-molecules of low density.[574a]

It is a well-known fact that *sodium restriction* is beneficial in the **treatment** of cardiac edema, especially if simultaneously, large amounts of water are given to help the elimination of Na.[575] The efficacy of this measure may be increased by treatment with *cation exchange resins*, which interfere with the absorption of Na from the alimentary tract [576] or the administration of *ammonium chloride* and *mercurial diuretics*,[577] which improve Na excretion and thus diminish

[570] Parrish B30929/49.
[571] Raab B23181/48.
[572] Merrill et al. B44429/46.
[573] Escher et al. B36361/49, Mokotoff et al. B32791/49.
[574a] Gofman et al. B46205/50.
[574] Morrison et al. B39310/48.
[575] Gorham et al. B3998/47, Iseri et al. B47879/50, Scott B45292/49, Soloff and Zatuchni B45299/49.
[576] Currens et al. B47863/50, Irwin et al. B43399/49, Kahn and Emerson B47883/50, Kraus B47884/50.
[577] Batterman et al. B36359/49, Donoven B2990/45.

the edema tendency. Since similar measures also combat the cardiovascular manifestations of corticoid intoxication, it is reasonable to suspect that the corticoids play a part in cardiac edema. Here again it should be emphasized, however, that toxic sodium-substitutes such as lithium,[577a] and excessive sodium-depletion (e.g., by severe salt restriction and simultaneous administration of mercurial diuretics),[577b] may cause serious complications.

Thioureas proved beneficial in many cases of congestive heart failure and angina pectoris.[577c] This is of special interest in connection with our problem since thyroid hormone markedly sensitizes experimental animals to the toxic effects of mineralo-corticoids upon the cardiovascular system and the kidney.

X-irradiation of the adrenals has been recommended in the treatment of angina pectoris.[578] In this case, it is not clear to what extent diminution of corticoid or adrenergic hormone production is involved and indeed the efficacy of the procedure has not yet been confirmed on a large material.

The alleged utility of *vitamin-E* therapy in the treatment of heart disease has not yet been definitely confirmed.[579]

Arteriosclerosis in general. — Arteriosclerosis is a much used but ill-defined term. The following are a few examples of attempts to give a **definition:**

"Abnormal thickening and hardening of the walls of the arteries, especially of the intima, occurring mostly in old age" (Webster's dictionary).

"A condition of loss of elasticity and thickening of the coats of the arteries with inflammatory changes, degenerative or productive".[580]

"Arteriosclerosis is the term in most general use for that disease of the arteries which leads to their loss of elasticity, and changes in the appearance and structure of the intima and other coats which lead to dilatation and deformity of the arteries".[581]

"Arteriosclerosis may therefore be defined as a progressive and irreversible affection of the arteries in which hyperplasia of one or more of the structural elements is a primary reaction with deposition of lipoids, collagenous tissue, hyalin and calcium as a secondary reaction, the totality of both components resulting in thickening, dilatation, deformity and loss of elasticity of the walls".[582]

Hueper [583] speaks of "the degenerative and sclerosing arterial diseases known under the collective term of arteriosclerosis".

Boyd [584] states that: "it is as if all the conditions which may produce a localized swelling of bone were grouped under one name and an attempt then made to discuss the etiology and pathogenesis. Accordingly we shall not consider the general condition known as hardening of the arteries but the subject will be divided into three sections: atherosclerosis, Mönckeberg's sclerosis and diffuse hyperplastic sclerosis".

Bishop [585] in his monograph "Arteriosclerosis" came to the conclusion that: "we know arteriosclerosis as familiarly as we know any person of our acquaintance, but of all diseases it most eludes definition."

[577a] Waldron B45300/49.
[577b] Soloff and Zatuchni B45299/49.
[577c] Rune Frisk and Lindgren **B45697/48.**
[578] Fisher and McMillan B34014/46, McMillan and Rousseau B34028/46.
[579] Travell et al. B43859/49.
[580] Dorland B19921/48.
[581] MacCallum A94851/38.
[582] Moschcowitz 91508/42.
[583] 91730/45.
[584] 99692/35.
[585] 96643/15.

In the present section we shall deal principally with atheromatosis (predominantly fatty deposits in arterial walls), atherosclerosis (atheromatosis with marked sclerosis), and problems pertaining to arteriosclerosis in general. A few special types of arteriosclerosis such as periarteritis nodosa, thromboangiitis obliterans, endarteritis obliterans, etc., will be discussed in separate sections below; not because we regard them as essentially distinct from the general group of the arterioscleroses, but merely because the rather characteristic morphologic features of these arterioscleroses have given rise to a special literature concerning each variety. It should also be noted at the outset that there is a gradual transition between many of these types of arteriosclerosis and the so-called rheumatic-allergic connective tissue diseases or "collagen diseases", perhaps because in all these derangements increased capillary permeability and hyalinosis are of primary importance. Accordingly, these maladies will be discussed synoptically here.

Experimental data have shown that various stressors, LAP, adrenergic substances (e.g., adrenaline) corticoids (e.g., DCA, desoxocortisone) and RPS can cause widespread arteriosclerotic changes in the vessels of animals. These observations led to the hypothesis that arteriosclerosis is also primarily a disease of adaptation.[586] Presumably stressors cause vascular lesions through the hypophysis-adrenal-kidney system as well as through the sympathetic-adrenomedullary system. The structural characteristics and the distribution of the resulting vascular changes are of course largely dependent upon heredity, diet, specific actions of the stressors, as well as the acuity and intensity of the stress situation. Such conditioning factors may well determine whether the vascular lesions will be mainly characterized by the deposition of one or the other storage material (hyalin, lipids, calcium), the proliferation of a cellular granulomatous or dense scar-like connective tissue, etc. In view of the important effect of corticoids upon the development and healing of inflammatory tissue and the R.E.S. — in patients with cardiovascular lesions caused by systemic infections — even the growth of micro-organisms may largely depend upon the G-A-S mechanism.

Numerous **clinical** observations agree with the interpretation of arteriosclerosis as a disease of adaptation. Thus the incidence of arteriosclerosis appears to be definitely higher among individuals exposed to much stress and strain than in the population at large.[587] Extensive statistics show, furthermore, that in this age of wars and hard competition arterial disease is the leading cause of death in "civilized" countries.[588]

Among the pertinent **metabolic** studies, let us merely mention that atherosclerosis is frequently associated with *hypercholesterolemia* and other disturbances in cholesterol metabolism,[589] a fact which agrees with the experimental observations showing that excessive feeding of cholesterol can produce arteriosclerotic changes in animals.

An extensive review of the pertinent literature "favors the conclusion that atherosclerosis develops from disturbances in the metabolism of lipid infiltrated into the tissues of the intima".[590] We have seen that various hormones produced during the G-A-S may render the intima more permeable to certain blood-borne substances, e.g., the proteins that form "hyalin". Perhaps these same

[586] Hirsch B33478/49, Selye **B1204/46.**
[587] Attinger B37955/47, Hirsch B33478/49.
[588] Davis B29880/48.
[589] Morrison et al. B37873/48.
[590] Hirsch and Weinhouse A63233/43.

hormones which under the usual laboratory conditions are especially conducive to hyalin infiltration of the vessel wall may under certain circumstances (e.g., in the presence of a disturbed lipid metabolism) favor the deposition of cholesterol and other lipids in these same regions. The finding that genetic factors play an important rôle in determining the blood-cholesterol level [591] may shed some light upon the hereditary predisposition of certain people to the development of arteriosclerosis.

Any study concerned with the relationship between cholesterol metabolism and arteriosclerosis must also take into account the *cholesterolytic power of the blood*. This was found to be low in patients with arteriosclerosis, especially coronary sclerosis.[592]

Systematic *fibrinolysin* determinations have not yet been made on the blood of arteriosclerotic patients, although, a deficiency of this enzyme may well result in abnormal deposits of fibrinoid "hyalin" material with the subsequent formation of arteriosclerosis.[593]

Since *sodium* plays such an important rôle in the production of arteriosclerosis by mineralo-corticoids, it is of special interest that using radioactive sodium as a tracer, the diffusion of intravenously administered sodium salts was found to be delayed in patients with non-specific arteritis, endarteritis, thrombo-angiitis obliterans and scleroderma.[594]

The extensive **morphologic** studies concerning the histogenesis of arteriosclerosis led to rather conflicting views regarding the mechanism through which lipids, hyalin and calcium are deposited in the vessel walls. While some authors believe that these materials infiltrate into the depot layers through the intima (either as such or in lipophages), others consider it more probable that they arise locally.[595] Of course, even in the latter case, the products from which such depot materials would arise must, in the final analysis, come from the blood.

Virchow [596] postulated, almost a century ago, that the primary lesion in arteriosclerosis is a "certain swelling of the ground-substance" of the arterial wall with a loosening of the intima and consequent penetration of blood-plasma into the sub-intimal spaces. This view is in conformity with modern concepts concerning the pathogenesis of "serous inflammation".[597] It also agrees well with morphologic observations on the histogenesis of the arteriosclerosis caused by mineralo-corticoids or RPS and helps to understand the fundamental similarity between these and the extra-vascular manifestations of "hyalinosis". Indeed, certain investigations suggest that "dysoria" (plasma infiltration into the intima) is an "indispensable prerequisite for the development of intimal sclerosis".[597a]

Data concerning the **therapy** of arteriosclerosis are still far too scanty to yield much information concerning the pathogenesis of this disease. Some improvement has allegedly been obtained with *testosterone*,[598] but this has never been very striking. The much more promising possibility of treatment with gluco-corticoids has not yet been investigated.

[591] Stecher and Hersh B29997/49.
[592] De Langen B37988/48.
[593] Anonymous B44433/49.
[594] Mufson et al. B38708/48.
[595] Bishop 96643/15, Gordon B38009/47, Hirsch B26305/43, B26307/41, Katz and Dauber **B36753/45**, Winternitz et al. B36754/38.
[596] B44431/856, B44430/856.
[597] Eppinger B37085/49.
[597a] Meyer B44579/49.
[598] Moreno B23772/43, Selye **94572/49**.

On the other hand, the same *dietary factors* which interfere with the production of experimental arteriosclerosis also appear to exert a beneficial effect upon the spontaneous arteriosclerosis of man. Thus, a particularly high incidence of severe atherosclerosis is found in obese persons at necropsy, while in people who suffered from prolonged undernutrition, such changes are rather rare. Even among patients who lost weight only during a comparatively short period prior to death, the arteriosclerotic changes tended to be mild. "It is inferred, therefore, that significant resorption of previously formed atheromatous lesions may occur during periods of marked weight loss."[599]

Statistical studies reveal, furthermore, that during wars — presumably as a result of undernutrition — the incidence of arteriosclerosis is considerably lower than in peace time. In this connection, lack of cholesterol, protein and total calories appear to be of particular protective value.[600]

Since lipotropic factors tend to prevent experimental atherosclerosis, it is interesting that "over a 3-year period the lipotropic agent choline was effective in significantly reducing the mortality rate, due to recurrent coronary thrombosis with myocardial infarction, in a series of 115 patients with proven coronary atherosclerosis".[600a]

In obliterative arteriosclerosis of the peripheral vessels, sympathectomy is often of great benefit.[601] Presumably, this is largely, if not entirely, due to elimination of the vasopressor nervous influences; it remains to be shown whether the improved nutrition of the denervated areas affects the underlying morphologic process itself.

Periarteritis (polyarteritis) nodosa. — Among all the vascular diseases, periarteritis nodosa has been most accurately and most consistently reproduced in **experimental** animals by stress, LAP, mineralo-corticoids and RPS,[602] hence, it was one of the first maladies which we considered to be a disease of adaptation.[603] As previously stated LAP, unlike the other hormones mentioned above, tends to cause marked periarteritis only in the heart, presumably because it stimulates the secretion of both mineralo- and gluco-corticoids. It will be recalled that the latter tend to inhibit the formation of periarteritis especially outside of the heart.[604]

Many **clinical** observations tend to support the interpretation of periarteritis nodosa as a disease of adaptation. Most of the monographs concerning this disease emphasize that rheumatic fever, allergies, infections, intoxications and a variety of other stressors may act as the eliciting agents. Allergic reactions to foreign sera, various micro-organisms, sulfa drugs, etc., are particularly prone to produce periarteritis nodosa.[605] It has even been claimed that periarteritis nodosa, endarteritis obliterans, thrombo-angiitis obliterans and arteriosclerosis are not separate nosological entities but "different stages of the same rheumatic process".[606] It is rather questionable whether we should extend the definition of a "rheumatic process" to include all these vascular diseases, but

[599] Wilens B37953/47.
[600] Vartianen and Kanerva B37923/47.
[600a] Morrison and Gonzales B46259/50.
[601] Blain et al. B28167/48, Gerber et al. B28168/48.
[602] Selye B223/44, A62756/43, Selye and Pentz A59789/43, Selye and Stone 94202/46.
[603] Selye **B1204/46**.
[604] Selye B41762/49.
[605] Allen et al. **B19968/47**, Bergstrand **B27907/46**, Fernandez and Malosetti **B33979/47**, Heck **B29947/49**, Karsner **B18113/47**, Kaufmann and Delaunay B38147/47, Miller and Daley **B27942/46**, Nicaud **99330/46**.
[606] Vasiliu B38050/46.

perusal of the pertinent publications clearly shows that this group of maladies, and even malignant hypertensive nephrosclerosis [607] has long been considered to be closely interrelated and presumably dependent upon essentially the same pathogenic mechanism. The possible rôle of the G-A-S mechanism, in the development of clinical periarteritis nodosa, is strongly suggested by these morphologic similarities.[607a]

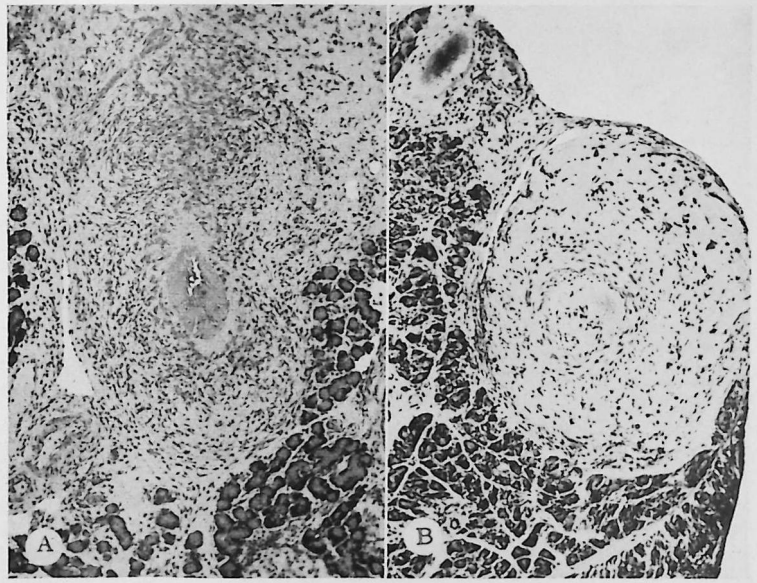
It should be clearly emphasized, however, that up to the present time, the ACTH, corticoid or RPS metabolism has not yet been studied in patients with periarteritis nodosa. Of course the actual eliciting agent (e.g., an allergen) does not necessarily affect the vessels through the pituitary-adrenal-kidney system. It is quite possible that the pathogen acts upon the vessels directly, although it depends upon the efficacy of the hormonal defense mechanism whether this action will lead to the formation of periarteritis. In certain animal species mineralo-corticoids or RPS in themselves suffice to produce typical periarteritis nodosa, but perhaps here potentially "vasotoxic factors" are constantly present although their damaging effect upon the vessels becomes manifest only in the presence of an excess of mineralo-corticoids or RPS. To illustrate these possibilities, let us recall again that neither gluco-corticoids nor mineralo-corticoids as such, exert any prominent and constant effect upon the joint structures, yet, they are highly effective in decreasing or increasing, respectively, the inflammatory response of the joints to some locally injected irritant such as formalin.[608] Of course these same possibilities should be considered in the interpretation of most other diseases of adaptation as well. In general, the diseases of adaptation are not due to a deranged hormone production as such, but to an abnormal humoral response to stressors. Hence, both the hormones and the stressor must be regarded as important pathogenic factors in the development of such maladies.

The **pathologic anatomy** of periarteritis nodosa reveals that not only the histologic structure of the individual lesions resembles the changes experimentally produced by stress, LAP, mineralo-corticoids or RPS; their distribution is also strikingly similar in the experimental and the clinical syndromes. Thus, in both instances, the renal, splanchnic, cardiac and cerebral arteries tend to be most severely affected and whenever the kidney vessels are markedly involved, the blood-pressure usually rises. Several students of this problem emphasize these similarities between the hormonally produced experimental and the clinical disease.[609] It is particularly interesting that in clinical cases of periarteritis nodosa the granuloma is very cellular and contains much hyalin material during the active stage, while in the course of healing, the cellularity of the granuloma greatly diminishes and a scar-like dense connective tissue layer is found beneath the intima.[610] Such arterial scars greatly resemble those seen in rats in which periarteritis changes, produced by DCA, were subsequently treated with cortisone.[611]

Since it is possible to produce periarteritis nodosa with hormones of the pituitary, adrenal and kidney, it is interesting that these organs are frequently affected in patients suffering from this disease. In the pituitary and adrenals,

[607] Davson et al. B29817/48, Meyer B38034/47.
[607a] Rackemann **B27677/48**, Selye **B1204/46.**
[608] Selye B39702/49.
[609] Etinger and Vi'k B44477/48, Kaufmann and Delaunay B38147/47, Maspetiol and Taptas B29886/48, Sampson et al. B38489/49, Selye B1204/46, Wold and Baggenstoss B29949/49.
[610] Hutchison B37572/48.
[611] Selye B41762/49.

apparently, both proliferative and destructive changes may occur; this is not unexpected, since mineralo-corticoids increase, while gluco-corticoids decrease, the tendency to develop periarteritis. Accordingly, in some patients with Cushing's disease, due to anterior-lobe or adreno-cortical hyperplasia, periarteritis-like vascular lesions may appear and nephrosclerosis is quite common.[612] Conversely, in some cases of periarteritis nodosa, the pituitary and/or adrenal was found to be hypoplastic or necrotic.[613] It is possible that in the former instances an excess of mineralo-corticoids, in the latter, a deficiency in gluco-corticoids acted as a sensitizing factor. Of course in the event of necrotic changes in the pituitary or adrenals, the possibility must also be considered that these may be merely the result of local periarteritic changes and not their cause. This same consideration applies to the rather common nephrosclerotic changes in patients with periarteritis nodosa. Here again the lesions in the kidney can be either the cause or the result of the primary disease process.

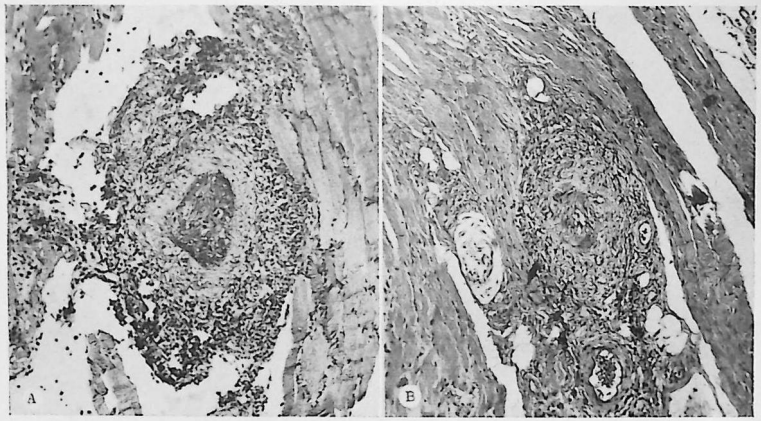


Curative effect of cortisone upon experimental periarteritis nodosa produced by DCA. — **A.** Periarteritis nodosa in a mesenteric artery of a rat overdosed by subcutaneous implantation of two 30 mg. pellets of DCA. The animal was sensitized by unilateral nephrectomy and a high-Na diet; it was killed on 31st day of treatment. Note marked hyalin deposition underneath the endothelium and intensely cellular, proliferating granuloma, which disorganizes the vascular structure. — **B.** Similarly treated animal in which DCA overdosage was continued two weeks longer than in "A", but during these last two weeks it also received 5 mg./day of cortisone. Note that despite more prolonged DCA overdosage, the vessel lesion is healing. The sub-endothelial hyalin has completely disappeared and the cellular granuloma has been substituted by acellular scar tissue. The few large black dots in this scar correspond to blood-pigment-containing phagocytes. (Selye 35035/ND.)

[612] Selye **94572/49.** Lindsay et al. B20657/44.
[613] Balo and Nachtnebel **A64492/29.**

Obviously, further anatomic research is required in order to elucidate these complex interrelations between the hypophysis-adrenal-kidney system and the development of periarteritis nodosa.

Much has been written about the therapeutic value of partial adrenalectomy, x-irradiation of the adrenal region, and denervation of the adrenals in periarteritis nodosa.[614] Most of these interventions were performed with a view to inactivating the adrenal-medulla which was held responsible for such arterial lesions by some of the earlier investigators. Although a few workers claim to have obtained some improvement, the data were not convincing.



Effect of ACTH upon periarteritis nodosa, in man. — **A.** Before treatment. Marked periarterial and muscle infiltration with lymphocytes and eosinophils. Fibrinoid necrosis of arterial wall. — **B.** Evidence of healing, four days after ACTH administration. Note disappearance of fibrinoid deposit, the cellular infiltrations are decreased in the wall and no longer visible in the muscle. (Courtesy of Dr. B. Rose, Royal Victoria Hospital, Montreal.)

ACTH appears to be highly effective in periarteritis nodosa,[615] however, not all individuals react equally well. In a recent study of seven patients treated either with ACTH or with cortisone, all "experienced prompt subjective relief after receiving the hormones; fever has subsided within 24 to 72 hours and sedimentation rates have decreased to normal more gradually. Partial relapses have occurred in five patients after withdrawal of the hormone, followed by improvement when treatment was resumed." Yet, among three patients of this series, in whom cortisone treatment was begun when the disease had already reached a very critical stage, two died in cardiac and renal failure, despite an initial improvement. The other still has severe and progressive hypertension at this time. Even the patients who died exhibited "complete healing of all arterial lesions" at necropsy. "However, in the process of healing, fibrous obliteration of the lumens of these vessels had occurred, resulting in widespread visceral infarction".[615a] Up to now no detailed autopsy

[614] Racine et al. **A62577/36.**
[615] Boland B47735/50,
Goldman et al. B46986/50,
Levin et al. B47887/50,
Rose et al. B45103/50,
Shick et al. B47390/50,
Stillman B47731/50.
[615a] Shick et al. B47390/50.

report has been published concerning patients treated with ACTH or cortisone for periarteritis nodosa. It will be recalled, however, that although the experimental periarteritis nodosa of DCA is prevented by cortisone in most organs, the renal changes may actually be aggravated. We should like to recommend, therefore, that, in the future, those who will attempt this type of treatment be on the look-out for renal complications.

Temporal arteritis. — The histologic appearance of temporal arteritis resembles periarteritis nodosa so closely that the former may be regarded as a special form of the latter. It is often accompanied by periarteritic changes in other vessels (e.g., those of the brain or heart), myocardial infarction, arthralgia, myalgia and thrombo-angiitis obliterans.[616] Because of these characteristics temporal arteritis has been interpreted as a disease of adaptation.[616a]

Thrombo-angiitis obliterans (Bueger's disease). — In this disease the earliest pathologic lesion is usually a proliferation of the intima, with an inflammatory reaction in the media and adventitia, affecting the arteries of the extremities. Subsequently, mural thrombi are formed which gradually become organized and substituted by a giant-cell and blood-pigment containing granuloma. Thus anatomically, the changes characteristic of thrombo-angiitis obliterans are rather reminiscent of those seen in periarteritis nodosa and endarteritis obliterans. Although the etiology of the disease is unknown, it appears to occur almost exclusively in males and with special frequency among heavy users of tobacco; Russian Jews, are particularly predisposed perhaps due to some genetic factor. However, the disease also occurs among females, non-Jews and non-smokers. Exposure to cold, various toxins, infections and mental stress have been considered as possible eliciting agents.[617]

It has been claimed that in Buerger's disease, the adrenals show a fairly characteristic picture of intense vasodilatation, adenomatous hyperplasia of the cortex and sometimes lymphocytic infiltration.[618] Several investigators reported most favorable results following partial adrenalectomy.[619] Here again the possible value of ACTH and gluco-corticoid therapy should be investigated.

On the basis of the above observations, and because of the great similarity between the histologic appearance of the thrombo-angiitic vessel lesions and those caused by LAP, mineralo-corticoids and RPS, the condition has been classified as a disease of adaptation.[620]

Endarteritis obliterans. — This process has also been referred to as "productive endarteritis" or more correctly, as thickening and hyperplasia of the intima. It is not a systemic disease and is usually not accompanied by any obvious signs of inflammation, but consists of a gradual obliteration of the lumen due to proliferative changes in the intima of individual arteries. Vessels which are no longer needed usually become obliterated through this process,

[616] Andersen B47761/47,
Cohen and Harrison B37576/48,
Crosby and Wadsworth B43413/48,
Harrison B37577/48,
Hausz and Burwinkel B44808/49,
Jennings B38052/48,
Robertson B38026/47.
[616a] Chavany and Taptas B45826/48,
Maspetiol and Taptas B29886/48.
[617] Cecil **A63152/43**, Leriche **B28471/46**,
Musser **88056/45**.
[618] Plauchu et al. B37574/47.
[619] Albanese B23403/43,
Carajannopoulos 94969/28,
Franco A62567/36,
Léger and Tchékoff B42798/47,
Leriche **B28471/46**,
Maillet et al. B37575/47,
Plauchu et al. B37574/47,
Ricard B40906/47,
Wertheimer and Gautier **B31771/47**.
[620] Maspetiol and Taptas B29886/48.

for instance: the ductus arteriosus at birth, the arteries of the reproductive organs in senile people, arterioles in the vicinity of a gastric ulcer and those of an inflammatory granuloma when the inflammation regresses. — In the course of healing, periarteritis nodosa and thrombo-angiitis obliterans may assume the appearance of an endarteritis obliterans. However, in the former an inflammatory granuloma, in the latter a thrombus, is gradually transformed into connective tissue, while in the common type of endarteritis obliterans the intima proliferation is not preceded either by obvious inflammatory or by thrombotic changes. Nevertheless, the end-result is rather similar and many pathologists doubt that endarteritis obliterans should be distinguished as a special entity.[621] Since some investigators used the terms endarteritis obliterans and thrombo-arteritis obliterans interchangeably, it is often difficult to interpret their findings. Thus it was pointed out that endarteritis obliterans is presumably an allergic disease,[622] but judged by the description, thrombo-arteritis was meant.

It has also been stated that partial adrenalectomy is of therapeutic value in the obliterating arteritides,[623] however, most, if not all of these patients almost certainly suffered from thrombo-angiitis obliterans and not merely from productive obliterating intima proliferations.

We regard the true, primarily proliferative, intima hyperplasia as related to the diseases of adaptation only in the widest sense of this concept, in that it is usually the result of an adaptive rearrangement of the vessel wall in response to a diminished circulatory strain. On the other hand, many types of so-called periarteritis nodosa, rheumatic arteritis, thrombo-angiitis obliterans, etc., which appear to be more closely related to derangements of the pituitary-adrenal-kidney system, may eventually assume the appearance of an endarteritis obliterans during the process of healing.

Focal, non-septic necrosis of arteries. — Following comparatively simple uncomplicated abdominal operations, focal necrosis may occur in various distant arteries, for instance in those of the cerebellum.[624] These have been interpreted as due to focal infarcts, but, in view of their morphologic resemblance to certain types of periarteritis nodosa, a humoral component in their pathogenesis may deserve consideration.

Rheumatic fever. — As we have mentioned before, cardiovascular changes similar to those seen in acute rheumatic fever have been reproduced **experimentally** in animals, for instance, by the administration of *allergenic sera and drugs*.[625] This led to the conclusion that rheumatic fever is an "allergic disease". Similar lesions have been obtained in rabbits by multiple successive skin infections with several serologic types of *"group A" streptococci.* Here the adrenals showed extreme cortical enlargement, especially in those animals in which the rheumatic-fever-like changes were most pronounced.[626] A carditis, arteritis and arthritis, structurally resembling that seen in acute rheumatic fever, has also been reproduced in experimental animals by *LAP, mineralo-corticoids* and *RPS*.[627] This led us to suspect that acute rheumatic fever is primarily a disease

[621] Boyd **99692/35.**
[622] Betts B26164/48.
[623] Carajannopoulos 94969/28.
Léger and Tchékoff B42798/47.
Ricard B40906/47.
Wertheimer and Gautier **B31771/47.**
[624] Kernohan and Woltman A61979/43.
[625] Fischel **B46889/49.**
Laipply and O'Neill B24825/47.
Rich and Gregory B526/44.
[626] Murphy and Swift B37498/49.
[627] Selye **B1204/46.**

of adaptation due to a deranged, or excessive, hormonal response to various stressors.[628]

It should be re-emphasized here that both the G-A-S and the specific effects of the stressor co-operate in determining the manifestations of the diseases of adaptation. Accordingly, not all stressors are equally capable of producing rheumatic changes. No doubt the so-called allergenic substances and among the microbes, the hemolytic "group A" streptococcus are the most common causes of rheumatic fever in man; apart from the above-mentioned hormones these agents are most suited to produce experimental similes of this disease in animals. According to the G-A-S concept, this may be due either to a particular ability of such stressors to cause abnormal hormonal defense reactions, or to their special tendency so to condition the target organs that the latter respond abnormally to the hormone secreted during the G-A-S. Indeed both of these mechanisms may simultaneously exert their pathogenic actions.

As we have said elsewhere, DCA rarely produces an acute arthritis unless some direct irritation sensitizes the joint to the hormone effect. Topical injection of formalin was used as such a sensitizing agent; its arthritogenic action is greatly aggravated by mineralo-corticoids and counteracted by glucocorticoids or ACTH. It had been assumed that in clinical arthritis an abnormal corticotrophic stimulation, or the abnormal "conditioning" of the peripheral target organs to the excess corticoids produced under stress (e.g., that of a hemolytic streptococcus or allergen), causes the joint lesions and that this could be overcome by the sudden flooding of the organism with great excesses of exogenous ACTH or cortisone. An A-R, produced by a variety of stressors, exerts an equally beneficial effect upon the course of a "formalin arthritis", hence we postulated that even endogenous ACTH is beneficial under these conditions; indeed excessive production of ACTH is probably an important component of various "non-specific therapies".[629] We were reinforced in this belief by the observation that certain anaphylactoid reactions, which are highly amenable to non-specific therapy by the A-R, likewise proved to be inhibited by ACTH or cortisone.[630] Others favor the view that "debility causing a general lowering of local tissue reaction" might be responsible for such non-specific therapeutic results. In support of this interpretation, a number of experiments have been surveyed which demonstrated that the arthritis, usually produced by the intravenous administration of streptococci, can be prevented by dietary deficiencies. Furthermore, inoculation with the virus of foot-and-mouth disease affects well-fed, healthy cattle much more than malnourished animals.[631] It is noteworthy, however, that adrenalectomy — undoubtedly a most "debilitating" intervention — not only fails to decrease, but actually increases the severity of "formalin arthritis".[632] This certainly suggests that "debility" in itself is ineffective unless the adrenals are intact and there is nothing to suggest that the various effective debilitating procedures, quoted above, have any direct beneficial effect of their own. Hence we feel that experimental data agree with the conception that, depending upon conditions, the hormonal response to stress can either sensitize or desensitize the organism to the production of rheumatic changes.

[628] Pirozynski and Akert B38484/49.
Selye **B1204/46.**
[629] Selye B39702/49.
[630] Selye B39703/49.
[631] Crowe **B44428/50.**
[632] Selye B39702/49.

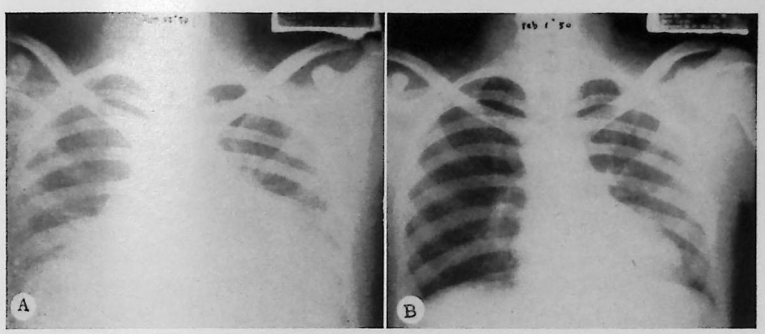
Perusal of monographs concerning clinical aspects of acute rheumatic fever reveal that although certain strains of "group A" hemolytic streptococci are commonly associated with this disease, they cannot always be held responsible for it. In many individuals such streptococci are demonstrable although there is no evidence of rheumatic fever and conversely, they may be absent in patients who develop typical manifestations of this disease. Furthermore, rheumatic fever may develop, or a latent form may be exacerbated, upon exposure to other stressors (exposure to cold, psychic or physical trauma, etc.).[633] Indeed Lichtwitz[633a] introduces his much quoted monograph with the sentence "rheumatic fever is a non-infectious disease". He believes it to be caused by sensitization to antigens, which in most cases are products of micro-organisms. However, he is forced to admit that in the rheumatic individual reactivation of the process can be brought about by a variety of non-specific factors not only by the specific antigen. "Thus, fatigue, a chill, an adventitious infection, a slight injury, a touch of indigestion, a mental upset, or increased bodily activity may cause the rheumatic to relapse from the quiescent into an acute febrile state." Others report rheumatic fever following mechanical trauma.[634] These and the above mentioned experimental observations lead to the view that rheumatic fever is primarily a disease of adaptation.[635]

Metabolic and **serologic** studies have so far contributed remarkably little to our understanding of this problem. The γ-globulin content of the blood is frequently high in acute rheumatic fever and tends to rise during recurrences;[636] the same is true of the anti-hyaluronidase titer.[637] On the other hand, extensive serologic studies "provide no evidence that those patients who develop rheumatic fever following group A hemolytic streptococcal infections have a pattern of antibody response to streptokinase that differs from the pattern of their response to other antigenic stimuli.[638]

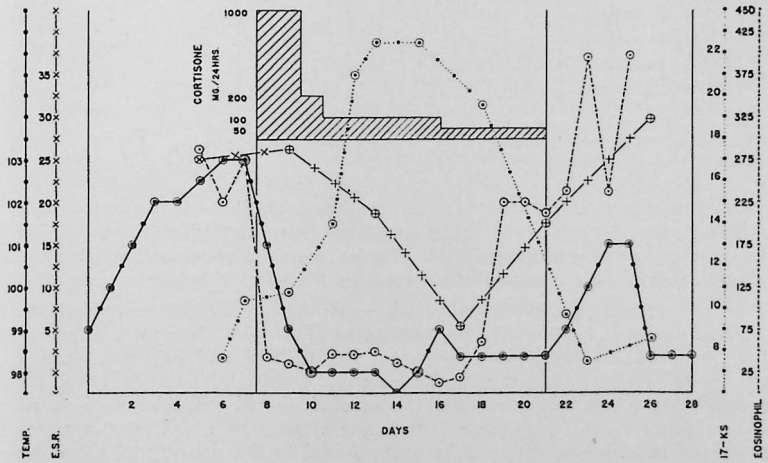
Of course, for the study of rheumatic fever as a possible disease of adaptation, the most important metabolic derangements would be those concerned with the biogenesis and fate of ACTH, the corticoids, RPS and those metabolites (glucose, glycogen, electrolytes, protein-degradation products) which depend particularly upon the activity of such hormones. Unfortunately, pertinent observations have not yet been undertaken.

Among the relevant **morphologic** investigations we have already mentioned that granulomatous nodules in the myocardium and skeletal muscles, occur not only in rheumatic fever, but also in rheumatoid arthritis (cf. arthritis). Furthermore, the experimental arthritides caused by mineralo-corticoids, formalin or combinations of both these agents, histologically resemble the arthritis of acute rheumatic fever in their acute stages, but gradually tend to assume the aspect of rheumatoid arthritis if they become chronic. These findings further emphasize the essential similarity between acute rheumatic fever and other rheumatoid conditions. Let us add that one of the most prominent students of "serous inflammation" concluded that the fundamental

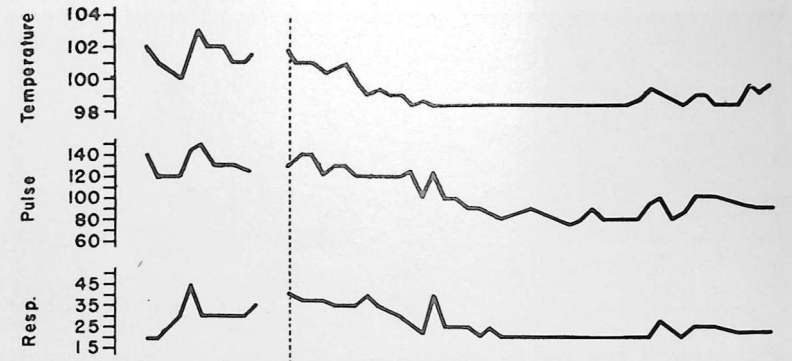
633 Fletcher **B27075/47.**
Lacapere **99333/46.**
Lichtwitz **B7055/44.**
Lutembacher **B29863/47.**
Swift **B43692/49.**
633a **B7055/44.**
634 Jokl **B19917/47.**
635 Baschieri B44500/48, Selye B1204/46.
636 Jager et al. B18606/48.
637 Quinn B26405/48.
638 Anderson et al. B26404/48.



Effect of cortisone upon rheumatic pancarditis. — **A.** X-ray of the chest, in an 18-year-old boy with a history of recurrent rheumatic fever, taken during a very severe attack of rheumatic pancarditis. The heart shadow is enlarged (chiefly the left ventricle), there is considerable infiltration in the right, middle and lower lobes. There was also gallop rhythm, a loud friction rub over the entire precordium and a loud systolic murmur with a soft aortic diastolic murmur. Upon admission to hospital all therapy was stopped and the patient received 2000 mg. of cortisone in the first 48 hours in divided doses, 200 mg. daily the next day, 100 mg. daily for the next six days and 50 mg. daily for the last seven days. — **B.** X-ray picture following cortisone administration. The lungs are clear although the heart shadow is still slightly enlarged. (For laboratory data see following chart.)



Effect of cortisone upon rheumatic pancarditis. Note decrease in body temperature, E.S.R. and eosinophil count, accompanied by increase in urinary 17-KS elimination during cortisone administration in the patient whose x-rays are shown in the previous picture.
(Courtesy of Drs. G. I. Bell, D. R. Wilson and R. E. Bell, University Hospital, Edmonton, Alberta.)



Arthritis	+++	+++	+++	++	+	0	0	0	0	0	0	0
Pericarditis	+++	+++	+++	+++	++	+	0	0	0	0	0	0
Gallop Rhythm	++	++	++	++	+	0	0	0	0	0	0	0
Sed. Rate mm/min.		1.7	1.7	1.7	1.3	1.5		1.1			0.7	0.6
WBC x 1,000		25	21	30	22	18		16			18	23
Eosinophils		181	178	25	17	33		36				43
17 K-S		2.6			4.0		5.3					
Sodium		5	1		11	29	39	64	33	32	12	29
Potassium		38	48		32	13	26	30	18	30	16	27
ACTH mgm	0	0	0	40	40	40	30	30	30	30	30	30
Day	1	2	3	4	5	6	7	8	9	10	11	12

Effect of ACTH in acute rheumatic fever. Clinical and laboratory course of an 11-year-old girl in her second attack of acute rheumatic fever. (After Thorn et al. B39546/49.)

primary change in this whole group of the rheumatic diseases, including acute rheumatic fever, is a derangement in membrane permeability which favors, first the development of a serous transudate in the intercellular spaces, and later its organization into a granuloma which contains fibrinoid or hyalin masses.[639]

In our opinion, the most convincing confirmation of the view that the adrenal cortex is involved in the pathogenesis of acute rheumatic fever has been furnished by observations showing that ACTH and cortisone exert a **therapeutic** effect in patients suffering from this disease.[640] Some investigators carefully point out that the word "treatment" should only be used in an "investigative sense" since these hormones are too scarce and may have too many undesirable side effects to be really useful in the therapy of rheumatic fever. Be this as it may, the above observations clearly show that whatever

[639] Eppinger **B37085/49.**
[640] Barnes and Smith B46422/50, Boland **B47735/50,** Elkinton et al. B45107/49, B46985/50, Helper et al. B46983/50, Hench et al. B37402/49, Massel et al. B46982/50, McEwen B46307/50, Thorn and Bayles B44425/49, Thorn et al. B39546/49.

the "pathogen" of this disease, it does not produce rheumatic changes if adequate amounts of gluco-corticoids are available. This agrees with the concept that the G-A-S is not particularly conducive to disease in itself, but largely determines whether a patient will or will not respond with disease when exposed to certain pathogens.

Those interested in the relationship between the therapeutic effect of ACTH and the rôle of the G-A-S in the pathogenesis of acute rheumatic fever, pointed out that the metabolic and hematologic actions of a single ACTH injection were essentially the same in normals and susceptible or active rheumatics.[640a] Hence the responsiveness of the adrenal cortex to ACTH is probably not deranged in rheumatic fever.

The well-known therapeutic effect of salicylates and gentisate in rheumatic fever has been ascribed to an inhibition of the "spreading factor" hyaluronidase. The activity of this enzyme has been suspected as a possible cause of the breakdown of interfibrillar cement substances in rheumatic disease.[641] The rôle of hyaluronidase during the G-A S and in the activity of corticoids has been discussed elsewhere (cf. above).

Other types of "rheumatism". — The close relationships between acute rheumatic fever and rheumatoid arthritis have been emphasized when discussing each of these diseases. A number of allied conditions have been designated with special names in order to emphasize the prominence of one or the other organ lesion, the rapidity with which the lesions progress and so forth. A study of pertinent cases clearly indicates, however, that these are not truly different nosologic entities, but rather different types of the same rheumatic disease. It is for this reason that the various manifestations of such syndromes overlap. Among these types of rheumatism are: **Still's disease,**[642] **Libman-Sacks' syndrome,**[643] **lupus erythematosus,** [644] **palindromic rheumatism,**[645] **Loeffler's syndrome,**[646] **Letterer-Siwe's disease,**[647] **Boeck's sarcoid,**[648] **dermatomyosis** (perhaps "a type of tuberculosis with high immunity"),[649] **psoriasis** especially in its arthritic form,[650] **scleroderma,**[651] and a variety of poorly defined **allergic conditions.**[652]

Those of the above disease types which are characterized by particularly prominent cutaneous lesions will be discussed in detail later (cf. skin), while the relationship to periarteritis nodosa, malignant hyalinizing nephrosclerosis (with the accompanying necrotizing arteritis and hypertensive disease), nonspecific myocarditis, etc., have been surveyed above. It may be well to reemphasize, however, that periarteritis-like changes often accompany typical

[640a] Hain and Wilson B44572/49.
[641] Meyer and Ragan B26401/48.
[642] Bunim et al. B44502/48, Desmarais et al. B44349/48, Musser **88056/45.**
[643] von Albertini B37951/47, Curtis and Horne B44842/49, Delafontaine et al. B44841/49, Eckerström B44843/48, Forster and Uehlinger B38146/47, Musser **88056/45.**
[644] Bunim et al. B44502/48, Forster and Uehlinger B38146/47, Teilum B38105/48. B38106/48.
[645] Gryboski B26329/48.
[646] Betz B26164/48.
[647] Teilum B38105/48.
[648] Bunim et al. B44502/48, Musser **88056/45.** Teilum B38105/48.
[649] Teilum B38105/48.
[650] Barber B44422/50, Grace and Combes B44786/49, Wassmann B44683/49.
[651] Bongini B43806/48, Cordoba et al. B40719/46, Ellman and Weber B44773/48, Hertz and Forsham B33416/49, Du Lac B44774/48.
[652] Betz B26164/48.

rheumatic fever,[653], myocarditis, valvular lesions and pericarditis, similar to those of rheumatic fever are common in rheumatoid arthritis [654] and a large percentage of hypertensive patients under fifty years of age give a clear cut history of previous rheumatic fever or rheumatoid arthritis.[655] All these observations suggest a close interrelationship between the various forms of the rheumatic and hypertensive diseases.

The term "**diffuse collagen disease**" has been applied to the above group of maladies — and particularly to rheumatic fever, lupus erythematosus, periarteritis nodosa and scleroderma — in order to emphasize that here we are dealing with a general disease affecting the whole collagen system.[656] It has been claimed that the morphologic similarities between the various members of this group do not justify the assumption of a common pathogenic mechanism [657] Undoubtedly, specific factors must determine which of these clinical syndromes will develop in individual instances. Nevertheless, we feel that the bulk of evidence points to some common pathway, since in experimental animals, the same hormones produced similes of the various members of this group, while both in clinical medicine and in animal experiments, gluco-corticoids or ACTH proved to be beneficial in most of these varieties.

The view has been expressed that the collagen diseases may represent a process of "accelerated aging",[658] similar to the normal aging which occurs under the influence of the stresses and strains of daily life. It is rather regularly accompanied by hyper-globulinemia.[659].

Some investigators dislike the term "diffuse collagen disease", because not only collagen but also reticular and elastic fibers [660] as well as the muscular coat of vessels [661] are involved. One might add that the capillaries of the renal glomeruli and the muscle fibers of the myocardium are also sites of predilection for hyalin changes both in the experimental and in the clinical variety of this syndrome.[662] Such terms as *hyalinosis, hyperglobulinosis, paramyloidosis,*[663] *fibrinoid degeneration,*[664] *collagenosis,*[665] *pararheumatic diseases*[666] or *dysoria* [667] have been suggested as alternatives. The latter name is supposed to indicate the increased permeability of the capillary endothelium, which appears to be the first change that leads to development of periarteritis nodosa-like lesions due to the penetration of plasma fluid into the vessel wall and the surrounding tissues. In our pertinent publications we used the term hyalinosis because the deposition of hyalin material appears to be a very constant and objective diagnostic index of these diseases.

It must be kept in mind, however, that hyalin or fibrinoid is not a chemically well characterized material. It appears to result from the coacervation of the acid mucopolysaccharides of the ground substance with an alkaline protein. It is not chemically identical in every instance allegedly because the precipitant may vary or additional substances may co-precipitate.[668] Its close relationship to blood-globulins and to amyloid have been emphasized [669] but a proper

[653] Kulka et al. B33423/49.
[654] Clark and Bauer B43978/48.
[655] Selye B4535/47.
[656] Klemperer B37941/47, Klemperer et al. A55797/42, Stewart B45301/49.
[657] Duff B38102/48.
[659] Teilum B38105/48.
[660] Duff B38102/48.
[661] Rapaport B19263/47.
[662] Selye B1204/46.
[663] Teilum B38105/48.
[664] Altshuler and Angevine B44348/48.
[665] Rapaport B19263/47.
[666] Forster and Uehlinger B38146/47.
[667] Schloss B26355/48.
[668] Altshuler and Angevine B44348/48, B41904/49.
[669] Teilum B38105/48.

chemical designation of the substance would be impossible on the basis of available data.

There may be a justified difference of opinion concerning the desirability of various terms listed above; yet the very fact that so many investigators felt the need of a generic designation which includes all the members of this disease group, supports the view that we are dealing with closely related conditions.

Fibrositis is usually defined as a non-suppurative inflammation of fibrous tissue which often gives rise to pain and stiffness. It is customary to differentiate primary fibrositis as a condition unrelated to any known disease, from the secondary form which is the consequence of stressful psychologic factors,[669a] rheumatic fever, gout, gonorrhea, rheumatoid arthritis or a trauma.[670] Both primary and secondary fibrositis may be elicited by many types of stressors and are manifestly related to the so-called rheumatic diseases. The term *"cellulitis"* [671] refers to closely allied lesions.

Fibrositis is often due to changes in the adipose tissue. A recent survey of this syndrome led to the conclusion "that several recognizable 'rheumatic' syndromes can be the result of an abnormal retention of fluid by fat lobules in certain situations. When this occurs, they endeavour to swell, but, being confined to indistensible fibrous tissue, they are unable to do so and tension pain results. This edema shows no sign of being inflammatory in nature. In some such cases a flaw occurs in the fibrous covering, resulting in herniation of the enclosed fat lobule into an adjoining layer." When such changes arise in the neighborhood of joints, the condition is often wrongly designated as arthritic.[672] This observation is of special importance as it further emphasizes the fundamental rôle played in the pathogenesis of the rheumatic diseases by intercellular fluid accumulations, due to deranged membrane permeability. Edema is usually a precursor of plasma transudation, which in turn is followed by condensation of the plasma-proteins into hyalin or fibrinoid material. In the case of fibrositis the lesion apparently does not proceed further than the first edema stage. It has been emphasized, in connection with fibrositis, "that cells, including fat cells, swell or contract in a predictable manner in response to variations in sodium concentration in the interstitial fluid, since all cell membranes permit the free passage of water but not of sodium and chloride. The water and salt levels are now believed to be controlled largely by the activity of the hormone of the posterior lobe of the pituitary and the influence of the desoxycorticosterone fraction of the adrenal cortex".[673] These remarks not only emphasize the fundamental similarity between fibrositis and the hyalinoses, but clearly point to hormones produced during the G-A-S as having a pathogenic significance in the development of these diseases.

Megacarotid. — From indirect evidence it has been concluded that the syndrome of extreme prolongation and dilatation of the carotid, known as "megacarotid" is also due to a derangement of the G-A-S.[674] Available data are not yet sufficient to discuss this possibility adequately.

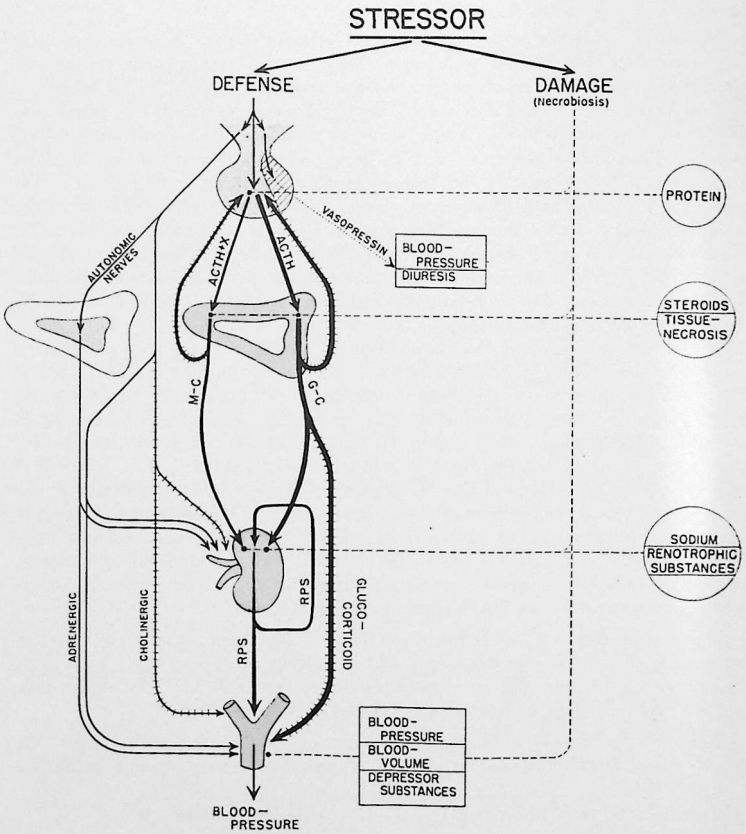
Athlete's sickness. — This is a syndrome which frequently occurs in athletes and consists of sudden attacks of weakness, sweating and headache,

[669a] Halliday B44599/43, B46202/48, Tegner B45609/46.
[670] Cecil **A63152/43**, Cyrax B45903/48, Musser **88065/45**, Slocumb **B537/43**.
[671] Meurs-Blatter B30665/38.
[672] Copeman B41284/49.
[673] Copeman B41284/49.
[674] Taptas B24872/48.

followed by marked nausea and vomiting. The etiology is not clearly understood, although the manifestations are obviously precipitated by the stress of excessive muscular exercise. The syndrome is closely related to, but not identical with, circulatory collapse.[675] Although it is certainly a manifestation of maladaptation, its relation to the G-A-S has not yet been examined.

Theories Concerning the Participation of the Cardiovascular System in the G-A-S

If we now attempt to integrate the many data concerning the participation of the cardiovascular system in the G-A-S, it will be useful to refer to the adjacent schematic drawing.



[675] Jokl 88491/33, 88490/35. 88494/36, 88492/39.

As is the case with so many other targets, the response of the cardiovascular system during stress depends: (1) upon the neuro-humoral regulators of the G-A-S, (2) upon conditioning factors (horizontal arrows in the drawing), which are not strictly part of the G-A-S mechanism but are capable of modifying its effects.

Neuro-humoral regulators of the G-A-S. — The factors responsible for the function of the adrenal during the G-A-S have already been discussed in a previous section (cf. Adrenals). We have seen that the secretion of the adrenal-medulla depends almost entirely upon its **sympathetic** innervation while that of the cortex is regulated by **ACTH.** Both the degree and the quality of this stimulation are subject to the action of conditioning metabolic factors.

The secretion of **vasopressin** by the posterior-lobe is likewise stimulated by stress. This hormone can cause renal vasoconstriction, sometimes to the point of severe cortical ischemia. It is highly probable that such a change in renal hemodynamics would increase the production of RPS somewhat like a "Goldblatt clamp". In addition, vasopressin also exerts a direct effect upon the blood-vessels; this can readily be demonstrated even in vitro on perfused organs. Through both these actions, the vasopressor hormone of the posterior-lobe probably tends to raise the blood-pressure during stress situations, but its action is also highly subject to conditioning factors and as we have seen under certain circumstances, vasopressin actually depresses the blood-pressure.

Adrenergic substances are secreted in large amounts, especially during the A-R phase of the G-A-S. These — somewhat like vasopressin — can affect the blood-pressure both through their action upon renal circulation and by a direct effect upon the peripheral vessels. It will be noted that in near-physiologic doses *adrenaline* tends to dilate the majority of the small peripheral vessels and hence may actually diminish the blood-pressure; *nor-adrenaline* exerts pronounced vasoconstrictor and pressor actions even at low dose levels. Hence the over-all effect of an adrenergic discharge is usually a rise in blood-pressure. Nevertheless, it appears that, at near-physiologic blood-titers, there is some antagonism between the cardiovascular actions of adrenaline and nor-adrenaline. This is reminiscent of the interaction between gluco- and mineralo-corticoids (cf. below).

The **corticoids** also appear to affect the blood-pressure both directly and through the kidney. Although their mechanism of action has not yet been fully elucidated, available data suggest that the *mineralo-corticoids* raise the blood-pressure primarily through their effect upon the production and detoxification of RPS by the renal tubules (especially the spiral segment). Evidence concerning a direct effect of mineralo-corticoids upon the peripheral vessels is less convincing, but certain in vitro experiments suggest that they may influence the permeability of capillaries, and perhaps also the contractility of the vessel musculature, due to direct peripheral effects.

There is no doubt, on the other hand, that mineralo-corticoids have a pronounced effect upon the proliferation of fibrous tissue and the deposition of intercellular proteinaceous ("hyalin") material. This effect becomes especially obvious in the case of local irritation by agents conducive to inflam-

[675] Yardumian and Kleinerman B44658/49.

matory changes (e.g., formalin or mustard arthritis). Here the mineralo-corticoids promote fibroplasia and wound healing through scar formation.

They can also raise the blood-pressure by increasing the circulating blood-volume. The resulting hypertension may in itself act as a local irritant, further stimulating granulosa formation.

The *gluco-corticoids* also exert direct actions upon the kidney. One of these effects (e.g., of cortisone) is apparently specific and not shared by the mineralo-corticoids. It is chiefly characterized by a pronounced hyperemia of the glomeruli and a shunt of the renal circulation conducive to marked congestion of the medulla. However, to some extent the gluco-corticoids can also stimulate RPS formation by the production of nephrosclerotic changes. This may well be due to a slight admixture of mineralo-corticoid potency. When gluco-corticoids are administered simultaneously with mineralo-corticoids, they actually aggravate the nephrotoxic action of the latter, hence — at least in the presence of adequate food and sodium intake — they increase the resulting vasoconstriction and hypertension.

Preliminary observations suggest that gluco-corticoids also exert a definite renotrophic effect in that they cause hypertrophy and hyperplasia of the renal tubules. It remains to be seen to what extent this is merely a compensatory phenomenon, that is, the direct result of the partial renal damage.

In addition, the gluco-corticoids exert a very pronounced inhibitory action upon the peripheral vasotoxic effects of mineralo-corticoids. In particular they prevent the development of the periarteritis nodosa by mineralo-corticoids, especially in the mesenteric area. They are less effective in counteracting the formation, by these steroids, of the rheumatic type of carditis.

The gluco-corticoids also antagonize the effect of mineralo-corticoids upon the connective tissue. Here, they inhibit the transudation of proteinaceous material into the intercellular spaces and the subsequent proliferation of fibrous granulosa tissue (e.g., in the event of a formalin "topical irritation arthritis"). The stimulation of a fibrosis by mineralo-corticoids and its inhibition by gluco-corticoids is particularly obvious if wound healing occurs after some local tissue damage. However, in the event of periarteritis nodosa, the mineralo-corticoids appear to suffice in themselves to produce a granuloma as long as the blood-pressure and pulse pressure are at or above the normal level. The inhibition of this arterial inflammation is highly reminiscent of the antiphlogistic effect of gluco-corticoids as manifested in other locations.

Conditioning factors. — The homeostasis of blood-pressure is very important for the maintenance of life, especially under conditions of stress. During exposure to damage, the blood-pressure tends to fall — presumably as a result of metabolic changes caused by "shock" — and nature has apparently foreseen **several alternative mechanisms** which, during the counter-shock and the resistance stages tend to prevent hypotension. Sometimes this defensive reaction is excessive so that hypertension results. If one or the other regulating mechanism (e.g., the adrenal-medulla, the sympathetic nerves, the adrenal-cortex or the kidney) is selectively eliminated, the blood-pressure may still remain within the physiologic range, even during exposure to stress. This multiple control assures homeostasis even in individuals in whom certain blood-pressure regulators have been destroyed.

Nevertheless, it is obvious that the complex pressor mechanism largely depends upon the integrity of the various links in the chain of events and can be modified by stimuli directly affecting any of these links. Thus, destruction of the adrenal (e.g., by tuberculosis) introduces a great danger of hypotension because both the adrenergic and the corticoid hormone mechanisms are inactivated. Conversely, a pheochromocytoma or a hyperfunctional tumor of the adrenal-cortex may derange blood-pressure regulation because of the excessive production of adrenergic or corticoid hormones respectively, even at a time when they are not required. Furthermore, the accumulation of adrenergic hormones in a hyperplastic or neoplastic adrenal-medulla, may result in an entirely disproportionate, exaggerated adrenergic discharge during exposure to a minor stress. Here, the entire G-A-S mechanism may evolve quite normally, but a nervous stimulus which usually causes only a discharge of small quantities of accumulated adrenergic substances, will release excessive amounts because the hormone stores are too plentiful.

The factors which condition the response of the cortex to ACTH have already been discussed elsewhere (cf. G-A-S → Adrenals ← ACTH).

At the **renal** level, *sodium* is an important conditioning factor. It accentuates the mineralo-corticoid actions and hence greatly augments the nephrosclerotic and hypertensive effect of pure mineralo-corticoids (e.g., DCA, desoxocortisone). However, apparently even the gluco-corticoids possess some mineralo-corticoid potency which is also augmented by an excess of sodium. It is principally through this effect that high-sodium diets augment, while low-sodium rations diminish, pressor responses mediated through the adrenal-cortex.

Neither the corticotrophic effect of ACTH, nor the peripheral vasoconstrictor action of RPS are significantly influenced by sodium. Hence it is almost certain that this cation acts at the level of the kidney itself, but the mechanism of its effect is not yet clear. Perhaps the reabsorption of sodium from the filtrate represents such a burden for the tubular cells that they cannot simultaneously detoxify RPS; it is also possible, however, that an abundant amount of Na is necessary for the enzymatic synthesis of RPS.

Renotrophic substances (e.g., testoids, thyroxin, somatotrophin) also affect the renal regulation of the blood-pressure during the G-A-S. Just as partial nephrectomy or partial destruction of the renal parenchyme (by anti-kidney serum, nephrotoxic drugs, etc.) increase the pressor and arteriosclerotic action of corticoids, so an increase in the renal mass, induced by humoral means, may have an opposite effect. This is understandable since both the production and the detoxification of RPS depend largely upon the integrity of the renal parenchyme.

At the level of the **cardiovascular system** itself, structural responses and blood-pressure regulation during the G-A-S may be conditioned by: (1) the tonus of the *vegetative nervous system,* (2) the *physical* (viscosity, volume, hydrostatic and osmotic pressure, etc.), and (3) the *chemical* (ATP, ADP, histamine, antigens, fibrinogen, etc.) *constitution of the blood.* The humoral derangements, which lead to hypotension and eventually to an almost complete lack of reactivity of the vessels in severe shock, should also be mentioned in this category. It is pertinent furthermore that certain hormones (e.g., thyroxine, somatotrophin) are especially effective in causing an enlargement of the heart and vessels; indeed the former even augments the pulse-rate and pulse-pressure.

Such hormonal blood constituents can also act as chemical conditioning factors during the G-A-S.

Finally, the response of the intercellular and **connective tissue substances** depends largely upon conditioning factors, e.g., by topical irritants. Although it is perhaps not entirely pertinent to the topic of this chapter, we discussed the reactions of the intercellular substances and the connective tissue conjointly with the cardiovascular system. We felt justified in so doing because this whole group of mesenchymal structures is regulated by essentially the same humoral mechanism, and because the intercellular substances and connective tissue stroma of the cardiovascular system itself play a prominent rôle in the pathogenesis of arteriosclerosis and allied "hyalin diseases". We have seen that the connective tissue throughout the body responds somewhat like the blood-vessel walls to mineralo- and gluco-corticoids respectively, the former stimulating, the latter inhibiting the formation of intercellular transudate and fibroplasia in experimental wound healing.

The importance of conditioning factors at this level is clearly illustrated by the experiments on the arthritis produced by topical irritation (e.g., formalin, mustard). Here the exogenous irritant is the conditioning factor whose ability to produce inflammatory phenomena is augmented by mineralo-corticoids and depressed by gluco-corticoids. The defective granulation of surgical wounds in cortisone-treated patients might be cited as an additional pertinent example.

Summary of Observations concerning the Participation of the Cardiovascular System in the G-A-S

Many stressors appear to affect the cardiovascular system in an essentially similar manner in that they produce hypertension and various types of arteriosclerosis. Although the character and the distribution of the cardiovascular lesions is not always identical, the same G-A-S mechanism probably plays a prominent part in their pathogenesis. These, as so many other ramifications of the G-A-S, are the results of biological chain reactions in which the response of one organ secondarily stimulates the activity of another. The further we progress along the course of such a chain, the more the responses of individual links become variable, depending upon the nature of the stressor used and the responsiveness of the reacting organs.

We have seen that the first links in this chain reaction, the vegetative nerve centers in the hypothalamus and the pituitary, react in a very stereotypical way to various stressors; almost any alarming stimulus elicits the same splanchnic discharge and adrenergic hormone secretion through the hypothalamic centers and the same ACTH discharge by the anterior-lobe. Presumably at the level of these first links in the chain of events, the reaction is not yet complex enough to be highly subject to qualitative conditioning. However, as we progress towards the periphery, more and more links and more and more branches of the chain participate in the G-A-S; at every one of these intermediate stations, the response may be inhibited or exaggerated by conditioning factors. Consequently, the eventual end-result — which represents the sum of the G-A-S and of all the conditioning factors — is capable of great variability, depending upon the circumstances under which exposure takes place.

Among the stressors examined, cold, parenteral administration of foreign proteins and other antigens, as well as certain micro-organisms proved most effective in eliciting cardiovascular changes of the rheumatic-hypertensive type. The morphogenetic actions of chronic nervous irritation have not yet been fully investigated, but it is already evident that nervous tension is highly capable of raising the blood-pressure and preliminary data suggest that it can also elicit cardiovascular hyalinosis. The fact that the above agents are more effective in producing such changes than many other stressors of equal intensity is ascribed to conditioning factors. These may act at different levels of the G-A-S mechanism. Apart from causing stress, they may possess certain specific properties (just like drugs with selective organotropic actions). These may enable them to produce: (1) an excessive secretion of ACTH, (2) the discharge of corticotrophins particularly suited to induce a mineralo-corticoid response in the adrenal, (3) specific direct effects upon the adrenal itself which could augment its mineralo-corticoid production, (4) they can so damage the kidney, through direct actions, as to augment the production or diminish the detoxification of RPS and (5) they may exert direct effects upon the peripheral vessels themselves, thus rendering the latter especially susceptible to vasopressor and vasotoxic influences.

Such considerations led to the view that all stressors affect the cardiovascular system through the same G-A-S mechanism, but the end results exhibit a great polymorphism because no stressor can produce stress alone without simultaneously exerting numerous and varied specific actions upon the many organs involved in the G-A-S response.

Among the hormones presumably produced during the G-A-S, several proved to be especially effective in causing hypertension and cardiovascular lesions of the hypertensive-rheumatic type.

Under certain conditions of sensitization even pure **ACTH** raises the blood-pressure. Impure anterior-pituitary preparations, such as LAP, are much more effective in this respect and, unlike ACTH, they tend to cause severe nephrosclerosis and arteriosclerosis in animals. In general, it can be said that ACTH acts upon the cardiovascular system like gluco-corticoids (e.g., cortisone), LAP like mineralo-corticoids (e.g., DCA, desoxocortisone). It is possible that separate corticotrophins regulate the production of gluco-corticoids and mineralo-corticoids respectively, ACTH being an example of the former, LAP of the latter. Since pure "mineralo-corticotrophins" have never been isolated, it would be premature to postulate their existence, especially since the LAP-effect may well be explained by the presence, in the impure extract, of conditioning substances which merely change the ACTH action so as to render it mineralo-corticotrophic.

Sodium does not appear to exert any important effect upon the production or action of ACTH. *Proteins* (and their constituent amino-acids) likewise fail to influence the action of ACTH significantly, but during stress, they appear to augment the production of this hormone by the anterior-lobe. The clinical value of low-protein diets in hypertension may well be due to this effect.

The **mineralo-corticoids** produced by the adrenal during stress, or under the influence of LAP, cause nephrosclerosis and cardiovascular hyalinosis. These effects can be duplicated by exogenous, crystalline, pure mineralo-corticoids, such as DCA or desoxocortisone. The hypertensive, nephrosclerotic and arteriosclerotic actions of mineralo-corticoids are greatly aggravated by

partial nephrectomy or a *sodium* excess and completely abolished by severe sodium deficiency. *Protein* does not influence the renal and cardiovascular effects of mineralo-corticoids.

The mild mineralo-corticoid actions of predominantly **gluco-corticoid** compounds such as cortisone are similarly affected by *sodium*. Thus, Na acts as a conditioning factor in the regulation of the cardiovascular responses during the G-A-S.

Partial nephrectomy, or extensive destruction of the kidney by anti-kidney sera, nephrotoxic drugs, etc., influence the action of corticoids essentially in the same manner as an excess of sodium.

The **RPS** produced by the "endocrine kidney" cause a hypertension and cardiovascular hyalinosis similar to that produced by mineralo-corticoids. Unlike the cardiovascular and renal effects of the corticoids, those caused by RPS are not subject to conditioning, either by *sodium* or by *protein*.

Ablation of the remaining normal kidney tissue augments the cardiovascular effects of RPS, presumably because healthy renal parenchyme facilitates the detoxification of renal pressor compounds.

Mineralo-corticoids and gluco-corticoids mutually antagonize each other in many respects. The vascular hyalinosis caused by mineralo-corticoids is effectively inhibited by gluco-corticoids. The intercellular fluid accumulation and fibroplasia caused by local irritants is increased by mineralo-corticoids and decreased by gluco-corticoids. On the other hand, some vasotoxic actions of these two types of steroids are mutually synergistic. Thus the renal hyalinosis, especially the damage to the glomeruli caused by desoxocortisone or DCA, is further aggravated by cortisone.

The so-called "collagen diseases" or hyalinoses of clinical medicine are closely imitated in animals by overdosage with LAP, mineralo-corticoids or RPS. Clinical studies suggest that these spontaneous diseases of man are precipitated by stressors especially suited to produce a G-A-S with a predominantly mineralo-corticoid response. ACTH (which elicits a predominantly gluco-corticoid response) and gluco-corticoids (e.g., cortisone) proved highly effective in the therapy of these clinical syndromes. On the basis of these observations, a number of so-called rheumatic, pararheumatic and hypertensive syndromes are ascribed to a derailment of the G-A-S, with an excessive predominance of the mineralo-corticoid over the gluco-corticoid production. In the sense of our definition, these would have to be classified as **diseases of adaptation.**

KIDNEY

The kidney, as one of the chief excretory organs of the body and an important regulator of blood-pressure, plays a prominent rôle during adaptation to systemic stress. It is not unexpected, therefore, that significant morphologic and functional changes develop in this organ during the G-A-S and in many of the "diseases of adaptation".

The vascular and epithelial components are so intimately interdependent in renal tissue, that it is impossible to discuss their reactions separately. Yet it would have been inadvisable to omit the renal vascular changes from our chapter on the cardiovascular system. Hence some repetition will be unavoidable in the following pages, but here we shall devote our main attention to morphologic lesions in the renal parenchyme itself and to changes in renal function (e.g., those detectable by clearance tests). To complete the picture the reader is referred back to the chapters on the cardiovascular system (cf. renal manifestations of the "hyalinosis" syndrome) and that on salt and water metabolism (cf. diuresis, electrolyte excretion).

Systemic Stress

Characteristic response. — As with most other manifestations of the G-A-S it would be impossible to discuss those renal changes which are truly characteristic of systemic stress without differentiating between the three stages of this syndrome. Unfortunately, up to now no one appears to have studied renal changes at various time-intervals during adaptation to "physiologic" degrees of stress. It is obviously impossible to distinguish sharply between physiologic and pathogenic stressors, but it must be kept in mind that almost all the evidence, cited in the following pages, is based on renal changes occasioned by very intense, sometimes fatal, exposure. Hence the material overlaps with the diseases of adaptation (cf. below).

The earliest strictly pertinent investigations had shown that **"cloudy swelling"** is frequently observed in the renal tubules of rats exposed to a variety of alarming stimuli and that this may even be accompanied by hematuria if the stress is particularly severe.[1] It will be recalled that cloudy swelling of parenchymatous organs has also been considered to be characteristic of **"serous inflammation"**. It was ascribed to a loss of the selective permeability of the cell membranes. In conditions of severe systemic damage many cells — and especially those of the convoluted tubules in the kidney — allegedly become permeable for plasma-protein. The consequent imbibition of the cytoplasm with the latter would be the cause of what pathologists are accustomed to designate as "cloudy swelling".[2]

A delayed effect of sudden exposure (especially to agents causing widespread tissue damage) is the so-called "lower nephron nephrosis" or **"crush syndrome"**. Because of serious consequences this definitely pathologic entity

[1] Selye 38798/37. [2] Eppinger **B37085/49.**

will be discussed with the "renal diseases of adaptation" (cf. below). However, even in this section we shall have to refer to this syndrome repeatedly, since so many stressors elicit it. Hence let us say now that it is characterized by medullary hyperemia, edema, dilatation and hyalin or blood-pigment cast formation in the tubules and degeneration or even necrosis of the tubular cells. It tends to cause severe, often fatal shock several hours, or days, after exposure.

Upon chronic exposure to systemic stress the non-specific renal changes are quite different. The glomerular lesions tend to progress towards sclerosis and the arteries of the kidney undergo hyalinosis, with subsequent connective tissue and intima proliferation. Many of the nephrons involute and they may even be completely absorbed. Some spiral segments, however, usually undergo proliferative changes and contain numerous mitotic figures. These changes have already been discussed at length in the cardiovascular chapter. They resemble those experimentally produced by LAP, mineralo-corticoids or the "endocrine kidney". The parallelism between the proliferative changes in the spiral segment and the development of the hyalinosis and hypertension, suggests that this segment, rather than the glomerulus and juxtaglomerular apparatus, is responsible for the hypertension and systemic hyalinosis which accompany certain renal lesions.[3]

Trauma. — Extensive tissue trauma causes renal changes corresponding to those which we considered to be characteristic of the A-R. Observations on dogs which died as a result of muscle trauma, revealed congestion of capillary tufts and other small vessels during the first three hours. Later there was degeneration, especially in the proximal tubules, formation of hyalin and pigment casts and desquamation of the lining cells into the lumen.[4] In cats, ligature of the pylorus causes marked medullary hyperemia, hydropic swelling of the proximal convoluted tubules and sometimes calcium deposition in the lumina.[5] Of course here the specific actions of the resulting hypochloremia are superimposed upon those of the trauma. In man, after trauma, there may be cloudy swelling and fatty degeneration of tubules[6] and the delayed renal changes correspond to those of the "crush syndrome".[7]

"Sludge formation" after traumatic injuries may also affect the kidney. It was shown in animal experiments that certain kinds of blood-sludge found in the neighbourhood of the traumatized area tend to "plug glomeruli and thus contribute to the crush syndrome".[8]

Parallel with the development of the above-mentioned morphologic changes the function of the kidney is also impaired by extensive tissue damage. Since urine formation may cease completely, the crush syndrome has also been referred to as "traumatic anuria". Recent observations suggest an interesting relationship between this syndrome and the disturbances of renal circulation in venous congestive myocardial failure. In man, if the legs are congested (by blood-pressure cuffs inflated on the thighs at less than diastolic pressure) for about twenty minutes, no noteworthy cardiovascular or renal changes are observed. However, about twenty minutes after the cuffs are released there ensues a marked antidiuretic effect with a decrease in renal plasma flow (PAH) and filtration rate (inulin, mannitol) as well as a reduction of Na, K and Cl

[3] Selye B4165/48.
[4] Cleghorn B2573/46.
[5] Gömöri and Romhányi B37586/48.
[6] Kalajà B37977/47.
[7] Lucké B18018/46.
[8] Warner B33081/49.

excretion. Similar changes have been observed even in hypertensive subjects who underwent lumbodorsal sympathectomy. It was concluded that venous congestion of peripheral areas may contribute to the causes of reduced renal plasma flow and excretion of salt and water, possibly through a humoral mechanism, since the effect was not prevented by sympathectomy.[9] In traumatized areas, venous congestion is often quite considerable (due to vascular damage, compression of veins by edema, etc.), hence it is probable that here, renal function is affected in a similar manner.

Hemorrhage. — Much work has been done concerning changes in renal function during shock caused by hemorrhage. It has been emphasized, however, that during conditions of shock, clearances are apt to be misleading, because after the blood-pressure falls below a certain critical level, urine formation ceases and the kidney fails to excrete. Hence clearances no longer measure renal blood flow. The results are further complicated by the fact, that, during shock, anoxia of the kidney may impair its function through a direct action.[10]

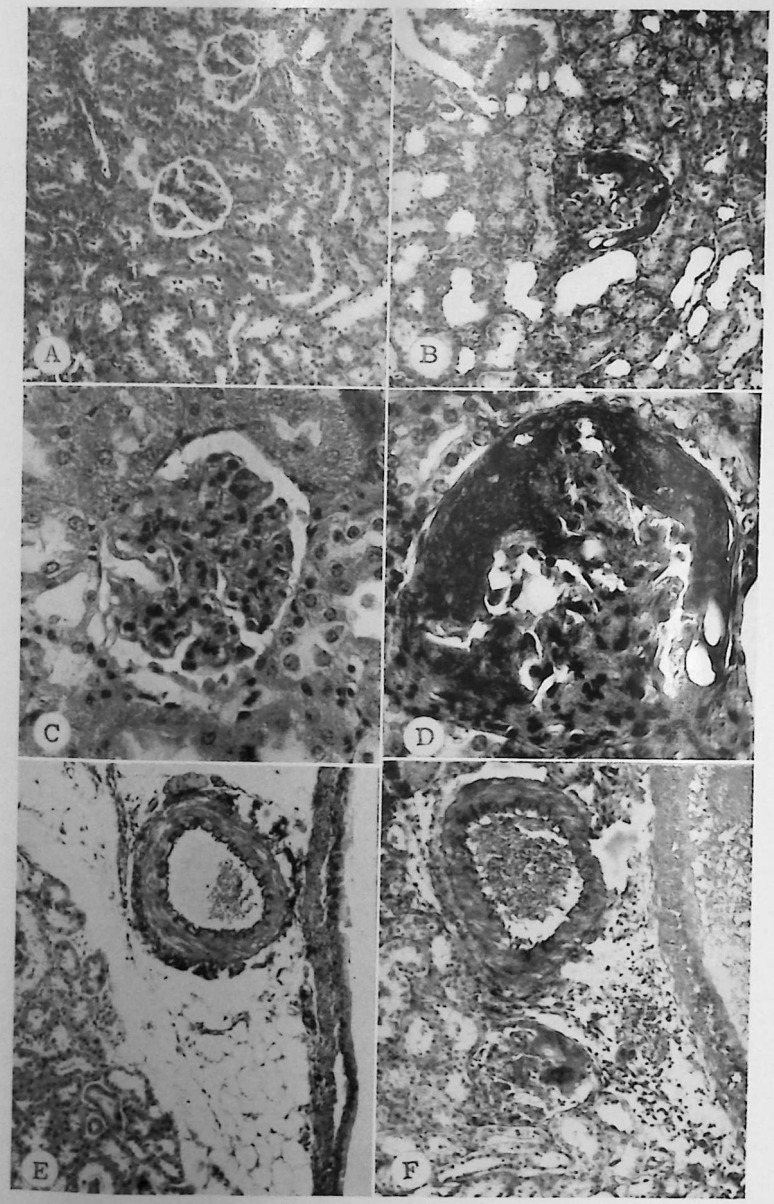
Histologic observations on the kidneys of dogs submitted to severe hemorrhage revealed a mild diffuse nephrosis with cloudy swelling, hydropic degeneration of the tubular cells and cast formation. The proximal convoluted tubules seemed to show the most pronounced lesions.[11]

Burns. — Under the influence of extensive surface burns, the kidney undergoes changes which are quite characteristic of those seen in the "crush syndrome".[12] During the first days after extensive scalds, complete anuria develops quite frequently. The renal glomeruli become congested and edematous and the capsular space may contain protein precipitates. The tubules undergo degenerative changes (sometimes progressing towards complete necrosis of certain segments) and many hyalin, granular and blood-pigment casts are formed, presumably because the kidney is flooded with decomposition products of burned tissues and particularly of damaged erythrocytes. It has been customary to speak of the nephritis of burned patients ("Verbrennungsnephritis" of the German authors),[13] but at least in the initial stages, true inflammatory phenomena are absent after burns and the changes are much more similar to those of traumatic anuria.[14]

The proponents of the "serous inflammation" theory believe that the selective permeability of the cell membranes is damaged by the "burn-toxin". Allegedly this leads to cloudy swelling and subsequent necrosis of the epithelia, or hyalinosis and perhaps even panarteritis of the larger arterioles due to imbibition with plasma of the renal parenchyme and vessels.[15]

Temperature. — In the section on the cardiovascular system, we mentioned that **cold** is extraordinarily effective in producing nephrosclerosis, especially in rats sensitized by unilateral nephrectomy as well as a protein- and Na-rich diet.[16] It is not known why cold is much more effective in this respect than most other kinds of non-specific stress. Perhaps the increased secretion of thyroxine and the resulting rise in the B.M.R. (which help to maintain the

[9] Wilkins et al. B33448/49.
[10] Selkurt **91144/ND**, 87832/46.
[11] Selkurt 87832/46.
[12] Erb et al. A57594/43, Lucké B18018/46, Moon B26013/47.
[13] Christophe B19955/39, Hilgenfeldt 38008/36.
[14] Hilgenfeldt 38008/36.
[15] Eppinger **B37085/49.**
[16] Hall B18146/46, Selye B17771/48, A62756/43.



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body temperature in cold surroundings), further sensitize the cardiovascular system to the hyalinosis-producing action of endogenous corticoids.

It has been especially emphasized that during the A-R the weight of the kidney remains unchanged (or may even rise), while that of most other parenchymatous organs diminishes considerably due to protein catabolism.[17] Perhaps the increased catabolism of extrarenal tissue protein (which augments the excretory load), the increased necessity for the production of RPS (to combat the hypotension of shock) and some renal edema (as part of a "serous inflammation") all contribute to augment renal weight despite the loss of body weight.

Allegedly, vasospasm within the kidney is responsible for the impaired renal function which usually accompanies the "cold pressor test".[18]

In rabbits in which fever was produced by exposure to **heat** (diatherm or radiotherm) for several hours, the kidney showed congestion with hemorrhage and some degenerative changes in the tubular epithelium. The epithelial cells tended to be desquamated and many of them were loaded with glycogen, although the liver-glycogen stores were depleted.[19] In patients who died of heat-stroke, the kidney usually reveals a more or less typical picture of "lower nephron nephrosis".[20]

Ionizing radiations. — In rats exposed to x-rays,[21] in mice treated with radioactive uranium [22] and in man exposed to the radiations of atomic explosions during World War II,[23] renal lesions were usually mild or absent. Yet in various species, lethal exposure to the atomic bomb caused extensive hemorrhages into the cortex, medulla and pelvis of the kidney, as part of the generalized hemorrhagic syndrome.[23a]

Unlike many other tissues (e.g., lymphoid tissue, the spermatogenic epithelium, the intestinal mucosa, hemopoietic elements of the bone marrow), the kidney is notoriously resistant to the direct effect of ionizing rays.[24] It would be surprizing, however, if the widespread tissue-disintegration incident to such treatment would not affect renal tissue in the same manner as traumatic injuries, burns, and other stresses which produce the "lower nephron nephrosis" type

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Renal changes produced by chronic exposure to cold in the rat. All the animals of this experiment have been sensitized to the mineralo-corticoid effect by unilateral nephrectomy, a 30% casein diet and 1% NaCl as drinking fluid. — **A.** Kidney of control animal kept at normal room temperature. (Low magnification.) — **B.** Kidney of a rat exposed to cold (+ 2 C°) during 27 days. Note dilatation and cast formation in some tubules, while others are collapsed and resemble the nephrons of the "endocrine kidney". The glomerulus in the center of the field is partly disintegrating and Bowman's space is filled with a dense hyalin mass. — **C.** Higher magnification of a normal glomerulus from the kidney shown in figure A. — **D.** Higher magnification of a hyalinized glomerulus from the kidney shown in figure B. — **E.** Low magnification of a large renal artery and the surrounding fat tissue in the renal pelvis of the rat shown in figure A. — **F.** Comparable region from the renal pelvis of the rat shown in figure B. Note that the glomerulus (underneath the artery) is hyalinized and the fat tissue of the renal pelvis is infiltrated with lymphatic and myeloid elements similar to those which occur in the renal pelvis of rats treated with LAP. There is marked protein precipitation in the renal pelvis itself (right edge of the picture) all the animals exposed to cold under these circumstances develop hypertension, cardiac hypertrophy, myocarditic nodules and other lesions similar to those caused by LAP or DCA. (After Selye 35935/ND.)

[17] Leduc and Guillemin B27410/49.
[18] Odell and Aragon B26603/47.
[19] von Haam and Frost A30282/39.
[20] Gore and Isaacson **B41903/49**, Lucké A18018/46, Malamud et al. B18019/46.
[21] Patt et al. B3611/47.
[22] Tobias et al. B4455/48.
[23] Anonymous B28192/48.
[23a] Tullis and Warren B41776/47.
[24] Bloom **B31225/48.**

of change. In future it may be well therefore to focus attention particularly upon the detection of such changes.

Electric injury. — In rats exposed to repeated electro-shocks, certain nephrons frequently exhibited changes which were compared to those seen in the "endocrine kidney". However, typical "lower nephron nephrosis" or nephrosclerosis was not obtained,[25] perhaps because treatment was too prolonged for the former and not chronic enough for the latter type of response.

Nervous stimuli. — The influence of the nervous system upon the renal circulation has been given special attention in the chapter on cardiovascular changes. Let it merely be recalled here, that according to Trueta et al.[26] in animals, irritation of the sciatic nerve (through a reflex) or direct stimulation of the renal plexus itself, opens a vessel "shunt"; this permits blood to by-pass the cortex and to flow directly through the medulla. Consequently PAH extraction becomes very incomplete so that clearance of the plasma of PAH is no longer a measure of the total renal plasma flow. It must be kept in mind, however, that clearance would still be a measure of the "effective" renal plasma flow, namely that traversing the glomeruli.

Subsequent observations on man showed that immersion of a hand in painfully cold ice-water produces a slight fall in PAH and inulin clearances with a slight rise in the mean blood-pressure. "These findings thus support, although they do not prove, the view that under great stress, many glomeruli may cease functioning". Yet the observations neither prove nor disprove the effectiveness of the renal shunt, since the changes observed could be "more simply explained on the basis of progressive vasoconstriction".[27] Interestingly, if "emotionally charged topics were intentionally introduced" in the course of psychiatric interviews with normal individuals, highly significant (both positive and negative) changes in renal plasma flow were quite frequently observed.[28] The underlying mechanism has not yet been elucidated.

Direct or reflex irritation of the renal nerves, by the local application of irritants, can produce nephrosis or even hematuric nephritis in animals. It was assumed therefore that in man nervous stress may also cause severe renal disease.[29]

The renal shunt produced by direct electrical stimulation of the kidney nerves can be prevented by adrenergic blocking agents.[29a]

Muscular work. — Intense muscular exercise tends to cause a diminution in PAH and inulin clearances perhaps because exercise diverts blood from the kidney to the muscles. Both in animals and in man these changes are rather similar to those seen after nervous stimulation.[30]

Anoxia. — The morphologic changes induced in the kidney by severe anoxia of comparatively short duration are essentially those of the "crush syndrome".[31]

In very acute experiments on rabbits, stimulation of the renal plexus merely opened the renal shunt. This effect was prevented by adrenergic blocking agents.[31a]

[25] Hirsch B37082/ND, B44957/49.
[26] 99193/47.
[27] White and Rolf B19867/48.
[28] Chalmers et al. B32720/49.
[29] Reilly 99381/42.
[29a] Cerletti et al. B45961/49.
[30] Chapman et al. B28562/48, Trueta et al. 99193/47, White and Rolf B19867/48.
[31] Moon B26013/47.
[31a] Cerletti et al. B45961/49.

In rats exposed three hours a day during 27 days to a simulated altitude of 25,000 ft. there was renal hyperemia and sometimes necrosis of peripheral tubules in the renal cortex. Since this was accompanied by pronounced polyuria, the picture is somewhat reminiscent of that induced by DCA overdosage.[32] Even after two hours of exposure to very low atmospheric pressure, the tubular epithelia of the rat kidney become swollen, the stroma edematous and the capsular spaces dilated.[33]

In view of the suspected relationship between the juxtaglomerular apparatus and compensatory vasopressor reactions to various kinds of systemic stress, it is noteworthy that in mice exposed to acute or chronic severe anoxia, there was no indication of any hypertrophy of the juxtaglomerular cell groups. Indeed, after several days of exposure, these often disappear.[34] Repeated exposure to excess atmospheric CO_2 causes necrosis and sometimes calcification of renal tubules in various animal species.[35]

Both anoxia and decreased atmospheric pressure cause irregular variations in the glomerular filtration rate, while the TmPAH tends to rise, the TmG is decreased or remains unaffected in man.[36] Allegedly the most pronounced effect of lowered oxygen tension on renal tissue in man is the increased excretion of Na and Cl.[37]

Diseases. — Various diseases and especially those conducive to the **"medical shock"** syndrome can cause renal changes of the *"lower nephron nephrosis"* type,[38] hence the possible participation of the G-A-S mechanism in the production of such renal lesions has been considered.[39]

In various diseases conducive to **"serous inflammation"** and especially in **petechial typhus,** hyaline nodules are often found in the renal veins. They are sub-endothelially located but resemble thrombi. Allegedly they arise from proliferation of lymphoid cells which underwent sudden hyaline degeneration. Similar nodules are also found in the myocardium in typhus. Because of the resemblance of this lesion to periarteritis nodosa it has been termed *"paraphlebitis nodosa"*.[40] Significantly these nodules are also common in the renal veins of rats overdosed with mineralo-corticoids.[41]

Acute nephritis is allegedly not an uncommon complication of **focal infections** and of **acute rheumatic fever.** This led to the assumption that "nephritis is but one of the multiple manifestations of rheumatism in its capacity of a preëminently protein disease".[42] The latter conclusion is perhaps somewhat daring, but the fact remains that essentially similar renal lesions can be elicited by a variety of diseases and hence, they must be regarded as largely non-specific. The most acute type is "lower nephron nephrosis"; nephritis takes an intermediate position, while nephrosclerosis is the most chronic form of these non-specific renal changes. It remains to be seen whether increased endogenous corticoid production plays a major rôle in their pathogenesis, yet even if this were proven, it is almost certain that corticoids alone could not explain the development of such nephropathies since the latter are uncommon in patients

[32] Silvette 84858/43.
[33] Thorn et al. B335/45.
[34] Hollinshead B33071/49.
[35] Meessen B38008/47, B37949/48.
[36] Kelley and McDonald B23901/48, B28220/48, McDonald and Kelley B28219/48.
[37] Berger et al. B37295/49.
[38] Meessen B23957/47, Lucké B18018/46.
[39] Leiter B29764/48, Prunty B37297/49.
[40] Günther B38011/47.
[41] Selye 35935/ND.
[42] Goia B25571/46.

with hyperactive cortical tumors. Animal experiments also indicate that the kidney is severely damaged by corticoids only in the presence of special conditioning factors such as partial nephrectomy, nephrotoxic nephritis, sodium. We believe that endogenous corticoids favor the development of the renal changes caused by exposure to systemic stress, but in many cases, other factors (e.g., nephrotoxic substances produced by bacteria or the hosts' tissues, allergic reactions) play at least an equally important part (cf. Renal Diseases of Adaptation, p. 637).

The renal changes characteristic of **hypertension** have been discussed in the chapter on the "Cardiovascular Diseases of Adaptation" (cf. above).

Serologic reactions. — In the section on the cardiovascular system we mentioned that various foreign proteins, sulfonamides and other compounds capable of producing "hypersensitivity reactions" can cause hyalinosis with rheumatic-like changes throughout the vascular system. Let us merely emphasize here that the kidney is usually a site of predilection for such changes. Thus, for instance, rabbits injected with horse **serum,**[43] **sulfonamides,**[44] or **nephrotoxic serum** [45] develop severe renal lesions resembling either nephritis or nephrosclerosis, depending largely upon the duration of treatment. The glomerular tufts tend to become adherent to the capsule, there may be epithelial crescents around the glomeruli and eventually the whole tuft becomes more or less hyalinized. The arterioles and sometimes even the larger vessels of the kidney undergo more or less pronounced hyalinization, sometimes conducive to sclerosis, while the convoluted tubules become dilated, filled with hyalin or cellular casts and the lining cells show degenerative lesions and even necrosis.[46]

In dogs treated with nephrotoxic serum the clearances of creatinine and urea as well as the tubular excretion of PAH decline rapidly, even if histologically visible glomerular and tubular damage is only moderate.[47]

By iodinating the globulin fraction of anti-kidney serum with iodine containing tracer amounts of I^{131}, it was possible to show (radio-autograph technic) that the anti-kidney serum is taken up selectively by the glomeruli.[48] This would suggest that the glomerular damage results from a direct local effect of the antibodies. The adrenal-cortex may perhaps participate in such responses. In agreement with the concept of "serous inflammation", hyalinosis results from a loss of the selective permeability of cell membranes and the consequent plasma imbibition of their cytoplasm.[49] As we have said elsewhere, DCA appears to act in a similar manner. It is possible, therefore, that the penetration of anti-kidney globulins into cells would also, at least partly, depend upon the simultaneous action of corticoids. It must be kept in mind that the so-called "specific nephrotoxic sera" cause hyalinosis not only in the kidney, but also in other parts of the vascular territory. Indeed, the above-mentioned studies with radioactive anti-kidney sera [50] gave clear evidence that several other tissues, particularly the spleen, also exhibit a selective affinity for these proteins. Furthermore, systemic stress, LAP, mineralo-corticoids and the products of the "endocrine kidney" can produce an almost identical hyalinosis throughout the vascular system, again with especially intense participation of the renal vessels. This occurs without any antibody formation, presumably due to intracellular penetration of the animals' own blood-proteins. If we accept the "serous inflammation" concept, the high activity of anti-kidney sera could be due to a greater toxicity of the immune bodies than of other proteins (e.g., those of the plasma), or to a greater power to penetrate into cells, even without sensitization by corticoids. In the latter case, the corticoids would still participate in the pathogenesis of the renal changes, by facilitating the penetration of the toxic antibodies into the cells. The fact that DCA sensitizes the rat to the vasotoxic properties of anti-kidney sera [51] appears to be consonant with the latter interpretation.

[43] Ehrich et al. B37492/48, Rich and Gregory A71373/43, 84496/43.
[44] Bakken B37943/47, Bras and Lie Kian B37897/48, Rich and Gregory A71373/43, 84496/43, Wernitz B37758/49.
[45] Heymann et al. B47628/50, Masugi B36588/34, B36589/33, Smadel B36592/37, B36590/36, Smadel and Farr B36591/37, Swift and Smadel B36593/37.
[46] Betz B26164/48.
[47] Moses and Thornton B32793/49.
[48] Pressman et al. B29999/49.
[49] Eppinger B37085/49.
[50] Pressman et al. B29999/49.

If rat kidney tissue is injected conjointly with killed "group A" streptococci into rats, **auto-antibodies to kidney** allegedly appear in their blood. These kidney auto-antibodies react with renal tissue in vitro and when injected into rats, produce glomerulonephritis. This led to the assumption that perhaps auto-antibodies also play a rôle in the pathogenesis of glomerulonephritis in man.[52] However, such changes cannot be produced consistently.[53]

Observations on man show that even the very acute renal damage characteristic of "lower nephron nephrosis" is frequently elicited by **transfusion with incompatible blood,** sulfonamides and other agents causing "hypersensitivity reactions".[54]

In rabbits receiving repeated intravenous injections of **formalin-killed pneumococci,** there develops a marked hyperglobulinemia, a high blood-titer of antibodies and intense proliferation of plasma cells in most organs but especially in the fat of the renal pelvis.[55] As we shall see below rather similar changes occur in the stroma of the renal pelvis in rats treated with LAP.

Drugs. — Those compounds which cause hypersensitivity reactions have already been mentioned. Let us merely add here that **various drugs conducive to intense acute systemic stress** also produce "lower nephron nephrosis" in man, even in the absence of hyperergic reactions.[56]

As previously mentioned, some authors considered the possibility that liberation of adenine derivatives might be an important factor in the pathogenesis of the circulatory derangements seen during shock in general and the "crush syndrome" in particular. This led to studies concerning the effect of **adenosine triphosphate (ATP)** upon renal function. Judged by various clearance tests in dogs, it was concluded that this compound causes a severe derangement in the renal circulation,[57] but of course this does not mean that its endogenous overproduction is responsible for the kidney lesion during shock.

In connection with the renal changes characteristic of human diabetes, it is noteworthy that typical hyalinosis of the renal glomeruli and arterioles have also been observed in **alloxan**-diabetic rats.[58] This may have some

[51] Knowlton et al. B3053/47, 91205/46.
[52] Kerr and Cavelti **B23078/47.**
[53] Humphrey B43996/48, Werkö B45656/46.
[54] Lucké B18018/46.
[55] Bjorneboe et al. B37877/47.
[56] Lucké **B18018/46.**
[57] Houck et al. B25996/48.
[58] Man and Goddard B33426/49.

bearing upon our interpretation of the Kimmelstiel-Wilson syndrome (cf. Renal Diseases of Adaptation, p. 638).

Carbon tetrachloride has been mentioned as one of the drugs particularly conducive to the development of the crush syndrome in man.[59]

Colchicine a notoriously caryoclastic drug, was found to cause cloudy swelling of the tubular cells, sometimes progressing towards more severe degeneration, with hyalin and granular cast formation and intense congestion of the glomeruli. These lesions were interpreted as an acute tubular nephritis,[60] but they are rather reminiscent of the "lower nephron nephrosis".

Intravenous **hemoglobin** infusions cause renal changes very similar to those of the crush syndrome, especially in animals previously subjected to dehydration[61] or hemorrhage.[62]

Repeated intraperitoneal administration of various **proteins** may result in renal enlargement, tubular damage and cast formation in rats. The possibility has been considered that certain renal lesions, seen in diseases which raise the blood-protein level, "may be secondary alterations due to excessive amounts of protein passed through the glomerular membranes".[63] However, these lesions do not resemble the experimental hyalinoses.

In rabbits, repeated intraperitoneal injections of homologous γ-globulin causes glomerular hyalinization reminiscent of the Kimmelstiel-Wilson syndrome. At the same time, hyalin droplets appear in the cytoplasm of the proximal convoluted tubules.[63a] The latter are similar to those frequently noted in rats receiving excessive amounts of DCA and probably represent tubular reabsorption of protein, filtered through the glomeruli. In the rat, repeated intraperitoneal injections of human hemoglobin caused "athrocytosis" of the proximal convoluted tubules, due to phagocytosis of hemoglobin particles which apparently passed through these glomeruli.[63b] These observations suggest that, contrary to common opinion, comparatively large protein molecules can traverse the glomerular filter, although this usually leads to little if any proteinuria, because much of the material is reabsorbed.

Among other particularly nephrotoxic drugs let us merely mention **lead,**[64] **mercury,**[65] and **uranium.**[66] None of these appear to act primarily through the G-A-S mechanism.

Diet. — Qualitatively or quantitatively inadequate diets may also cause renal lesions similar to those which we considered to be characteristic of the response to systemic stress as such.

Chronic **undernutrition** among concentration camp inmates during World War II, often caused severe derangements in renal function. These have even been held partly responsible for the development of hunger edema, although the concomitant fall in the protein-osmotic pressure of the blood is usually more important in the pathogenesis of this syndrome.[67] Typical nephritis was rarely observed among these malnourished individuals and when present, it could often be ascribed to incidental infections (e.g., typhus, typhoid, erysip-

[59] Cabot B37879/48.
[60] Dustin 94160/41.
[61] Lalich B37215/47.
[62] Hamilton et al. B40945/47.
[63] Baxter and Cotzias B39142/49.
[63a] Sussman and Freed B47643/50.
[63b] Rather B46097/47.
[64] Chiodi and Sammartino B37984/47.
[65] Longley A37552/42. Selye A31126/40.
[66] Rinaldi and Mazzola B37898/47. Feyel 99416/43.
[67] Brull et al. B3026/45. Brull and Lambrechts B26140/45.

elas). Perhaps other incidental stresses of life in a concentration camp also play a rôle, especially exposure to cold and fear.

It has been customary in Europe to distinguish "hunger edema with nephritis" from "war nephritis", but accurate delimitation of these entities is hardly possible.[68] Even those who interpret most of the manifestations of the "hunger disease" as due to the G-A-S, had to admit that the renal changes are so mild that it is difficult to hold them responsible for the well known edema-tendency of undernourished people.[69] Since the low-protein diets of the concentration camps tend to protect the kidney against the damaging action of stress, it is not unexpected that renal complications were uncommon and that the patients died from the purely catabolic manifestations of the G-A-S before they could have developed marked renal injuries.

Conversely, a high-**protein** intake is notoriously nephrotoxic. Numerous experiments show that nephrosclerosis frequently develops in animals (especially rats) if they are kept for many months on high-protein rations.[70] High-protein diets greatly sensitize rats to the nephrosclerosis-producing action of stress (e.g., cold) and LAP (cf. Cardiovascular System, p. 516-517). It is possible, therefore, that on a very high protein intake such lesions develop even if the blood contains only physiologic amounts of corticotrophin. Furthermore, diets very rich in protein may, in themselves, cause a stress which increases ACTH discharge. In this sense, the nephrosclerotic action of proteins may be related to those humoral factors which cause kidney damage under the influence of systemic stress.

For the sake of completeness, it should be mentioned that certain amino-acids, for instance **glycine,** also exert pronounced nephrotoxic actions. These are mainly characterized by focal necroses[71] and probably bear no direct relationship to the G-A-S.

It has been stated that dried, fat-free **liver tissue** and **sodium nucleate** are particularly effective in producing a "granular kidney" in the rat, but perusal of the published data reveals the frequent occurrence of calcified casts in the tubular lumina.[72] It must be kept in mind that the dietary ingredients used are rich in phosphorus and that high-**phosphate** diets are in themselves conducive to the formation of calcified casts in the tubules of the rat kidney, presumably because insoluble calcium phosphates are precipitated. This causes considerable destruction of renal tissue with subsequent sclerosis. If rats are kept on a phosphate-rich diet and simultaneously given DCA, the nephrosclerotic action of the latter is increased, presumably because the renal destruction caused by the diet sensitizes to the corticoid hormone just as partial nephrectomy does.[73]

The **sodium** salts which so actively increase the nephrosclerotic effect of stress, LAP and mineralo-corticoids, do not cause any severe renal damage in mammals (cf. Cardiovascular System, pp. 514, 527 ff).

Acute or chronic **choline** deficiency causes subcapsular hemorrhages or nephrosis-like renal lesions, which are not accompanied by hypertension and do not resemble nephrosclerosis.[74] However, if rats are kept on a choline-

[68] Gsell B27611/48.
[69] Uehlinger B27612/48.
[70] Newburgh and Johnston B23020/31.
[71] Hay 93491/47.
[72] Newburgh and Johnston B23020/31.
[73] Friedman et al. B25983/48. Selye et al. B235/45.
[74] Sobin and Landis B37533/47.

deficient diet for a few days during early life, and survive a severe acute attack of subcapsular hemorrhages, they may develop hypertension and typical malignant nephrosclerosis later. Perhaps fibrotic organization of the hemorrhages acts somewhat like experimental perinephritis, by compressing the renal parenchyme.[75]

Acceleration. — Because of possible implications concerning problems of aviation medicine, the effects of acceleratory forces upon the kidney have also been studied. In rats exposed to various positive and negative *g* forces over periods of 8 to 24 days, marked polyuria and albuminuria developed. "Histological examination revealed that the renal glomeruli of the accelerated animals were ischemic and the proximal convoluted tubules showed cloudy swelling and contained casts". Since such treatment represents considerable stress, the possibility was envisaged that the renal lesions may result from a disturbed adreno-cortical function.[76]

Stimuli Influencing the Kidney During the G-A-S

Hypophysis. — Hypophysectomy tends to cause fairly severe renal atrophy, accompanied by a diminution of the functional capacity of the kidney.[77] It is obvious that the important renotrophic effect of the hypophysis cannot be neglected in an analysis of the changes which occur in the kidney during the G-A-S.

It will be recalled that while mineralo-corticoids cause nephrosclerosis, other steroids (see below) which are also secreted under the influence of the anterior-pituitary, possess an actual renotrophic or kidney-stimulating effect. Studies on hypophysectomized rats have shown that both DCA and *renotrophic steroids* (e.g., testosterone, progesterone) enlarge the kidney even in the absence of the pituitary, hence "the effect of these hormones is not mediated by the hypophysis, but is probably direct." A priori it would have been tempting to assume that the pituitary influences the kidney merely through the intermediary of the corticoids and gonadal hormones secreted under the influence of ACTH and the gonadotrophins respectively. However, in this same experimental series, it was noted that the effects of DCA, progesterone and testosterone, though definitely demonstrable, are much less marked in hypophysectomized than in intact rats. It was concluded "that under physiological conditions, besides the gonadotrophic and corticotrophic hormones, the pituitary possesses additional means for the maintenance of the normal kidney structure"... "Since thyroid hormone likewise stimulates kidney growth, it appears probable that the thyrotrophic hormone is also responsible for part of the renotrophic effect of the hypophysis. The growth hormone, which conditions the growth of the body as a whole, must similarly be considered in this connection".[78]

Unfortunately, at the time these experiments were done, we had not yet learned to differentiate between the renal enlargement due to nephrosclerosis and that resulting from true renotrophic stimulation. In retrospect, however, we may deduce from the above observations that both the kidney-damaging, nephrosclerotic steroids (e.g., DCA, desoxocortisone) and the renotrophic compounds (e.g., testosterone) are enhanced in their respective activities by some

[75] Best and Hartroft B43574/49.
[76] Silvette and Britton B29985/48.
[77] Selye **A35219/41, 94572/49.**
[78] Selye A35219/41,
Selye and Bassett A33566/40.

pituitary factor(s), although, to some extent, they can also affect the kidney directly.

Thyroxine causes renal enlargement in the rat even after hypophysectomy, hence this effect is also, at least partly, a direct one.[79]

Treatment of hypophysectomized rats with impure *anterior-lobe extracts* tends to restore the subnormal kidney weight to normal.[80] It was shown on hypophysectomized dogs, furthermore, that purified *growth hormone* raises the greatly depressed inulin clearance and TmPAH to or above the normal levels. The authors concluded from these observations in connection with other experiments which they had previously published, "that loss of gonadotrophic and adrenotrophic hormones is not responsible for the great depressions of the renal functions seen after hypophysectomy, and that the effect of loss of thyrotrophic hormone is slight. The principal effect is due to loss of growth hormone or of some substance not yet separated from it".[81]

Apparently several hormones whose production is impeded by hypophysectomy, regulate the normal morphologic and functional status of the kidney; among these hypophyseal-growth hormone, the testoids, the corticoids and thyroxine are of special importance.

The compensatory hypertrophy of the remaining kidney after *unilateral nephrectomy* is diminished, but not abolished, by previous hypophysectomy in the rat.[81a]

X-irradiation, which has little effect upon the kidney even in intact rats, also failed to produce any important lesion after hypophysectomy.[82]

It is important to consider the rôle of the *diet in* the production of renal atrophy by the ablation of the pituitary since the voluntary food intake is greatly diminished after this operation. Hypophysectomized rats gain body weight if they are forcibly fed quantities of food approximately isocaloric with that consumed by intact controls. At the same time, the post-hypophysectomy changes in the weight and composition of the liver were also completely prevented, yet the weight losses of the kidneys remained unaffected.[83] This gives us additional evidence suggesting that the renal atrophy caused by hypophysectomy is not merely due to malnutrition.

Crude **anterior-lobe extracts** (or LAP) tend to cause nephrosclerosis on Na-rich and renotrophic effects on Na-poor diets.[84] Unilateral nephrectomy sensitizes the remaining kidney to both these actions of LAP, but particularly to the nephrosclerotic effect.[85] All this agrees with the previously mentioned observations (cf. Cardiov. Syst., p. 514) showing that these factors also enhance hyalinosis in other parts of the vascular tree.

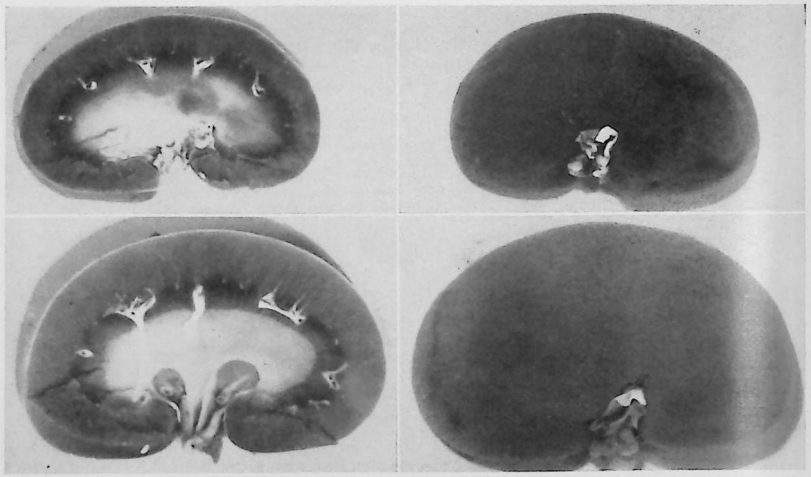
Curiously, whenever intense nephrosclerosis is produced by LAP or similar impure anterior-lobe preparations, the connective tissue in the renal pelvis tends to become edematous and infiltrated with an inflammatory exsudate.[86] Somewhat similar changes have been produced in rabbits with killed pneumococci.[87] In this connection it will be remembered that under certain conditions, LAP

[79] Swann A30182/39.
[80] Selye A35514/41.
[81] White et al. B36854/49.
[81a] Braun-Menendez and Houssay B45945/49, Selye et al. 30634/34.
[82] Patt et al. B33711/48.
[83] Levin A71832/44.
[84] Selye A71896/44.
[85] Hall B18146/46, Selye et al. B124/45.
[86] Selye et al. B124/45.
[87] Bjorneboe et al. B37877/47.

can even produce intense myeloid infiltration of the renal pelvis stroma in the rat (cf. Hemopoietic System). If very large doses of LAP are administered to optimally sensitized rats (unilateral nephrectomy, NaCl) acute nephritis may develop.[88] This suggests that even true inflammatory renal lesions may be diseases of the hormonal adaptation mechanism involved in the G-A-S.

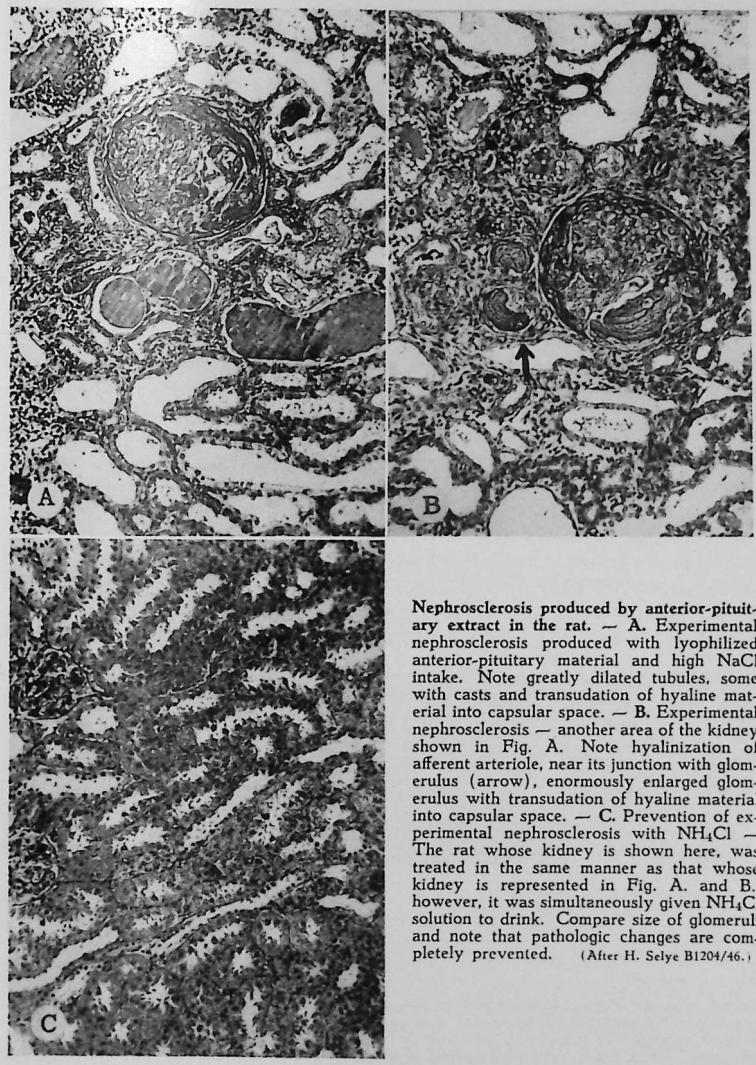
LAP-treated rats usually eat much more than untreated controls. It is important to point out, therefore, that an increase in renal weight is produced by LAP, even if the food intake is kept down to the amount ingested by untreated controls. Furthermore, in rats fasted up to four days, LAP still elicits a renotrophic action; presumably due to transfer of protein from other tissues into the kidney. However, even on a reduced caloric intake the renal enlargement obtained by a given dose of LAP is roughly proportional to the protein content of the diet.[89] Unfortunately the interpretation of the above experiments is somewhat difficult, because no distinction was made between a renal enlargement due to renotrophic or nephrosclerotic effects.

If the ureter of one kidney is completely severed between two ligatures the resulting hydronephrosis causes marked pressure atrophy of the kidney in the rat. This atrophy is greatly delayed by daily treatment with LAP.[90] Apparently the beneficial "renotrophic" action of the anterior-lobe can protect the kidney tissue even against direct mechanical damage.



Hormonally produced renal lesions similar to those occurring in diseases of adaptation. — Top row, normal kidney of a female dog (weight 19 lbs.). — Bottom row, experimental nephrosclerosis in a female dog (weight 19 lbs.) treated with anterior-lobe extract, DCA and thyroxin for 10 weeks. As explained in the text, thyroxin augments the nephrotoxic action of both anterior-lobe and corticoid preparations. Great increase in renal size is mainly due to cortical enlargement. The organ is reminiscent of the "large white kidney" of human pathology. Note also "flea bitten" appearance of surface, due to numerous glomerular hemorrhages. These were histologically confirmed; microscopic examination also showed signs of typical nephrosclerosis.

[88] Hall and Selye B22454/45.
[89] Hay B1213/46.
[90] Selye and Hollett A71885/45. Selye and Nielsen 84644/44.

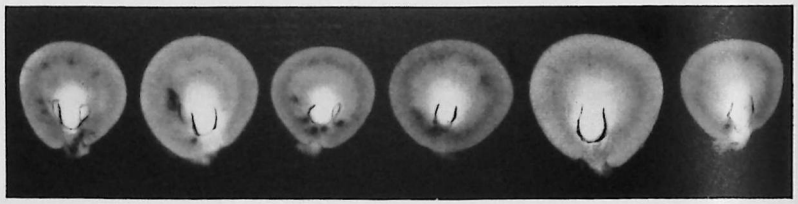


Nephrosclerosis produced by anterior-pituitary extract in the rat. — **A.** Experimental nephrosclerosis produced with lyophilized anterior-pituitary material and high NaCl intake. Note greatly dilated tubules, some with casts and transudation of hyaline material into capsular space. — **B.** Experimental nephrosclerosis — another area of the kidney shown in Fig. A. Note hyalinization of afferent arteriole, near its junction with glomerulus (arrow), enormously enlarged glomerulus with transudation of hyaline material into capsular space. — **C.** Prevention of experimental nephrosclerosis with NH_4Cl — The rat whose kidney is shown here, was treated in the same manner as that whose kidney is represented in Fig. A. and B., however, it was simultaneously given NH_4Cl solution to drink. Compare size of glomeruli and note that pathologic changes are completely prevented. (After H. Selye B1204/46.)

In connection with the renal changes which are often seen in diabetic patients, it is interesting that "intercapillary glomerulo-sclerosis" has been noted in a dog in which chronic diabetes was produced with an anterior-pituitary extract.[91]

[91] Lukens and Dohan B2087/46.

In certain strains of mice, purified *ACTH* allegedly produces a transitory stimulation of the epithelioid cells in the juxtaglomerular apparatus.[92] The significance of this change is not known and further experiments will be necessary to show whether it can be reproduced consistently in various species. Typical nephrosclerosis has not yet been obtained with pure ACTH, perhaps because up to the present time no investigator performed chronic experiments with large doses. We have administered up to 12 mg. of ACTH/day (given in six equally spaced doses throughout the day and night) up to 40 days in adult rats (sensitized by unilateral nephrectomy and a high-protein, high-sodium diet). This did not cause either nephrosclerosis or any other manifest sign of hyalinosis, although the blood-pressure rose from 135 to 180 mm.Hg. However, if this treatment was combined with simultaneous administration of in themselves almost inactive doses of LAP, then marked renal enlargement, nephrosclerosis and polyuria ensued. Apparently, the "mineralo-corticotrophic" effect of LAP is enhanced by ACTH. Similarly prepared lyophilized liver given in combination with ACTH under identical experimental conditions, did not result in mineralo-corticotrophic activity; in particular it caused no marked renal enlargement or nephrosclerosis. Hence we concluded that the production of hyalinosis by LAP is due to the combined effect of the ACTH and some other factor(s) present in anterior-lobe tissue. In other words, the typical gluco-corticotrophic effect is apparently due to ACTH itself and the "mineralo-corticotrophic" action to ACTH + X. The nature of this synergistic *"X-principle"* in the pituitary is not yet known. It may be identical with one of the already identified pituitary hormones or it may be a hitherto undescribed principle. In any event, it is not merely a non-specific effect of foreign proteins as such, since lyophilized liver did not possess these conditioning properties.[92a]



Treatment		Normals	LAP	ACTH	L. Liver	ACTH + LAP	ACTH + L. Liver
Kidney weight	mg.	907	1,255	909	982	1,567	867
	mg. / 100 gm.	509	624	669	536	837	619

Effect upon the kidney of combined treatment with LAP (containing the "X-factor" which conditions for mineralo-corticotrophic action) and ACTH. — Macroscopic view of cross-sections through the kidneys of rats having received the treatments indicated in the legends underneath each figure. All preparations were given sub-cutaneously (LAP and lyophilized liver, 20 mg. twice daily; ACTH, 2 mg. six times daily). The experiment was terminated after 35 days. Note that greatest renal enlargement was obtained in group receiving ACTH + LAP, especially if expressed as % of body weight. Despite growth inhibition, kidney continued to develop. Histologically marked nephrosclerosis occurred only in this group and only here was the blood-pressure consistently far above normal throughout the experiment. (Selye 35935/ND.)

[92] Dougherty B18316/48.

[92a] Selye 35935/ND.

Interestingly, recent experiments suggest that ACTH inhibits the production of myocarditis, periarteritis nodosa and renal lesions by *DCA* in the rat.[92b] Since ACTH is predominantly gluco-corticotrophic, it is in agreement with the above observations, concerning the antagonism between cortisone and DCA, that ACTH inhibits the cardiovascular manifestations of a mineralo-corticoid. It is more difficult to understand the alleged inhibition of "focal glomerulitis", since under our experimental conditions, the renal changes caused by DCA were actually aggravated by cortisone.

Much more work will have to be done to clarify this complex problem, we nevertheless discussed very recent pertinent observations in some detail here, since they touch upon a most fundamental aspect of the G-A-S, namely the interplay between qualitatively distinct corticotrophic effects.

Purified *thyrotrophin* was found to be renotrophic in the rat, but this action is not merely secondary to the increased production of thyroid hormone, since it remains demonstrable after thyroidectomy.[93]

Vasopressor posterior-lobe extracts tend to cause ischemic infarcts in the rat kidney, presumably due to intense arterial spasms.[94] However, at the same time, necrotizing arteritis may develop both in the kidney and in other tissues, perhaps because the vessel spasms are maintained so long that the nutrition of the arterial walls suffer.

These changes have been compared to the allergic and eclamptic types of necrotizing arteritis.[95] Pretreatment with *folliculoids* sensitizes the kidney to this effect. Since such hormones are produced in large quantities during pregnancy, this has been regarded as a further point in favor of the similarity between the lesions produced by vasopressin and those seen in eclampsia.[96]

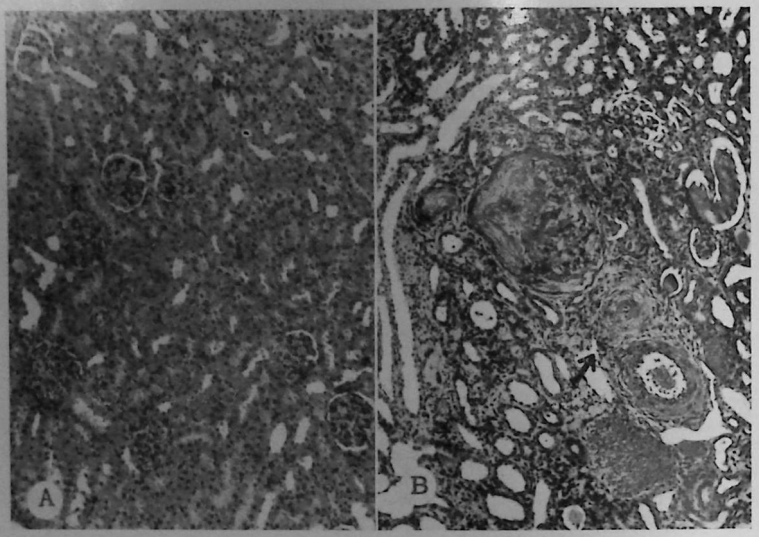
Adrenals. — Adrenalectomy causes no specific morphologic changes in the kidney, but it diminishes both the size and the functional capacity of the organ.[97] This may partly account for the changes in electrolyte metabolism which develop during adrenal insufficiency, but perhaps even more important are an increased uptake of Na and Cl, with an increased elimination of K from the cells of various organs (cf. sections on Electrolyte Metabolism).

Adrenaline causes no striking structural changes in the kidneys of adrenalectomized animals, but *DCA* produces the same kind of nephrosclerosis as in intact animals.[98] Indeed after adrenalectomy the nephrosclerotic action of DCA is perhaps even aggravated.[99]

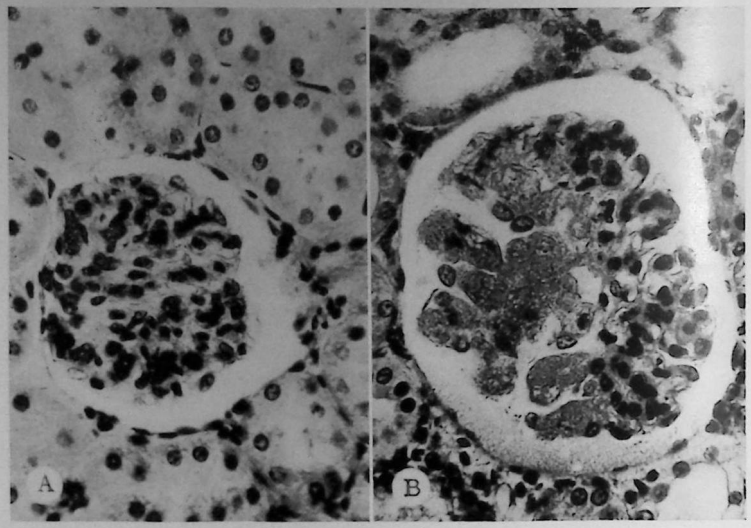
Adrenaline also fails to produce any consistent and typical renal lesions in intact animals. Only a slight diuretic effect is often obtained with small doses of adrenaline. This is allegedly due to an increased filtration pressure, occasioned by a constriction of the efferent glomerular vessels, at a time when the systemic blood-pressure is high.[100]

In rabbits it could be demonstrated that adrenaline opens the "renal shunt" with the typical deviation of blood from the cortex to the medulla. In this respect the hormone acts in the same manner as direct electrical stimulation of the renal nerves. In both instances the shunt can be prevented by adrenergic blocking agents such as ergot derivatives.[100a]

[92b] Woodbury et al. B47201/50.
[93] Hay B1213/46.
[94] Byrom A8247/37, Selye 94572/49.
[95] Byrom A8247/37.
[96] Byrom A9905/38.
[97] Gaudino and Levitt B43395/49, Selye 94572/49.
[98] Selye 35935/ND.
[99] Pirozynski and Akert B38484/49.
[100] Selye 94572/49.
[100a] Cerletti et al. B45961/49.



Nephrosclerosis produced by corticoids in the rat. — A. Normal kidney. — **B.** Experimental nephrosclerosis produced by DCA. Note greatly enlarged glomerulus with transudation of hyaline material into the capsular space and dilated convoluted tubules, many of which contain hyaline casts. A medium sized arteriole (arrow) shows hyaline necrosis of its walls. (After H. Selye B1204/46.)



Glomerular hyalinization caused by desoxocortisone in the rat. — A. High magnification of a glomerulus from a normal control kidney. — **B.** Comparable glomerulus from the kidney of a desoxocortisone treated rat. Note hyalinization of several glomerular loops and dilatation of surrounding tubules. (After Selye B43385/50.)

In the chapter on the cardiovascular system we reviewed in detail that widespread hyalinosis which can be obtained in experimental animals with **mineralo-corticoids** such as DCA or desoxocortisone. We have seen that some species (e.g., chick, rat) are especially sensitive to this effect but if sufficiently large doses are given for a long period, most laboratory animals respond in essentially the same manner. The renal vessels, particularly the glomerular capillaries and the afferent arterioles, are much more subject to hyalinosis than the larger vessels. The veins are apparently almost immune.

Usually the first morphologic changes detectable in the kidneys of DCA-overdosed animals are: distension of the convoluted tubules, with some hypertrophy and hyperplasia of the lining cells and a slight hyperemia of the glomeruli. In comparatively DCA-resistant species (e.g., dog, monkey) this condition may persist for many weeks and even months. Eventually, however, glomerular hyalinization and hyalin necrosis of the arterioles ensues; then the picture resembles an acute malignant nephrosclerosis. When the glomerular circulation becomes seriously damaged by hyalinosis the corresponding tubules undergo the well known transformation into "endocrine nephrons". The proximal convoluted tubules lose their eosinophilia and brush border while their lumina disappear. Thus the originally tubular structures are transformed into more or less solid, diffusely basophilic cords. It has been our impression that these tubular changes, rather than any glomerular or juxtaglomerular lesion, are responsible for the resulting hypertension. As we have said elsewhere, it remains to be seen whether the increased production or the decreased inactivation of R.P.S. is more important in the pathogenesis of the ensuing hypertensive disease.[101].

Desoxocortisone produces essentially similar renal changes.[102]

As judged by observations on the rat, the most evident change in renal function caused by DCA is a reduction in the PAH clearance, while the filtration rate is maintained at a normal level. While there is no reduction in renal plasma flow, the filtration fraction is elevated per unit of tubular excretory tissue. Later, however, when the vascular lesions produce renal ischemia, filtration is seriously interfered with.[103] The increase in the rate of urine flow without an accompanying rise in glomerular filtration is ascribed to decreased tubular reabsorption of water.[104] In the dog C (Inulin) and C (PAH) is increased while Tm (PAH) is decreased by DCA.[105] In normotensive patients DCA diminishes inulin and diodrast clearances, while the peripheral renal vascular resistance (calculated by Lamport's formulae) rises.[106] Experiments with water-soluble desoxycorticosterone glucoside showed that this compound lowers the tubular maximal capacity (TMG) [106a] and slightly raises the glomerular filtration rate and renal plasma.[106b]

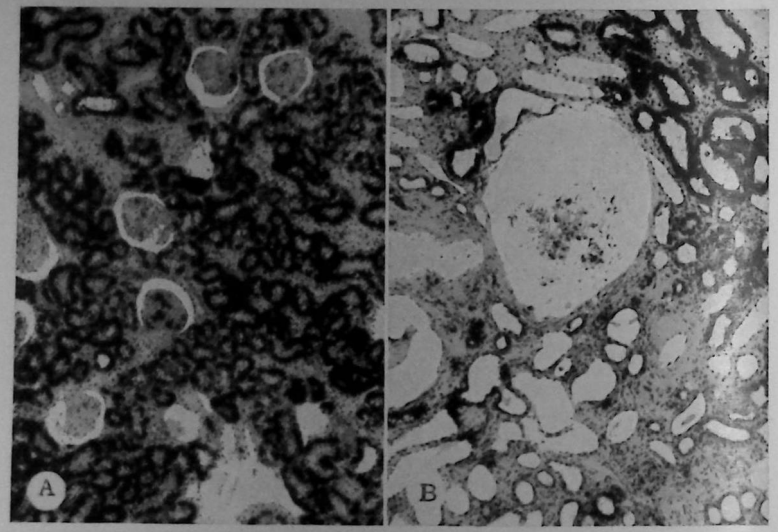
The oxygen consumption of the kidney itself falls under the influence of DCA. However, at the same time the renal parenchyme is damaged, while the stroma contains much proliferating granuloma tissue and some edema, hence this may not be an indication of decreased respiration by the remaining renal cells.[106c] Indeed, the diminution of oxygen consumption was so slight that from

[101] Selye B4165/48, 94572/49.
[102] Selye B43385/50.
[103] Friedman and Friedman B18266/48, Friedman et al. B18570/48.
[104] Boss et al. B35915/49.
[105] Gaudino and Levitt B43395/49.
[106] Luft and Sjögren B43391/49.
[106a] Lambert et al. B45214/49.
[106b] Green et al. B47259/50.
[106c] Prado B47392/50.

these experiments it was "tentatively concluded that anoxia of the renal tissue is not involved in the production of DCA-hypertension".[106d]

The acid phosphatase content of the rat kidney decreases under the influence of chronic DCA overdosage. This is particularly obvious in the proximal convoluted tubules. The functional significance of this change is not yet clear.[106e]

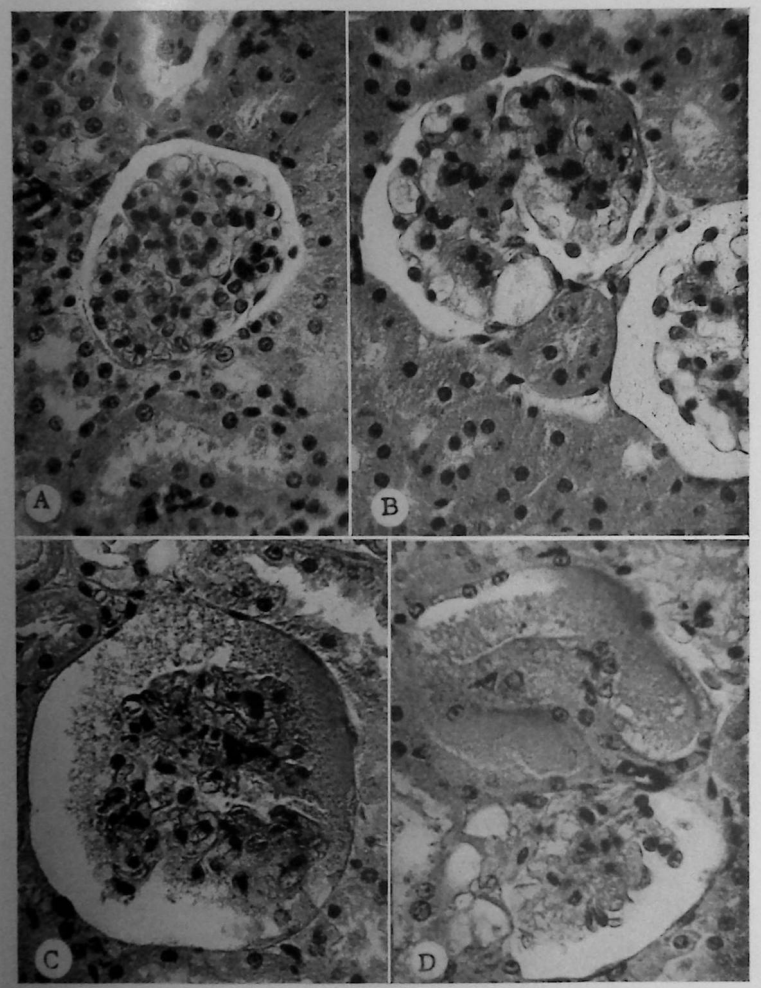
The various "conditioning factors" which influence the production of hyalinosis by mineralo-corticoids have also been discussed (cf. Cardiov. Syst., p. 514 ff.). To avoid unnecessary repetition, let us merely state here that among all the many electrolytes tested only *sodium* salts proved to enhance the nephrosclerotic effect of these steroids. Acidifying salts, such as *ammonium chloride* or *calcium chloride* and certain *cation exchange resins* which cause a sodium loss exert an opposite effect. *Phosphates* tend to precipitate insoluble calcium salts. These form calcified casts within the tubular lumina, thus causing renal tissue destruction. This also increases the nephrosclerotic action of DCA, probably through the same mechanism which is responsible for the sensitization by *partial nephrectomy* or *nephrotoxic sera*.



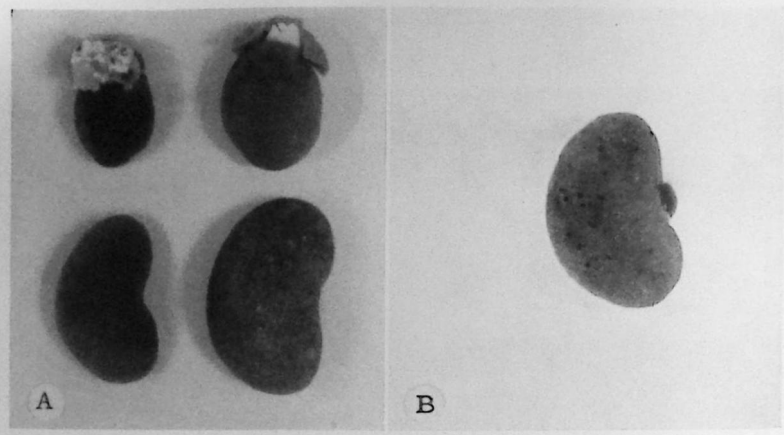
Effect of DCA upon acid phosphatase in the kidney of the rat. — **A.** Distribution of acid phosphatase in the kidney of the normal control. The enzyme was determined using glycerophosphate as a substrate at pH 4.7. Note positive reaction especially in the proximal convoluted tubules. — **B.** Kidney of rat which, after sensitization by unilateral nephrectomy and NaCl, received DCA during 35 days. Note that some proximal tubules still give a positive reaction, but others have apparently become free of acid phosphatase. Note also severe lesions in the glomerulus in the center of the field and dilatation, as well as cast formation, in several tubules. (Courtesy of Drs. M. Herlant and P. S. Timiras.)

[106d] Prado B47392/50.

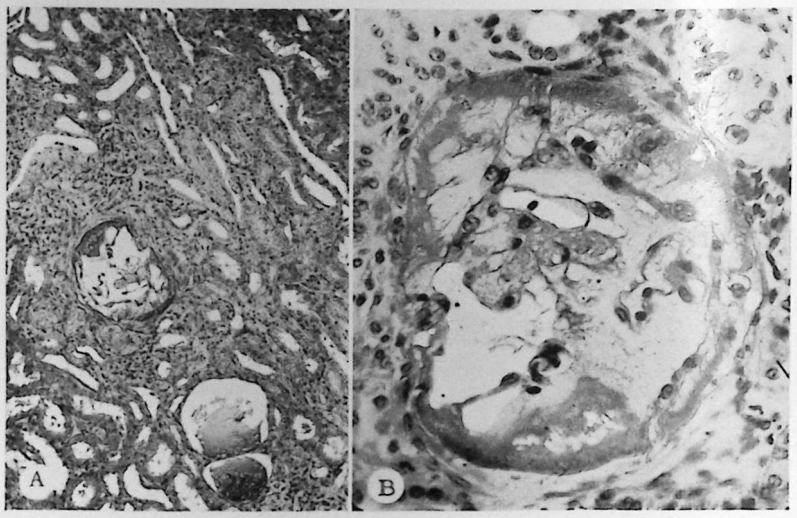
[106e] Herlant and Himiras (unpublished).



Renal changes caused by cortisone overdosage in the rat. — **A.** Kidney of normal control rat given cholesterol (15 mg./day during 7 days) as an example of a hormonally inactive steroid. — The others are sections through the kidneys of rats receiving toxic doses (15 mg./day during 7 days) of cortisone. — **B.** Intense and irregular dilatation of the glomerular capillaries, hypertrophy of the visceral lamina of Bowman's capsule, with very large and irregularly shaped nuclei. Note also beginning disintegration and hyalinization of the glomerular loops, near the upper right corner of the field. — **C.** Complete disintegration of the glomerular loops, with bleeding into the distended Bowman's space. — **D.** Completely disintegrated glomerulus (lower part of field) and dilatation of the corresponding tubule (upper part of field) by a hemoglobin and erythrocyte cast. The lining cells of this glomerulus are greatly flattened. (Selye 35935/ND.)

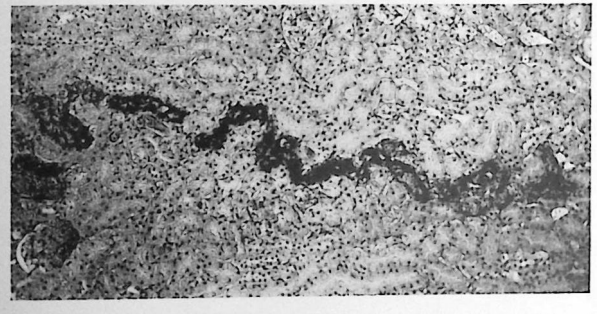


Effect of corticoid-overdosage upon the kidney, in the rat. All these animals were sensitized by unilateral nephrectomy and 1% NaCl. — **A.** Macroscopic appearance of heart and kidney in otherwise untreated control. On the right, corresponding organs of a rat heavily overdosed with DCA. Note numerous, white, nephrosclerotic nodules on the renal surface and great enlargement of the heart with the typical rounding of its apex. The animal developed pronounced hypertension. — **B.** Kidney of a rat acutely overdosed with large doses (5 mg./day) of cortisone and the same amount of DCA. Note that the renal effects of the mineralo-corticoid were aggravated by simultaneous gluco-corticoid treatment. Due to the glomerular hyperemia, caused by cortisone, numerous glomerular hemorrhages occurred and the kidney assumed the typical "flea-bitten" appearance. This animal also developed marked hypertension, but, since it died after eight days of treatment, the heart was not yet enlarged. (After Selye 35935/ND.)



Legend →

It has been especially emphasized that *potassium* deficiency does not augment the nephrosclerotic and hyalinosis-producing action of DCA. This is noteworthy because potassium deficiency is known to cause tubular hyperplasia and an increase in renal weight. Histologically, these changes are more comparable to the renotrophic than the nephrosclerotic action of steroids and appear to be manifestations of a compensatory hypertrophy. Presumably they represent the morphologic expression of increased tubular work, which becomes necessary whenever the re-absorption of very small quantities of potassium from the filtrate is of vital importance.[107]



Pigment deposition in a nephron following corticoid treatment, in the rat. This animal was chronically overdosed with both desoxocortisone and cortisone. Note hemorrhage in glomerulus near left edge of the field and intense pigmentation of the corresponding tubule. Here we are probably dealing with the storage of blood-pigment derivatives. (Selye 35935/ND.)

The most characteristic acute renal changes produced by **gluco-corticoids** are a marked hyperemia of the glomerular capillaries and a shunting of the blood towards the medulla which becomes greatly congested. Upon prolonged treatment with high doses of cortisone, this change may eventually result in hypertension and nephrosclerosis. Simultaneous administration of gluco-corticoids (e.g., cortisone) and *mineralo-corticoids* (e.g., DCA and desoxocortisone) results in particularly severe renal changes and hypertension, especially in rats sensitized by unilateral nephrectomy and NaCl. Thus, the gluco-corticoids actually aggravate the renal damage caused by mineralo-corticoids, at least in sensitized animals.[108]

In man, the "tubular secretion of PAH, following load administration, increased (up to 35 per cent) with cortisone. With ACTH no change in PAH

←

Renal changes caused by simultaneous treatment with DCA and cortisone, in the rat. — **A.** Kidney of a rat (sensitized by unilateral nephrectomy and 1% NaCl) after 33 days of 1.25 mg. DCA + 1.25 mg. cortisone/day. Note marked disintegration of the glomerulus in the center of the field, blood-containing casts near the lower edge of the field and pus-cell containing cast just above the disintegrated glomerulus. Invasion by leucocytes and subsequent suppuration of casts frequently causes multiple abscesses in rats treated with cortisone, with or without simultaneous DCA administration. Note also several solid "endocrine nephrons". — **B.** High magnification of the glomerulus shown in fig. A and of one "endocrine nephron" in upper right corner of this field. The picture illustrates that the renal effects of DCA are not inhibited by cortisone, indeed they are usually aggravated. (Selye 35935/ND.)

[107] Masson and Beland A72916/43.

[108] Selye 35935/ND, B41762/49.

secretion occurred, but blood-levels were not as high after ACTH as during control periods".[108a]

In rats in which nephritis has been produced by *anti-kidney serum*, cortisone increased the blood-pressure, but curiously "the nephritic rats rendered hypertensive by the administration of cortisone presented no greater histological evidence of renal damage than did normotensive control nephritic animals".[109] Since partial nephrectomy is so effective in increasing the nephrotoxic action of cortisone, it is difficult to understand why the partial destruction of kidney tissue by sera exerts no such effect. It must be kept in mind, however, that even DCA does not appear to aggravate an advanced nephritis caused by anti-kidney serum "perhaps because of the unusual severity of the process resulting from anti-kidney serum alone".[110]

Kidney. — Intense renal lesions are produced by the various **interventions on the kidney itself,** which are in common use for the production of renal hypertension. These changes have also been described in the chapter on the cardiovascular system so that it will suffice here merely to recapitulate the most important facts. The "endocrine kidney" technique produces the most clear-cut and generalized transformation of nephrons into the solid "endocrine nephron" type. However, partial constriction of the renal artery, extensive partial nephrectomy, cellophane perinephritis, nephrotoxic nephritis, and indeed any intervention capable of producing renal hypertension, causes similar changes at least in certain nephrons, particularly those whose glomeruli have ceased to filter. We have already mentioned that in the endocrine kidney the acid phosphatase decreases in total amount though its concentration remains normal. On the other hand, there is an almost complete disappearance of both arginase and alkaline phosphatase.[111]

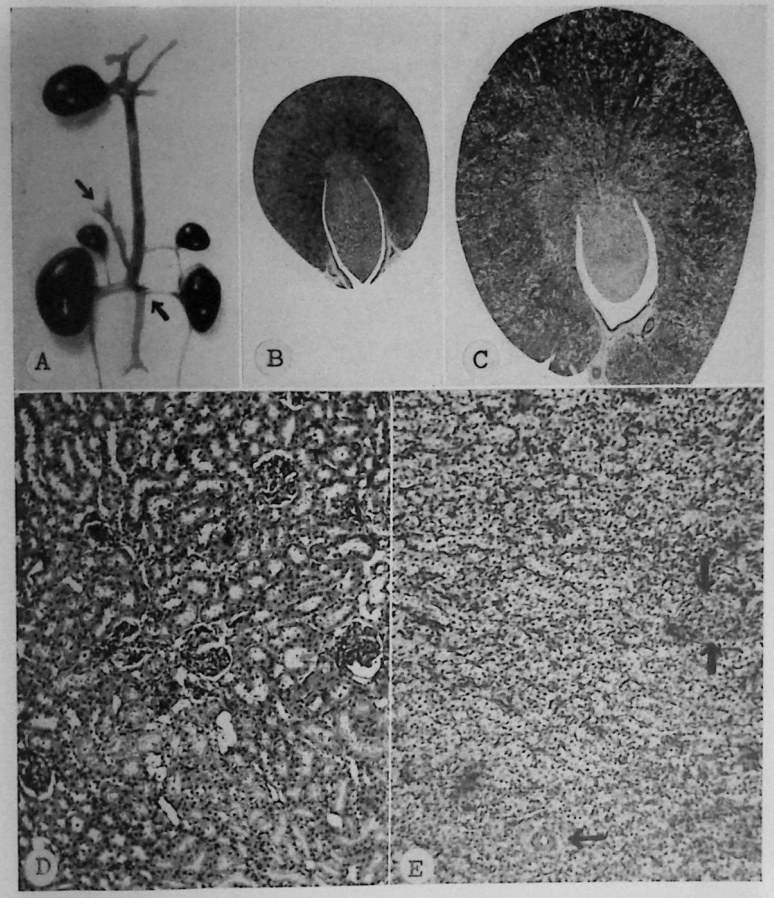
Hyalinosis is not observed in kidneys protected against high blood-pressure by partial constriction of their arteries. Thus an "endocrine kidney" can cause generalized vascular hyalinization in the opposite kidney and in extra-renal tissues throughout the vascular system, but remains protected itself.[112] Since the humoral milieu is obviously the same in both kidneys this experiment clearly shows the importance of physical factors (blood-pressure) in the production of hyalinosis.

This protection is not only effective against humoral substances formed by the kidney. Treatment with *LAP* for instance produces nephrosclerosis only in the normal and not in the endocrine kidney.[113]

We have seen that under the influence of *renotrophic anterior-pituitary extracts* both the glomeruli and the tubules become enlarged and numerous mitotic figures in the tubular epithelium show that in addition to hypertrophy there is also actual hyperplasia. Following unilateral nephrectomy the compensatory hypertrophy of the contralateral kidney is greatly enhanced by such renotrophic anterior-pituitary preparations.[114]

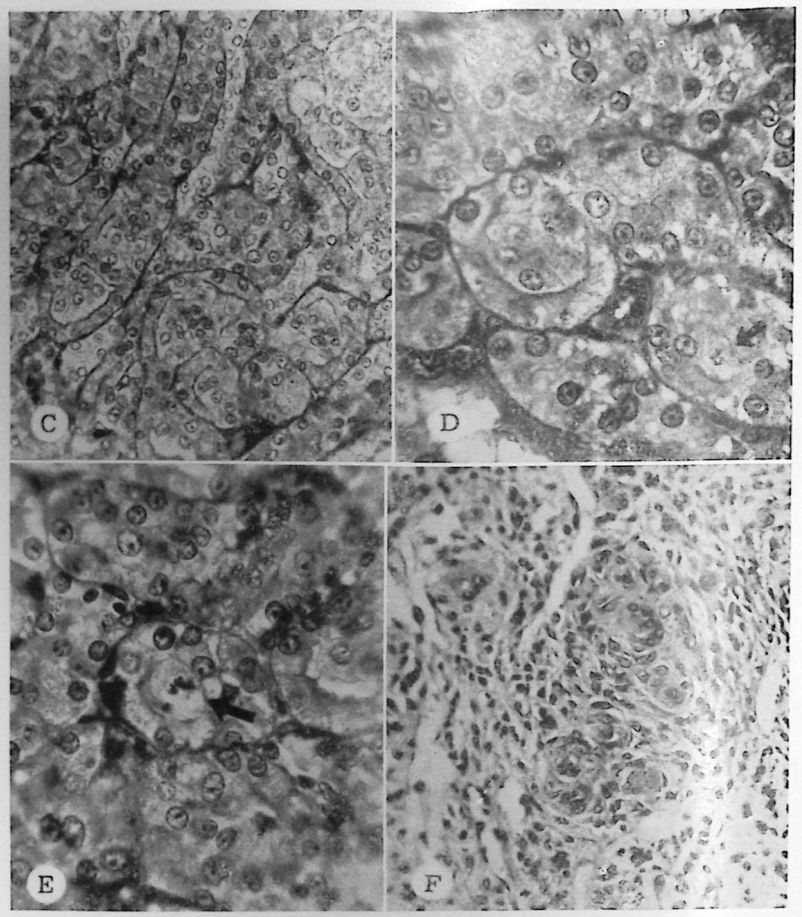
Although the endocrine kidney does not participate in urine formation it is still responsive to the renotrophic effect of LAP [115] and *testosterone*.[116] The

[108a] Ingbar et al. B47881/50.
[109] Knowlton et al. B44790/49.
[110] Knowlton et al. B43547/49.
[111] Kochakian and Dontigny B3631/48.
[112] Selye B4165/48, Selye and Stone 94202/46.
[113] Selye and Stone 94202/46.
[114] Selye and Hollett A71885/45, Selye and Nielsen 84644/44.
[115] Selye and Stone 94202/46.
[116] Selye and Stone 96099/47, B19379/49, 93772/47.

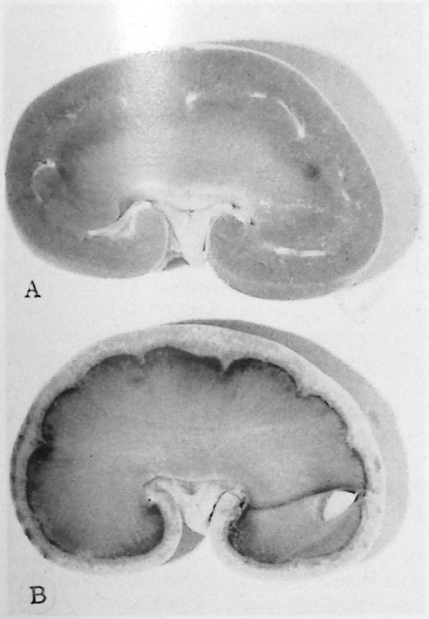


Endocrine kidney in the rat. — **A.** Macroscopic view of heart, aorta, kidney and adrenals. In this animal the aorta was partially ligated between origins of 2 renal arteries (lower arrow) and LAP treatment was given during 14 days. Note great enlargement of heart, adrenals and right kidney, to stimulate growth of endocrine kidney. Heart contained macroscopically visible Aschoff (?) nodules, kidney surface is irregular (beginning nephrosclerosis), adrenals are dark (hyperemia and discharge of lipid granules) and there are several periarteritic nodules on superior mesenteric artery (upper arrow). Aorta is thickened but only in section above partial ligature. Left kidney, whose artery originates below ligature, is subnormal in size but entirely free of nephrosclerotic nodules. — **B.** Cross-section through left kidney of rat shown in A. Note great decrease in kidney size mainly due to involution of medulla. Cortex is almost as wide as in normal kidney, small decrease in width of the renal cortex is readily accounted for by disappearance of nephronic lumina and partial collapse of glomeruli. Renal pattern is very regular, showing no trace of nephrosclerosis. — **C.** Cross-section through right kidney of rat shown in A. Note irregularity of pattern, due to patchy nephrosclerosis. (Same magnification as Fig. B) — **D.** Medium magnification of an area from normal control kidney. — **E.** Medium magnification of an area from left "endocrine kidney" of a rat, whose aorta was partially ligated between origins of two renal arteries. Note that all tubular lumina and Bowman's capsule spaces have disappeared. Glomeruli tend to melt in with tubular parenchyme but are still distinguishable in places (2 arrows). A small arteriole, near lower margin (1 arrow) shows no trace of hyalinization. General pattern of this kidney is reminiscent of an adrenal or parathyroid, since it consists exclusively of solid, epithelial cell cords. (Same magnification as A.)

(After H. Selye and H. Stone 94202/46.)



Endocrine kidney in the rat. — **C.** High magnification of an area from left "endocrine kidney" of an LAP treated rat whose aorta was partially ligated between the two renal arteries. Note solid epithelial parenchyme, although no secretion of urine occurs and tubular lumina are absent, epithelial cells are well preserved and show no sign of degeneration or necrosis. — **D.** Another field of same kidney under oil immersion. Note that tubular lumina are filled with proliferating epithelial cells. A mitotic figure (arrow) is seen in a convoluted tubule. Note also syncytial formation near upper and lower right-hand corner and rather polymorph appearance of nuclei. — **E.** Another area of the kidney shown in A. Polymorph appearance of nuclei and a large mitotic figure in center of field (arrow) are clearly visible here under oil immersion. Many mitotic divisions in these kidneys clearly indicate that renotrophic stimulation is possible even in small "endocrine kidney." — **F.** Section through a myocardial nodule of another rat treated with LAP. Note proliferation of capillary endothelia which tend to fuse and thus form polynuclear giant cells (arrows) similar to those seen in acute rheumatic fever. In this area, myocardial fibres have been completely replaced by granulomatous tissue.
(After H. Selye and H. Stone 94202/46.)



Endocrine kidney ,in the dog. — **A.** Macroscopic view of a cross section through the kidney of a normal control dog. — **B.** Similar view of the "endocrine kidney" in a dog six days following partial constriction of the main renal artery. The cortex is sharply demarcated from the medulla; there is marked medullary hyperemia and cortical ischemia. The cortical portion of this kidney exhibited the characteristic yellowish light aspect often seen in the endocrine kidney of the rat and there were histologic signs of endocrine nephron formation . The animal developed marked hypertension. For technical reasons, in the dog this operation is much more difficult than it is in the rat.
(Selye 35935/ND.)

effect of LAP and testosterone on the non-excretory endocrine kidney shows that the renotrophic action of hormones is not merely secondary to an increased demand upon the excretory work of the renal tissue.

The characteristic eosinophilic granules of the proximal convoluted tubules disappear rapidly after the endocrine kidney operation, but curiously they remain very evident if the animals are treated with a renotrophic steroid such as testosterone.[117] The functional significance of these histochemical changes in the endocrine nephrons is not yet understood.

Other stimuli. — Among the other steroids, the **testoids** exhibit the most clear-cut renotrophic actions.[118] This effect is much more marked in the mouse than in the rat. In the latter both the convoluted tubules and the glomeruli are enlarged but otherwise essentially normal, while in the mouse the cells of the parietal lamina of Bowman's capsule become very hyperplastic and assume the appearance of a cuboidal or cylindric epithelium.[119] This is merely an exaggeration of the normal sex difference in renal structure which exists in most strains of mice.

The renotrophic effect is much more pronounced in *castrates* or females than in intact males,[120] probably because in many species the kidney of the male is larger than that of the castrate male or intact female. In the mouse for instance, the hyperplastic "male type" of Bowman's capsule is normally present in intact

[117] Selye and Stone B19379/49.
[118] Anonymous A57073/43, Selye A18307/39.
[119] Selye A18307/39.
[120] Selye A35514/41.

males, but not in females or castrates. Testosterone causes exaggerated hyperplasia of the capsular cells in both sexes, but this is especially evident in castrate males or females in which these cells are otherwise inconspicuous.[121]

It is particularly noteworthy, that renotrophic testoids can enlarge the kidney even considerably above the normal level.[122] This should be pointed out because earlier investigators claimed that testoids restore the weight of the kidney in castrate rats "to or towards normal, but are unable to cause supernormal enlargements".[123]

Comparative studies of the renotrophic and testoid actions have shown that, although the most active renotrophic compounds are also testoid, there is no strict parallelism between these two pharmacologic properties. Generally speaking, the saturated androstanediols and especially androstane-3(β), 17(α)-diol, as well as the corresponding 17-methyl-androstanediol, proved to be the most active renotrophic compounds so far discovered.[124] It appears however, that among the steroids there is a very close correlation between renotrophic and nitrogen-retaining potency.[125]

The mechanism of the renotrophic effect is still unknown. As we have pointed out previously, even the non-excreting *"endocrine kidney"* responds very distinctly to the renotrophic effect of testoids. Hence this action cannot be attributed simply to increased work in connection with urine production. Since the most renotrophic steroids are also the best protein-anabolic compounds, there may be some correlation between the kidney-stimulating and the nitrogen-retaining effect of steroids. However, testosterone-treated mice survive *bilateral nephrectomy* longer than untreated controls. "These observations appear to be in contradiction with the conception that the effect of testosterone on the kidney is due to metabolic changes necessitating increased renal activity".[126] It is more plausible to assume that under the influence of such protein-anabolic stimulation, the kidney participates most intensely, and most rapidly in the formation of new tissue, perhaps in order to prepare itself for the increased work, which may arise as a result of the newly formed extrarenal tissues.

The possible relationship between *potassium* and renotrophic action has already been touched upon. It will be recalled that, contrary to the statements of earlier investigators,[127] stimulation of the kidney by testoids cannot be interpreted as a consequence of a low blood-potassium level, which would necessitate increased tubular reabsorption of K and hence increased tubular work. Firstly, the testoids do not cause hypokalemia in rodents, although they do in man,[128] yet they stimulate renal growth in all mammals so far examined. Secondly, administration of excess dietary K fails to inhibit the renotrophic action of testoids.[129]

The *tissue-aldehyde* content of the rat kidney is increased by renotrophic testoids, especially along the cortico-medullary border-line, where the spiral segments are located. This effect is diametrically opposed to that of folliculoids and progesterone, which deplete the tissue-aldehydes in this region.[130] Some

[121] Selye **A35219/41.**
[122] Feyel 99416/43,
Ludden et al. A35818/41,
Selye A18308/39, B3476/48.
[123] Korenchevsky et al. A19771/39.
[124] Beland **B18144/46.**
Beland et al. A72288/44.
[125] Kochakian 98428/47.
[126] Selye A30863/40.
[127] Durlacher et al. A55528/42.
[128] Selye **94572/49.**
[129] Masson and Beland A72916/43,
Selye **94572/49.**
[130] Oster B508/45.

relationship between tissue-aldehydes and R.P.S. has repeatly been suspected, but the significance of the above-mentioned histochemical changes is unknown.

Thyroxine, which causes considerable kidney enlargement in itself, presumably as a result of its general metabolic effects,[131] greatly augments the renotrophic action of testoids.[132]

From a practical point of view it is especially interesting that renotrophic steroids, and especially testoids, proved very effective in protecting the kidney against damage and in accelerating the compensatory renal hypertrophy following partial destruction of this organ. Thus it was found that after *partial nephrectomy* the compensatory hypertrophy of the remaining kidney is greatly enhanced.[133] Renotrophic testoids also protect the kidney against the nephrosclerotic action of *DCA*,[134] the pressure atrophy caused by unilateral *ligature of the ureter*,[135] the tubular necrosis caused by *mercury*,[136] the glycosuria and tubular damage elicited by heavy overdosage with *phlorhizin*,[137] and the so-called toxic nephritis caused by *uranium* nitrate.[138] The loss of renal weight during *starvation* is likewise counteracted by renotrophic steroids.[139]

Only a few pertinent clinical observations have so far been published and their results are somewhat controversial. It has been claimed that testosterone is useful in the therapy of various urological disturbances associated with *male hypogonadism*,[140] *gynecological disorders*[141] as well as in the protection of the kidney against the nephrotoxic actions of *cholera*.[142]

In the light of all these positive findings we must not be discouraged by the fact that under certain experimental conditions testosterone and its derivatives proved inaffective; for instance, in preventing *sublimate* damage to the kidney of rats,[143] the nephritis induced in rats by rabbit *anti-kidney-serum*[144] or renal damage in patients suffering from certain kidney diseases.[145] It is obvious that the relative dosage of the kidney-damaging and renotrophic compounds, the time-interval between the administration of the toxic and protective substances, etc., must all be properly adjusted in order to obtain good results. Testoids cause marked mitotic proliferation of the tubular epithelium and during division, cells are unusually sensitive to damage. The experiments on the enhancement of compensatory renal hypertrophy after surgical ablation of kidney tissue show most convincingly that under suitable conditions regeneration is facilitated by renotrophic steroids. Hence, it would appear worthwhile to verify the value of such therapy, if not as a preventive, at least as an adjuvant in the treatment of diseases which cause considerable renal destruction.[146]

Unlike the testoids, **folliculoids** tend to cause renal atrophy. When they enlarge the kidney, this is usually due to the development of the degenerative changes, not to any true renotrophic effect.[147]

[131] Selye **94572/49.**
[132] Selye et al. B124/45.
[133] Mackay A35432/40,
Selye et al. B124/45, Wrete 88806/45.
[134] Selye and Rowley A72302/44.
[135] Selye and Friedman A35722/41,
Homburger et al. B47878/50.
[136] Donatelly B38554/47,
Imbriano B45480/48,
Longley A37552/42,
de Oliveira et al. B43032/47,
Selye A31126/40, Vargas B44689/48.
[137] Winter and Belanger A36751/41.
[138] Feyel 99416/43.
[139] Kochakian B4280/46.
[140] Klotz
and Debray B39651/49, B39463/49.
[141] Fried A63231/43.
[142] Henderson et al. B23880/48.
[143] Feyel 99416/43, Levy et al. B47634/50.
[144] LeCompte B6374/44.
[145] Patrono and Pincelli B36782/48.
[146] Anonymous A57073/43.
[147] Albert and Selye A37637/42,
Selye 94572/49, Wrete 88806/45.

In hamsters, folliculoids may produce metastatizing, malignant renal tumors.[147a]

Thyroxine tends to enlarge the kidney, without causing nephrosclerosis, due to hypertrophy and hyperplasia of its normal constituents.[148] While thyroxine stimulates, thyroidectomy or thiouracil treatment inhibit the compensatory hypertrophy induced by unilateral nephrectomy in the rat.[149] All this is pertinent to our problem since thyroxine may be discharged under the influence of systemic stress. Furthermore, even the normal blood-level of this hormone probably influences the renal actions of other materials (such as mineralo-corticoids and renotrophic anterior-pituitary principles) which are more regularly discharged during the G-A-S.

Extensive partial **pancreatectomy** causes nephrosclerosis in the rat, whenever it leads to severe chronic diabetes.[150] The changes thus produced resemble those caused by alloxan (see above).

Adrenergic blocking agents (e.g., ergot derivatives) prevent the opening of the "renal shunt", which is normally produced by adrenaline, anoxia or direct stimulation of the renal nerves in the rabbit.[150a]

Anti-histaminics (e.g., antergan) inhibits the development of nephritis and proteinuria in rabbits treated with anti-kidney sera,[150b] or DCA (cf. above).

As we have said above, it is particularly interesting that **protein-** and/or **sodium-rich** diets greatly enhance both the renal enlargement and the production of nephrosclerotic changes in rats exposed to stress (e.g., cold).

Albino rats kept on a high-sodium or high-**potassium** diet, but given no water, are severely damaged and show hyperemia of the glomeruli, the formation of solid "endocrine type" nephrons accompanied by extrarenal manifestations of the G-A-S. "The reaction in these animals then could be considered to be a non-specic reaction, a part of the general-adaptation-syndrome". On the other hand, the Desert Kangaroo Rat, which is very resistant to water deprivation, does not manifest such changes under comparable dietary conditions.[150c]

Potassium deprivation on the other hand caused marked dilatation of the renal tubules in the rat. This was accompanied by a myocarditis, somewhat reminiscent of that produced by DCA, but without the massive hyalinization characteristic of the latter.[150d]

It has been claimed that overdosage with **ascorbic acid** prevents the renal enlargement usually caused by exposure to cold in the rat.[151] Further work will be necessary, however, to show whether this action of vitamin-C is directed only against the renal changes induced by cold, or whether it could protect against any alarming stimulus.

Renal Diseases of Adaptation

Primarily renal diseases. — We have emphasized that disturbances originating in the organs which regulate the G-A-S, are also conducive to what may be described as a disease of adaptation. In this sense, any disease directly

[147a] Kirkman and Bacon B46502/50.
[148] Herlant B41072/49, Selye 94572/49, Selye et al. B124/45, A72284/44.
[149] Herlant B41072/49.
[150] Foglia et al. B41177/48, B31714/48.
[150a] Cerletti et al. B45961/49.
[150b] Reubi B46937/45.
[150c] Nichols B44434/49.
[150d] Smith et al. B46713/50.
[151] Dugal and Therien B23325/48.

affecting the function of the kidney could be regarded as a primary disease of this organ of adaptation. Attempts to classify disease according to any principle will meet with the difficulty that there is necessarily a great deal of overlap between the individual groups, since usually the entire organism participates in any major derangement. Indeed, an "incidental" complication is often the immediate cause of death (e.g., apoplexy or lung edema in cardiovascular disease, cardiac decompensation in malignant diphtheria). Furthermore many diseases belong with equal justification to several accepted classes; it would be difficult to decide whether subacute bacterial endocarditis should be grouped with the "infectious" or the "cardio-vascular" diseases. We therefore emphasized that only those maladies in which a derangement of the G-A-S mechanism is the major factor, should be classified as a disease of adaptation. This formulation immediately calls to mind the lack of precision and the subjectiveness of such definitions. Yet this manner of grouping disease is no less precise than any other used in standard textbooks of medicine and we feel that it is useful for the understanding of many pathologic phenomena to examine them primarily for the derangement in adaptation which they cause.

Among the diseases which affect the kidney directly, **embolic nephritis, ascending pyelonephritis, toxic nephritis and nephrosis** due to the direct renotoxic action of certain compounds (e.g., mercury, uranium nitrate), **compression of the renal arteries** (e.g., by local scars or neoplasms), **malformations** of the kidney, etc. Indeed perhaps primary renal tumors may even raise the blood-pressure through increased RPS production by the neoplastic cells.[152] All these could be regarded as primary maladies of this adaptive organ which may secondarily lead to derangements of the G-A-S mechanism, by interfering with the participation of the kidney (hormone production, excretion) in homeostasis. We mention them here merely for the sake of completeness since they are not strictly within the province of this volume.

Much more pertinent to our topic are the secondary renal diseases of adaptation, that is, changes in the kidney which are the direct result of maladaptation to stress. However, we are only beginning to learn about the participation of the corticoids and the kidney in the homeostasis of the blood-pressure, hence it is impossible at present to discuss adequately the pathogenesis of the secondary renal diseases of adaptation. Nevertheless, in the following pages we shall attempt to give a brief outline of the most obviously pertinent conditions.

Crush syndrome. — Attention has recently been focused upon the so-called "crush syndrome" especially as a result of observations made on civilian casualties during the second World War in Britain.[153] This entity has been described under many names such as *traumatic anuria,*[154] *traumatic uræmia,*[155] *"lower nephron nephrosis",*[156] *toxic nephritis,*[157] *acute hematogenous interstitial nephritis,*[158] *acute interstitial nephritis,*[159] *clinical acute nephritis,*[160] *nephrosis,*[161] *hepatorenal syndrome,*[162] *extrarenal azotemia,*[163] etc.

[152] Lindner B44720/47.
[153] Bywaters B36587/44, 89889/45, Bywaters and Beall A53986/41.
[154] Wilkins et al. B33448/49.
[155] Demardy et al. B19923/44, B45436/47.
[156] Blitz and Straub B45318/49, Burch and Ray B43693/49, Harman B38035/47, Hoffman and Marshall B46720/49, Iseri et al. B33421/49, Lucké B18018/46.
[157] Brown et al. B37086/23.
[158] Kimmelstiel B37090/38.
[159] Melnick B36586/43.
[160] Bell B37089/37.
[161] Wilbur B37088/37.
[162] Helwig and Schultz B37087/32, Wilensky B3270/46.
[163] Jeghers and Bakst B19997/38.

In the previous pages we already referred to this syndrome since so many stressors are capable of eliciting it. Let us add here that this derangement is chiefly characterized by delayed shock-like clinical manifestations often terminating in uremia. However, in the event of recovery the blood-pressure tends to rise above normal,[164] perhaps because of an activation of the renal pressor mechanism.

Morphologic studies revealed that the kidneys are usually enlarged and congested. If one makes a section through the kidney, the cortex appears to be anemic, swollen and tends to protrude above the surface, while the medulla is often hyperemic and the cortico-medullary border line indistinct. Microscopic examination shows that the tubules are dilated and the epithelial cells reveal various degrees of degeneration, sometimes even complete necrosis. While some observers believe that the degenerative changes involve chiefly the proximal[165] or distal "lower" segment of the convoluted tubules,[166] others claim that all parts of the convoluted tubules are almost equally involved.[167] Often the tubular epithelia contains acidophilic, hyalin granules and many cells are desquamated into the lumen. This may be accompanied by the formation of hyalin, cellular or blood-pigment casts. Occasionally there are phenomena of cellular regeneration ("endocrine nephrons"?) and sometimes the dilated damaged tubules perforate into engorged venules. The glomeruli may be congested and edematous, the capsular space being filled with protein precipitates; however, usually they are less seriously affected than the tubules. The interstitial tissue tends to be edematous and is often infiltrated with lymphocytes, plasma cells and polymorphonuclear leucocytes.[168]

Significantly, the adrenals of patients who died from the crush syndrome often showed extensive infarction,[168a] such as is characteristic of an extremely acute A-R.

As regards the **pathogenesis** of the crush syndrome, a number of theories have been proposed. It has been claimed that widespread erythrocyte destruction could liberate hemoglobin, and muscle damage myohemoglobin, during crush injuries and various intoxications. Such *heme compounds* would then tend to precipitate in the renal tubules and damage the kidney. Under normal conditions hemoglobin and myohemoglobin are not particularly nephrotoxic but some investigators hold that highly toxic derivatives are formed and hemecasts are precipitated if the reaction of the urine is acid.[169]

Perhaps *other nephrotoxic substances* are also produced by the kidney. It has been shown that a substance causing renal damage can be extracted from the muscles of limbs which have been tightly bound for some hours, but not from normal muscle.[170]

Temporary *partial occlusion of one renal artery* in unilaterally nephrectomized rabbits leads to renal changes comparable to those seen in the crush syndrome.[171] This and related observations led some investigators to believe that *anoxia* of the kidney tissue itself may be the principal eliciting factor.[172]

[164] Anonymous **B24780/48.**
[165] Bywaters and Beall A53986/41.
[166] Dunn et al. A38038/41, Lucké B18018/46.
[167] Moon B19951/48.
[168] Beall et al. A53987/41, Dunn et al. 82769/41, Fruchaud and Baumann 97260/45, Lucké **B18018/46**, Morison A38040/41, de Scoville B24774/47.
[168a] Wyatt and Goldenberg B45843/48.
[169] Bywaters 89889/45, Lucké **B18018/46.**
[170] Eggleton B692/44, Eggleton et al. A61910/43.
[171] Badenoch and Darmady B41880/47.
[172] Lucké **B18018/46.**

In experimental animals *choline deficiency* causes hemorrhagic lesions in the kidneys and the liver (cf. p. 613). These have also been compared to the "fulminant form of the so-called hepato-renal syndrome. Its possible dietary origin and control may have practical significance beyond the specific pathologic condition in question, and may extend to the humoral regulation of blood-pressure, including shock-prevention and vascular reactions to hemorrhage".[173]

Many other theoretic possibilities have been considered[174] but none have actually been proven to be invariably related to the development of the crush syndrome. From our point of view it is interesting that this condition can occur following exposure to the most diverse stressors such as: *infections, transfusion with incompatible blood, hemorrhage, traumatic injuries, intestinal obstruction,* severe *hepatic disease,* intoxication with a variety of *drugs.*[175]

In fact, several investigators emphasized that the only common denominator which seems to characterize the conditions conducive to the "crush syndrome" is a state of shock due to systemic damage.[176] Since this syndrome is often accompanied by other typical manifestations of the A-R (gastric ulcers, adrenal enlargement with lipid discharge and so forth) it may be related to the G-A-S.[177]

The possible rôle of *corticoids* in the production of the crush syndrome is suggested by some of the experiments which we discussed in the preceding pages. Very acute overdosage with cortisone, or mixtures of cortisone and mineralo-corticoids, cause medullary hyperemia with the formation of heme casts, degenerative and regenerative changes in the tubules which eventually may result in death from uremia. These changes are rather reminiscent of the crush syndrome.

Bilateral renal-cortical necrosis. — Symmetrical, bilateral necrosis of the renal cortex can occur in combination with preëclamptic manifestations during pregnancy and especially after difficult deliveries complicated by considerable loss of blood. However, under certain conditions it may also occur outside of pregnancy, especially in combination with hypersensitivity reactions.[178]

Since this syndrome tends to develop after exposure to some allergen or major stress it should be considered as a possible disease of adaptation. The shunting of the renal circulation towards the medulla has already been mentioned as characteristic of the **crush syndrome** and of **acute corticoid overdosage.** It is particularly marked after the **endocrine kidney** operation, indeed the latter may be associated with renal-cortical necrosis if the constricting ligature is too tight. The relationship between the **"renal shunt"** mechanism and bilateral cortical necrosis has been discussed by several investigators.[179] It is also noteworthy in this connection that bilateral cortical necrosis tend to occur in connection with **periarteritis nodosa.**[180]

Several cases of this comparatively rare disease have been noted in association with **necrosis of the hypophysis**[181] or **Addison's disease.**[182] While

[173] Györgi B19250/48.
[174] Lucké **B18018/46.**
[175] Herbut **93650/46,** Locascio B44819/49, Lucké **B18018/46,** Paxton et al. B36240/46.
[176] Herbut 93650/46, Moon 98691/47, B19951/48.
[177] Moon B19951/48, Selye B1204/46, Wilensky B3270/46.
[178] Duff and More **B44581/41.** Penner and Bernheim **B41485/40.**
[179] Anonymous 95430/46, Cabot B44338/48, Solymoss B46096/49.
[180] Doniach and Walker B34067/46, Wordley 94512/23.
[181] Doniach and Walker B34067/46, Grasby B34888/47.
[182] Cabot B44338/48.

it is quite possible that the association with hypophyseal or adrenal lesions is purely coincidental, it is well to keep in mind that derangements of ACTH and corticoid production tend to increase susceptibility to hypersensitivity reactions. Since increased vasopressin production is characteristic of the A-R it is perhaps also pertinent that this pressor principle may cause extensive, bilateral renal-cortical infarction in experimental animals (cf. above).

We have already mentioned that choline deficiency tends to produce extensive, bilateral, hemorrhagic cortical infarction in the rat. The possibility has therefore been considered that bilateral, symmetrical cortical necrosis in man may also be partly dependent upon conditioning by dietary factors.[183]

Nephritis in general. — The various forms of nephritis have always puzzled pathologists because they can appear following — and probably as a result of — such diverse noxious agents as tonsillitis, colds, scarlet fever, influenza, other infectious diseases, exposure to cold, pregnancy, intoxication with various drugs and allergic conditions.[184] Although it is customary to distinguish a variety of allegedly quite different nosologic entities, a comparative anatomic study in patients "...emphasized the non-specificity of lesions observed in the glomerulus of the kidney and offers this non-specificity as an explanation of many similarities in the signs and symptoms of renal diseases".[185] It has also been pointed out "that the transudation of protein through the glomerular capillaries represents a classical example of "albuminuria into the tissues" in the sense of a serous inflammation.[186]

A critical analysis of the various forms of hemorrhagic nephritis shows that "the clinical pictures encountered are extremely varied. In the initial phase the onset may either be acute and fulminating or insidiously symptomless. The disease process may pursue a variety of courses. The initial phase can heal completely or it may pass through a subacute to a chronic, active state, or again to a latent phase. The chronic, active or latent phases can result in healing or may progress to a terminal stage of renal insufficiency by a series of acute or subacute exacerbations of activity. A nephrotic form of hemorrhagic nephritis, which is distinguished from true nephrosis with difficulty, is often encountered in the subacute or chronic active stages".[187]

Depending upon the predominant manifestations of the disease, it is customary to distinguish acute, subacute, chronic (diffuse or focal) glomerulonephritis, embolic glomerulonephritis, acute tubular nephritis and acute interstitial nephritis from each other and from the primarily vascular types of nephrosclerosis. Yet, the many transitional forms suggest a close relationship as regards the etiology of these renal diseases. The most acute type of non-specific renal damage is exemplified by the crush syndrome and perhaps also by the symmetrical, bilateral renal cortical necrosis. The acute, subacute and chronic types of nephritis take an intermediate position, while nephrosclerosis and the secondary contracted kidney represent the most chronic forms of non-specific renal damage. A prominent feature of all these nephritides is that they can be elicited by a variety of stressors and it may well depend upon incidental conditioning factors (e.g., intensity of the stress, hereditary predisposition, diet, specific actions of individual stressors) what course the disease will take.

[183] György B19250/48, György and Goldblatt B25553/40.
[184] Arnold B41249/49, Bell B4501/47, Lichtwitz B186/42.
[185] Christian A56705/42.
[186] Eppinger B37085/49.
[187] Musser 88056/45.

Acute diffuse glomerulonephritis is clinically often associated with an infection by streptococci (in association with scarlet fever, tonsillitis and sometimes rheumatic fever or erysipelas), more rarely pneumococci or other germs. "The fact that no organisms are present in the kidneys indicates that the renal lesions are probably toxic in origin, but the nature of the toxin and its mode of action are still unknown".[188] There is much to suggest that an excess of corticoids is involved. Studies with radio-sodium suggest that the elimination of sodium is delayed in nephritics [189] somewhat like after DCA overdosage. Furthermore, corticoids can cause nephritis in rats (cf. above) and experimentally produced adreno-cortical tumors are often associated with glomerulonephritis in mice.[190]

The various sodium-deficient diets — for instance the rice diet — are sometimes strikingly effective in cases of nephritis with hypertension and congestive cardiac failure.[190] It will be recalled that sodium deprivation also protects against the renal damage produced by corticoids.

Preliminary communications suggest that **ACTH** causes remissions in certain cases of acute or subacute glomerulonephritis.[190b] This is somewhat unexpected in view of the severe renal damage obtained by heavy overdosage with corticoids in experimental animals. It is possible, however, that at a lower dose level the glomerular hyperemia induced by gluco-corticoids may be advantageous, especially in those cases of nephritis in which the glomeruli become anemic as a result of edema and proliferative changes in the capillary walls. Even when temporary benefit appears to be obtainable by ACTH or cortisone therapy, it remains to be shown whether prolonged treatment would not be detrimental. In any event it is too early to discuss the possible mechanism of alleged improvements since other investigators, who used ACTH, obtained no remission in nephritis.[190c]

Many investigators believe in an **allergic** etiology of glomerulo-nephritis, perhaps as a result of "auto-antibody" formation against kidney tissue [191] and there is ample evidence to show that anti-kidney sera can cause nephritis in animals (cf. above). In support of this view it has also been mentioned that sulfonamides and other allergens are especially conducive to nephritis and that this is often accompanied by periarteritis nodosa in extrarenal vessels, a lesion considered to be rather typical of allergy.[192]

In this connection it is especially interesting that *anti-histaminic* drugs often appear to be very beneficial in the treatment of nephritis.[192a]

Allegedly, the serum of nephritic patients — unlike that of normal individuals — can cause diffuse capillary leakage [193] or even typical nephritis [194] in experimental animals. However, the active principle (allergens, toxins, corticoids ?) have not been identified and these claims require confirmation.

The **nitrogen mustards** resemble gluco-corticoids in that they exert a direct lympholytic action. It is interesting therefore that they may cause spectacular remissions in clinical glomerulonephritis.[194a]

[188] Ogilvie B26346/47.
[189] Threefoot et al. B44700/49.
[190] Kirschbaum et al. B44718/49.
[190a] Scott B45292/49.
[190b] Farnsworth B46974/50.
[190c] Astwood et al. B47853/50.
[191] Betz B26164/48, Sarre and Mahr B44821/48.
[192] Harrestrup and Andersen B46494/48, Meyer B38034/47, Rigdon et al. B44820/49.
[192a] Craig et al. B46899/49, Steinmann and Re·bi B46931/46, Volhard B46392/49.
[193] Eppinger B37085/49.
[194] Stefanelli B38130/47.
[194a] Chasis et al. B47861/50.

War-nephritis (trench nephritis). — This is an acute glomerulo-nephritis which tends to develop in soldiers — but sometimes also in the civilian population — upon exposure to cold, dampness and inadequate hygienic conditions. Allegedly, among those afflicted by this disease, many "...were in a state of sensitization, which facilitates the outbreak of allergic disease by non-specific stimuli such as cold and fatigue".[195] Most students of this malady ascribed a prominent rôle to systemic stressors such as cold, infections, skin parasites, fatigue and allergic hypersensitivity reactions.[196]

There appears to be a **generalized capillary damage** even in extra-renal tissues [197] and this may account for the frequent occurrence of lung edema.[198] Severe capillary damage in the diencephalic region may also accompany war nephritis and it has even been postulated that the hypertension and edema of these patients is not the result of the renal damage but the direct consequence of the accompanying so-called "war diencephalosis".[199]

Significantly, in many cases the **E.S.R.** is increased.[200] In the **renal glomeruli** there is thickening of the basal membranes and proliferation of nuclei in the glomerular capillaries, but sometimes certain loops become entirely devoid of nuclei and necrosis ensues. At the same time, the mucosa of the **renal pelvis** becomes edematous and infiltrated by lymphocytes and histiocytes.[201a] Often there is a concomitant severe **myocarditis.**[201a] All these changes are very similar to those which we produced in experimental animals by exposure to cold, LAP and corticoids.

It is perhaps also worth mentioning in this connection that nitrogen mustard and typhoid vaccine — two typical alarming stimuli — may cause temporary remission of the clinical manifestations in human glomerulonephritis.[202] We mention this merely because it appears to be yet another example of **non-specific therapy** by an acute stressor in a disease apparently elicited by another non-specific stressor. This is rather reminiscent of "crossed-resistance" as we also see it, for instance in rheumatoid arthritis after exposure to stress.

Dietary factors also play an important rôle in the production of war-nephritis. It is especially noteworthy that withdrawal of food and drink during the first few days greatly reduces mortality from war-nephritis, although the condition may then pass into one of chronic nephritis.[203] Conversely, among people who had to spend a long time in subterranean caves during the second World War, acute diffuse glomerulonephritis appeared in a large number of cases upon return to normal life and food.[204]

On the basis of such observations certain types of nephritis including war-nephritis have been considered to be typical examples of **diseases of adaptation.**[205]

Nephrosclerosis and the Kimmelstiel-Wilson syndrome. — In describing the renal changes produced in experimental animals by stress (e.g., cold, foreign proteins), LAP or corticoids, we emphasized their similarity to the

[195] Lichtwitz B186/42.
[196] Aschenbrenner B42369/48. Illchmann-Christ B41784/47. Randerath B41783/48, Röllinghoff B45390/48.
[197] Goldeck B44219/47.
[198] Nissen B44822/48.
[199] Henkel B23581/43.
[200] Keibl and Pilgerstorfer B44755/48.
[201] Günther B38012/47.
[201a] Bohn and Feldmann B46010/47.
[202] Chasis et al. B39065/49.
[203] Kramer B44479/49.
[204] Bassi B37375/46.
[205] Bassi B37375/46, Koranyi B45773/47. Selye B1204/46.

"idiopathic" malignant nephrosclerosis of man. It has also been shown that extensive partial pancreatectomy or alloxan diabetes, if conducive to prolonged glycosuria, tends to cause essentially similar lesions in animals (cf. above). The so-called "intercapillary glomerulosclerosis" or "Kimmelstiel-Wilson syndrome" is a constant accompaniment of the nephrotic syndrome in diabetics. The latter is clinically characterized by albuminuria, hypoproteinemia, hypercholesterolemia, edema and hypertension. Histologically, the lesions do not differ markedly from those of glomerulosclerosis in non-diabetic patients, although in the Kimmelstiel-Wilson syndrome the hyalinization appears to be intercapillary and usually begins at the center of the glomerular tuft.[206] Such minor differences may well be due to "conditioning" of the response by the metabolic disturbances typical of diabetes. It should also be kept in mind that it is usually impossible to determine whether a hyalinized focus within a glomerular tuft results from the complete hyalinization of an entire loop or the deposition of hyalin between loops.

Significantly, **pyelonephritic changes** — similar to those experimentally produced by LAP — frequently accompany the Kimmelstiel-Wilson syndrome.[206a]

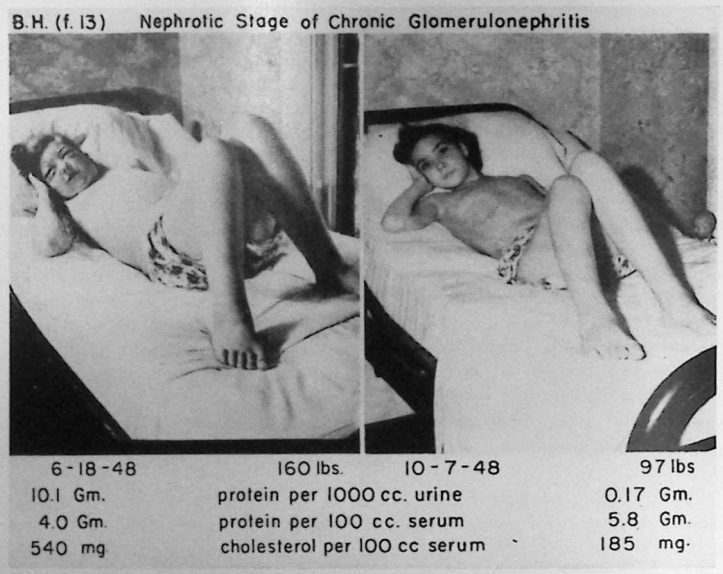
Nephrosclerosis frequently develops as the chronic stage of a preceding nephritis. We do not believe that the pathogenic mechanism is necessarily quite different if an initial acute nephritic stage is absent. In either case the hyalinization and sclerosis of the glomeruli and arterioles may be largely dependent upon abnormal or excessive corticoid formation during stress, although undoubtedly incidental conditioning factors can impart a certain degree of specificity to the aspect of the resulting lesions. In this sense renal changes of the Kimmelstiel-Wilson syndrome may also be regarded as predominantly due to a derailment of the G-A-S mechanism.[207] It will be recalled in this connection that some authors brought forth evidence suggesting that even the diabetes itself is a disease of adaptation (cf. Diabetes).

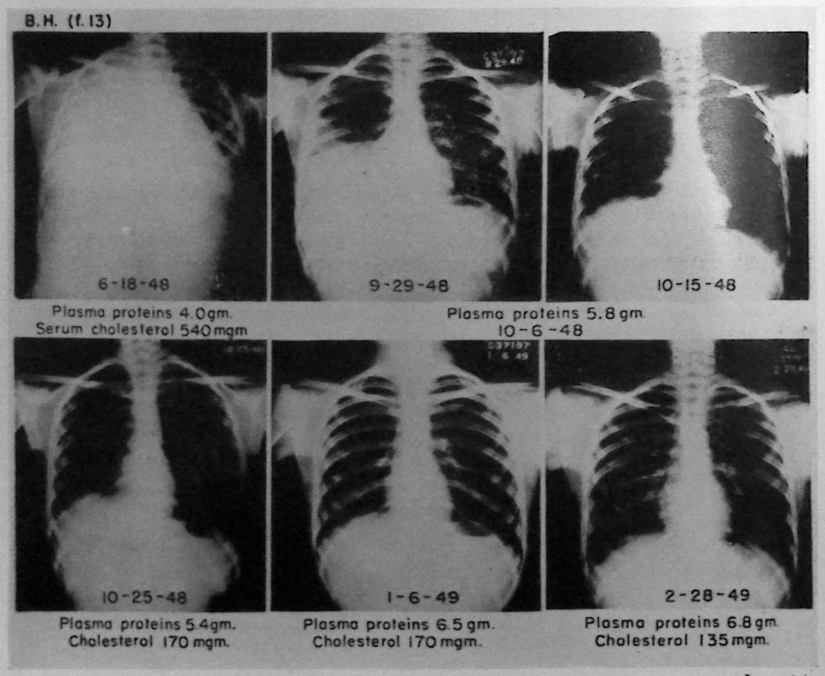
Nephrosis. — The rôle played by derailments of the G-A-S in nephrosis has not yet received as much attention as it would deserve. It has been noted that an acute intercurrent illness may be followed by a permanent regression of the symptoms of lipoid nephrosis.[207a] The urinary excretion of mineralocorticoids is increased in nephrosis.[207b] Furthermore, many manifestations of clinical nephrosis are duplicated by DCA overdosage in animals, for instance the edema tendency, tubular changes and hypercholesterolemia.

Data concerning the effect of DCA, cortisone and ACTH upon the serum lipids of man are somewhat contradictory [207c] (cf. also p. 145), perhaps because up to now systematic studies on a large scale have not yet been performed under comparable conditions of dosage, duration of treatment, diet, etc.

ACTH [207d] or cortisone [207e] may cause marked remissions in patients with nephrosis, this being accompanied by a decrease in edema, blood-cholesterol

[206] Colwell B44719/48, Kimmelstiel and Porter **B26316/48, B26318/48,** Mann et al. B36594/49.
[206a] Root B45340/49.
[207] Selye B1204/46.
[207a] Nicaud and Lafitte B45655/47. Volhard B46392/49.
[207b] Deming and Luetscher B47866/50.
[207c] Adlersberg et al. B47851/50. Farnsworth B46974/50.
[207d] Farnsworth B46974/50.
[207e] Deming and Luetscher B47866/50.





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and proteinuria, as well as an increase in plasma proteins. Sometimes the diuresis and sodium excretion occurs only upon discontinuation of the treatment so that intermittent administration of the hormone may be desirable.

It is tempting to assume, in the light of these observations, that the beneficial effect of intercurrent infections upon the course of nephrosis (e.g., remissions caused by measles) may be largely due to endogenous ACTH discharge.

Physiologic albuminuria. — Various alarming stimuli (e.g., muscular exercise, injection of formaldehyde or histamine) cause albuminuria in rabbits. These and other observations led to the suggestion that the so-called physiologic albuminuria sometimes observed in stress situations is part of the A-R.[207f]

Pullet disease or "avian Bright's disease". — In the fowl, a spontaneous disease resembling Bright's disease of man has been known for some time under such names as pullet disease, blue-comb disease, contagious indigestion, cholera-like disease, summer disease, etc. It has been reproduced in fowl by excessive doses of NaCl or mineralo-corticoids.[208] Since the fowl is particularly sensitive to sodium intoxication, it develops nephrosclerosis, even without excess mineralo-corticoid administration, if its diet contains large amounts of NaCl. Probably, in many instances the spontaneous pullet disease is merely due to the ingestion of excess sodium chloride. It remains to be seen whether it could also result from corticoids produced as a result of exposure to stress.

Theories and Summary of Observations Concerning the Participation of the Kidney in the G-A-S

The changes which occur in the kidney during the G-A-S are so intimately related to the renal blood vessels that they had to be considered in the chapter on the Cardiovascular System to which the reader is referred.

Let us merely re-emphasize here that the kidney is a particularly important organ of adaptation. It helps to maintain homeostasis both through its excretory activity and through the production of blood-pressure-regulating humoral products. Under the influence of a variety of stressors, the kidney undergoes essentially similar structural and functional changes, which are not specific of any one eliciting agent. They can be reproduced in their most non-specific form by the administration of LAP, corticoids or RPS. If such lesions are severe, they may be conducive to disease and even death.

Among the spontaneous renal maladies which are considered to be predominantly diseases of adaptation we mentioned: the crush syndrome, bilateral renal-cortical necrosis and various types of nephritis and nephrosclerosis.

←

Effect of rice diet in nephrotic stage of chronic glomerulo-nephritis. 13-year-old girl in the nephrotic stage of chronic nephritis with marked edema and hypoproteinemia. Note disappearance of edema, pleural infusion and ascites during administration of the rice diet.
(After Kempner B45953/49.)

[207f] Karady and Földi B44928/43 Selye and Stone A56585/43.
[208] Selye **A56631/43.**

RESPIRATORY SYSTEM

Systemic Stress

Animal experiments have shown that in the lung, **congestion, edema, dilatation of the perivascular lymphatic spaces and plasma-transudation into the alveoli** are common and typical manifestations of the A-R. These changes are sometimes conducive to acute pneumonia. At the same time **pleural transudates** are often observed, especially if the A-R is produced by peritoneal interventions.[1] It is noteworthy however, that certain agents (e.g., anoxia, heat, adrenaline injections) have an especially marked tendency to produce an A-R accompanied by severe pulmonary manifestations. Apparently the participation of the lung is highly subject to incidental conditioning influences.

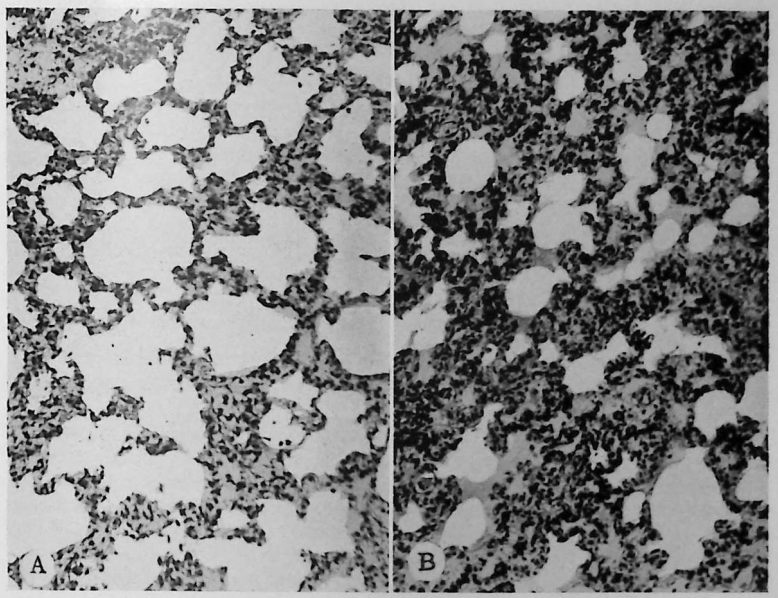
Observations on patients who died from "secondary shock" as a result of exposure to diverse alarming agents (trauma, hemorrhage, infection, anesthesia, burns, drugs, anoxia, intestinal obstruction, allergic reactions, etc.) showed that pulmonary hyperemia or edema and pleural transudates are also common manifestations of the A-R in man. When death is delayed 48 hours or longer, a secondary or terminal pneumonia often occurs. Some degree of atelectasis and hemorrhagic infarcts suggesting embolism, were found in many cases. Impairment of the circulation and filling of alveoli with albuminous fluid have been considered to play a very important rôle in the pathogenesis of this pneumonia. Since these pulmonary lesions are associated with other manifestations of the A-R (adrenal stimulation, gastric ulcers, etc.),[2] we are inclined to believe that they actually represent part of the A-R.

The **phagocytes of the alveolar lining** normally take up very few carbon particles after intravenous injection of India ink. However, they become highly active in phagocytosing this substance during an A-R, for instance one produced by cold, forced muscular exercise or spinal-cord transection.[3]

The following observation is also of interest in this connection. Leucocytes marked with radio-active phosphorus (P^{32}) cause a pronounced immediate fall in the blood-leucocyte count. Since cell-free aqueous extracts of leucocytes produce a similar leucopenia the reaction is probably humorally mediated. The distribution of the radio-activity shows that almost 50% of the injected leucocytes are retained in the lungs, while the liver (20%) and spleen (1%) retain much less.[4] Both this selective retention of **phagocytic leucocytes** by the lung, and the above-mentioned stimulation of phagocytosis by the sessile pulmonary macrophages probably participate in the defense phenomena of the A-R. The widespread disintegration of lymphocytes during the caryoclastic phase of the A-R, may well act in the same manner as the intravenous injection of leucocytes or leucocyte-extracts.

[1] Selye 36031/36, 36030/36, B1204/46, 35935/ND.
[2] Moon B19951/48.
[3] Timiras and Selye B36271/49.
[4] Weisberger et al. B33446/49.

At first sight it is difficult to appraise the purpose, if any, of the selective stimulation of phagocytosis by the alveolar epithelia or the accumulation of phagocytic leucocytes in the lung. Perhaps these reactions help to protect against pneumonia; by phagocytosis they might help to clear the pulmonary alveoli from the transudate formed as a result of increased capillary permeability.



Stimulation of pulmonary macrophages during the A-R in the rat. — **A.** Lung of normal rat following intravenous injection of India ink. Note almost complete absence of pigment granules. — **B.** Lung of a rat in which an A-R was produced by exposure to cold during 24 hours. Here the same amount of India ink was injected intravenously as in Fig. A, but due to stimulation of R.E.S. macrophages, much of the pigment is retained in the lung.
(After Timiras and Selye B36271/49.)

The principal characteristic features of this pulmonary reaction (especially the congestion, atelectasis, transudate and exsudate formation in alveoli, often conducive to hemorrhagic lung-edema and even secondary pneumonia) have repeatedly been described in man and animals exposed to a great variety of alarming stimuli. Among these stressors are: **trauma,**[5] **hemorrhage,**[6] extensive surface **burns,**[7] exposure to **heat,**[8] especially if conducive to heat-stroke,[9] **freezing** of certain parts of the body,[10] intense exposure to **x-rays,**[11] the

[5] Cleghorn B2573/46, Moon B19951/48.
[6] Eaton B38221/47, B37563/47, B42311/49, Moon B19951/48.
[7] Eppinger **B37085/49,** Ficarra and Naclerio B808/44, Hilgenfeldt 38008/36, Moon B19951/48.
[8] v. Haam and Frost A30282/39.
[9] Haymaker et al. B37920/47, Malamud et al. B18019/46, Moon B19951/48.
[10] Muirhead et al. A67426/42.
[11] Ellinger 68685/35, Prosser B26618/47.

radiations of the **atomic bomb,**[12] or even severe **solar irradiation,**[13] **anoxia,**[14] various kinds of **infections** (especially those conducive to fever) [15] and **allergic reactions.**[16]

A great variety of intoxications with drugs [17] produce similar pulmonary changes. Of course those which act directly upon the lung such as the *"war gases"* are especially effective in this respect,[18] but this is largely due to local actions and not to systemic stress. However, transcutaneously applied *vesicants* [19] and even the so-called *"dehydration shock"* (elicited by the subcutaneous injection of 25% NaCl solution in the dog) causes pulmonary edema with petechial hemorrhages in the visceral pleura.[20].

Sulfa drugs may produce pulmonary lesions reminiscent of "rheumatic pneumonia".[21]

Among **undernourished** concentration camp inmates of World War II, edema, atelectasis and inflammatory infiltrations in the lungs (particularly broncho-pneumonia) were common, especially in those who developed generalized hunger edema. These changes tended to be accompanied by a decrease in the mucous secretion of the bronchial tree, the development of bronchial catarrhs and sometimes even pulmonary abscesses and gangrene.[22]

Stimuli Influencing the Response of the Respiratory System during the G-A-S

Allegedly the catabolism (loss of weight) of pulmonary tissue is even more completely inhibited by **adrenalectomy** in the starving rat than that of lymphatic tissue.[22a]

We know very little about the humoral factors which influence the respiratory organs in the course of exposure to systemic stress. Toxic doses of **adrenaline** tend to cause very acute hemorrhagic lung edema in various animal species. Even the endogenous discharge of adrenaline into the bloodstream can elicit fatal lung edema, for instance in patients with chromaffinomas.[23] It is possible therefore that during the A-R, the acute pulmonary congestion with subsequent edema and inflammation may also be provoked, or at least enhanced, by the characteristic adrenaline discharge which occurs during the acute phase of exposure.

Curiously, "it has been shown that an A-R produced by treatment with adrenaline, formalin, exposure to cold, forced exercise, or surgical trauma, increases the resistance of the rat to the subsequent intravenous injection of lethal doses of adrenaline. This observation eliminates the possibility that the A-R increases resistance only because it delays the absorption of toxic agents into the blood stream". Examination of the lungs revealed that in the previously alarmed rats, unlike in the controls, adrenaline actually failed to produce the characteristic lung edema".[24] It has therefore been suspected that during

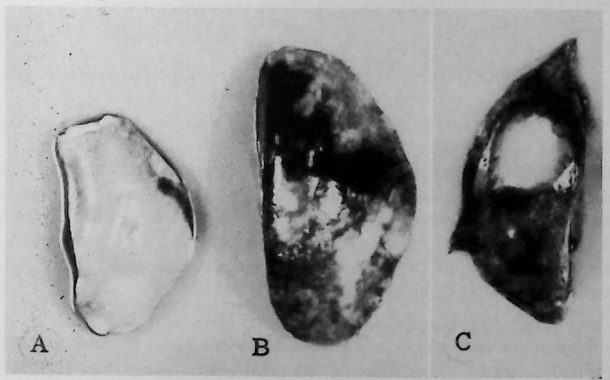
[12] Anonymous B26330/48, B28192/48, De Coursey B38048/48, Tullis and Warren B41776/47.
[13] Pinner and Margulis 37822/36.
[14] Lawson et al. 84772/43, Leblond A30385/39, Meessen B37949/48, Moon B19951/48, Thorn et al. B335/45.
[15] Harrell et al. B24809/47, Kelsey and Harrell B24821/48, Palmer 95299/46.
[16] Griep and Mayer B38223/49. Moon B19951/48.
[17] Moon B19951/48.
[18] Winternitz B19943/20.
[19] Dekanski B37985/48.
[20] Davis A37428/41.
[21] Mallory B37942/47.
[22] Gsell B27611/48, Uehlinger B27612/48.
[22a] Pellegrino B46742/49.
[23] Selye **94572/49.**
[24] Selye A7154/38.

counter-shock the A-R can protect the lung against edema formation by the phenomenon of "crossed resistance".

This view received further support from experiments on bilaterally *nephrectomized* rats which were given large quantities of physiologic *NaCl* solution intravenously. Such treatment regularly causes fatal lung edema, yet even here a previous A-R (cold, muscular exercise, trauma or histamine injections) exerted its usual protective influence.[25]

Various *antihistaminics* [26] and *adrenergic blocking drugs* [27] likewise prevent adrenaline lung edema, although the results with phenergan have not been uniformly confirmed.[28] The lung-edema-preventing action of the antihistaminics may be due to their general transudation-inhibiting effect, while perhaps the adrenolytics act by virtue of their specific adrenaline-neutralizing properties. However, since so many other alarming stimuli produce similar effects, the rôle of mere systemic stress must be examined in every case before the specificity of this action is accepted.

It has been claimed that substances belonging to the *vitamin-P* group (e.g., rutin) can be assayed by their ability to prevent hemorrhagic lung edema formation in mice exposed to decreased barometric pressure. However, the specificity of this test was questioned because numerous other drugs, e.g., glycol, glucose [29] and ascorbic acid [30] exert a similar protective effect. Since, in the doses given, these protective compounds were rather toxic, they may have acted by eliciting an A-R.



Pulmonary abscesses following cortisone treatment, in the rat. — **A.** Lung of normal rat. — **B.** Multiple hemorrhages (red) and necroses with abscess formation (white), in the lung of a rat receiving 15 mg. of cortisone/day during two weeks. — **C.** Circumscribed pulmonary necrosis with abscess formation in a similarly treated rat. Note hyperemic halo, which usually surrounds such abscesses. Multiple abscesses were often also seen in the kidneys and sometimes in the livers of rats treated with very high doses of cortisone. This may be due to spreading of normally circumscribed and latent infectious foci, due to deficient encapsulation by fibrous tissue. (Selye 35935/ND.)

[25] Selye A7154/38, A8050/38.
[26] Maksimovich B44710/48.
[26] Halpern and Hamburger B23153/48, Halpern et al. B38109/48, Reuse B37635/48.
[27] Stone and Loew B36931/49.
[28] Stone and Loew B36931/49.
[29] Raiman and Necheles B33739/47.
[30] Bariéty and Kohler B39314/48.

Mineralo-corticoids predispose to the formation of lung edema and even lobar pneumonia as a result of capillary leakage.[31] **Gluco-corticoids** on the other hand combat the formation of lung edema or lobar pneumonia, but (at least in the rat) they predispose to the formation of pulmonary abscesses, presumably due to a diminution of resistance against the normally non-pathogenic microbes of the bronchial tree.[32]

Antihistaminics prevent the "mesenchymal defense reaction" (histiocyte proliferation, edema, hyperemia, hemorrhages) in the lung of animals exhibiting anaphylactic or papain shock.[33] Here again the protection may have been due to "crossed resistance".

The mechanism through which the A-R prevents lung edema is not yet understood. It is possible that alarming stimuli act because they release gluco-corticoids or because they cause a mild adrenaline discharge. A previous injection of adrenaline notoriously diminishes the response of the lung to a subsequent toxic dose. The pronounced stimulation of phagocytosis by the histiocytes of the alveoli could also intervene inasmuch as it may expedite the reabsorption of transudate. Finally, the effect of the A-R upon capillary permeability in general (increased during the shock-phase) may deviate fluid from the lung to other tissues.

Since in clinical medicine, pulmonary complications are a very common and serious accompaniment of various infections, intoxications and other kinds of acute systemic stresses, a further analysis of the production and prevention of lung edema by the A-R would appear to be most rewarding.

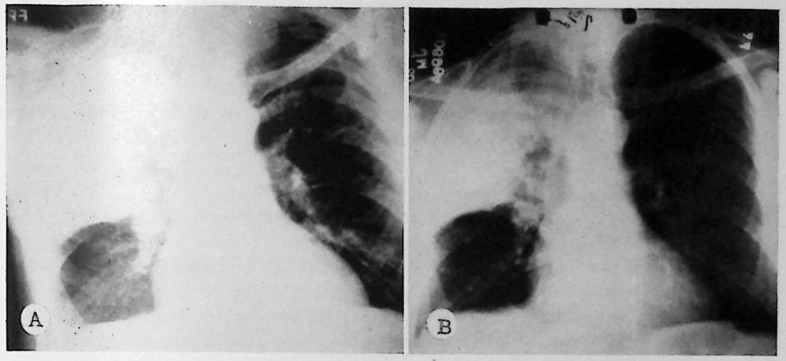
Respiratory Diseases of Adaptation

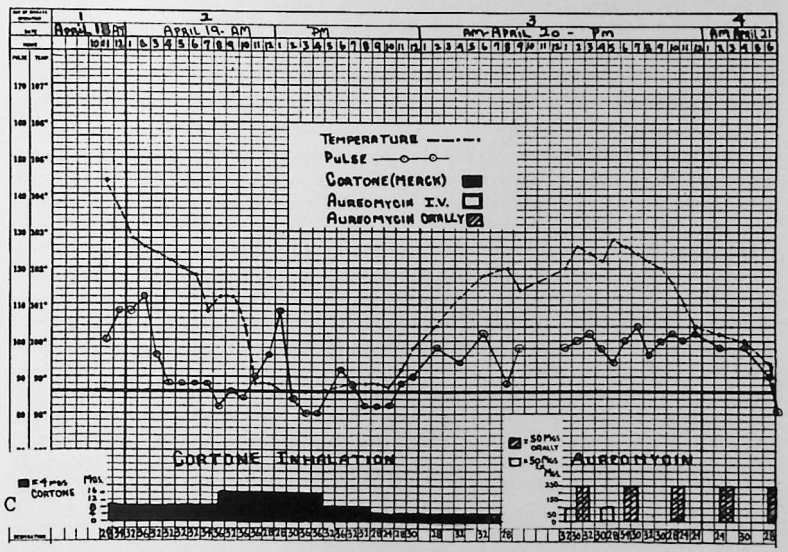
Lung edema and pneumonia in general. — We discuss these two conditions conjointly since lung edema usually precedes the formation of pneumonia. As we have seen in the preceding pages, the development of lung edema can be expedited by acute stress, as well as by some of the hormones discharged during stress (e.g., adrenaline, mineralo-corticoids). Conversely, during the counter-shock phase of the A-R (produced by various stressors including adrenaline) and under the influence of pretreatment with gluco-corticoids, the formation of lung edema is actually inhibited.

We considered the possibility that during the shock phase of the A-R capillary leakage in the pulmonary circulation may be increased, at least partly, through a discharge of adrenaline and mineralo-corticoids. On the other hand, some time after an adrenaline injection or after the liberation of endogenous adrenal hormones during stress, the formation of lung edema is inhibited by the "crossed resistance" phenomenon which is largely dependent upon gluco-corticoids.

This interpretation agrees with clinical experience showing that ACTH or cortisone are beneficial in primary, atypical pneumonia and pneumococcus pneumonia inasmuch as they expedite the resolution of the pulmonary lesion, although they do not affect the micro-organisms themselves.[33a]

[31] Selye B1204/46.
[32] Selye 35935/ND.
[33] Zacco B39572/48.
[33a] Finland et al. B46994/50.





Effect of cortisone inhalation upon lobar pneumonia. 60-year-old male with acute lobar pneumonia of six days duration. "Type 7" pneumococcus (Quellung's technique) was isolated from blood-culture. Initial white-cell count, 18,400 (predominantly polymorphonuclears). The patient was given 10 mg. of cortisone every hour, by aerosol inhalation of a saline suspension. No other medication was administered during the hormone treatment. The patient showed clinical improvement with a fall in temperature, pulse rate and diminished dyspnea. Within 8 hours the white-cell count fell to 8,800 (95% polymorphonuclears). Then cortisone treatment was gradually diminished and after 33 hours, discontinued. Six hours after this, dyspnea, cyanosis and other signs of acute illness returned so that aureomycin had to be given. — A. Chest x-ray before therapy. — B. After administration of 313 mg. of cortisone over a period of 33 hours. — C. Temperature and pulse chart during hormone treatment, its withdrawal and subsequent aureomycin administration. Note that although there is some improvement in the x-ray shadow, this is comparatively mild, especially considering that photographic technique does not appear to have been quite comparable (compare bone shadows). Perhaps improvement in pulse, temperature and well-being is due to systemic rather than local effects of cortisone; the latter may have difficulty in penetrating a completely solidified pulmonary lobe. Nevertheless, principle of applying cortisone locally (to avoid systemic overdosage and save hormone) may be applicable to other pulmonary conditions and certainly proved efficient in ophthalmology (cf. below). (Courtesy of Drs. R. R. Margulis and G. S. Mackey, Henry Ford Hospital, Detroit.)

In one case of lupus erythematosus, treated with large doses of cortisone, congestive heart failure and pulmonary edema occurred.[33b] It would be interesting to determine whether such complications could arise as a consequence of the previously discussed renal actions of gluco-corticoids.

Rheumatic pneumonia. — A certain rather specific granuloma tissue tends to develop in the lungs of patients suffering from acute rheumatic fever. There is usually proliferation of the alveolar epithelium, dilatation of the capillaries, with accumulation of erythrocytes and mononuclear cells in otherwise typical broncho-pneumonic foci, brown induration of the lungs and fibrinoid necrosis of small vessels with thrombosis of larger vessels and recanalization of hemorrhagic infarcts. In addition there is marked inflammation of blood vessels and interstitial pneumonia. All these lesions are allegedly due to increased capillary permeability with escape of a serous exudate into the alveoli and the formation of hyalin membranes. Although none of these changes is in itself specific, their simultaneous occurrence is believed to be characteristic of rheumatic fever.[34] Rather similar changes are observed in the lungs of animals overdosed with LAP or DCA; [35] hence we regard rheumatic pneumonia as a disease of adaptation in the same sense in which other rheumatic changes were so interpreted.

Tuberculosis of the lungs. — It has long been known that the progress of pulmonary tuberculosis is accelerated by various incidental damaging agents, especially those causing loss of weight. This is in sharp contrast with certain other diseases — e.g., rheumatoid arthritis, psoriasis — which tend to undergo remissions under the influence of such stressors. It agrees with our interpretation of the "crossed resistance" phenomenon that ACTH and corticoids, which also induce remissions in rheumatoid arthritis or psoriasis, actually aggravate the course of pulmonary tuberculosis.[35a] Apparently here the gluco-corticoids promote the spreading of infection just as they enhance abscess formation in the lungs of rats, presumably because they interfere with the formation of an encapsulating fibrous scar.

The effect of stress and adrenal hormones upon the course of pulmonary tuberculosis clearly exemplifies the tenet that, in the diseases of adaptation, the G-A-S mechanism does not affect the causative pathogen (in this case: tuberculosis bacillus) directly, but alters the response of the host. Hence, in the final analysis, it will largely depend upon the defensive powers of the organism whether an infection with tuberculosis bacilli will cause the disease known as tuberculosis.

Tuberculosis of the larynx. — In four patients with laryngeal tuberculosis, treatment with ACTH (100 mg./day) was followed within 6-8 hours by amelioration and subsequent rapid disappearance of the systemic manifestations of acute illness. The fever disappeared, the voice improved, the patients felt much better and the previously positive cutaneous hypersensitivity to tuberculin became negative. At the same time the laryngeal edema receded, granulations became less elevated and were covered with epidermis. It is not yet known whether prolonged (or perhaps even permanent) remissions can thus be obtained, but "regardless of ultimate outcome, it has clearly been possible to abolish the evidences of tuberculous illness by the administration

[33b] Baehr B46308/50.
[34] Griffith et al. B45177/46. Maksimovich B44710/48.
[35] Selye 35935/ND.
[35a] Freeman et al. B46993/50.

of a substance which presumably acts solely on the host".[35b] This is in contrast with what we have said above about the effect of ACTH in pulmonary tuberculosis, but perhaps it depends largely upon conditioning factors (intensity of the infection, site of lesions, serological defense, diet, etc.) whether the diminution of defensive granuloma formation by ACTH is an advantage or a disadvantage for the patient.

Asthma. — As an essentially allergic disease, asthma must also be regarded as primarily a disease of adaptation. It is often elicited by non-specific (e.g., emotional) stress [36] and sometimes prolonged remissions can be obtained by non-specific therapy, for instance with insulin shock.[37] It is difficult to explain why in other cases shock therapy (e.g., electro-shock) actually aggravated the asthmatic state,[38] but this same inconsistency in the effect upon asthma has been noted in patients treated with ACTH. In most instances ACTH greatly ameliorates the asthmatic condition [39] but occasionally attacks of asthma are actually precipitated by this hormone.[40] Significantly, the urinary excretion of histamine and histidine rises in asthmatics, during remissions caused by ACTH.[40a]

The anti-asthmatic effect of the gluco-corticoids and of adrenergic substances [41] suggests that endogenous discharge of adrenal hormones may be a normal defense reaction against this abnormal or allergic response to certain agents. An inadequacy of this response may well play a rôle in the pathogenesis of asthma. These, and many other observations, induced several investigators to consider the possible relationship between asthma and the G-A-S.[41a]

Loeffler's syndrome. — The pathogenesis of this condition is still unknown, but it is pertinent to note that in one case ACTH caused a virtual disappearance of the eosinophils from the blood and of the pulmonary infiltrations as shown by x-ray photographs.[42] The possible rôle played by derailments of the G-A-S in the pathogenesis of this syndrome, has been analyzed elsewhere.[42a]

Theories and Summary of Observations Concerning the Participation of the Respiratory System in the G-A-S

During the shock phase of the A-R, there tends to be marked congestion of the lung with transudation of plasma into the interstitial spaces and the alveoli. This may progress towards frank **lung edema** and even **pneumonia.**

Conversely, during the counter-shock phase, even a lung edema produced by other agents is inhibited by the A-R. This is apparently a phenomenon of **"crossed resistance".**

[35b] Tompsett et al. B47903/50.
[36] Cohen and Holbrook B40717/47, Halliday B44599/43, **B46202/48.**
[37] Anonymous B44407/47, Godlowski B36136/46.
[38] Cohen and Holbrook B40717/47.
[39] Anonymous B45084/50. Astwood et al. B47853/50, Bordley et al. B44913/49, Elkinton et al. B46985/50, Spies and Stone B45101/50, Randolph and Rollins B44574/50, Randolph and Rollins B46990/50, B46521/50. Rose B46991/50. Rose et al. B45103/50.
[40] Rose et al. B45103/50.
[40a] Rose et al. B47897/50.
[41] Levy and Seabury B45905/48. Selye **94572/49.**
[41a] Randolph and Rollins B46521/50, Rackemann B45439/47.
[42] Herbert and Rose B44963/49. Rose B41837/49.
[42a] Rackemann B45439/47.

Acute overdosage with adrenaline can cause fatal lung edema. Prolonged overdosage with mineralo-corticoids likewise tends to cause capillary leakage in the lung. Both types of hormones can create a predisposition to the formation of lobar pneumonia.

After pretreatment with adrenaline, the tendency to develop lung edema is diminished, but since a similar inhibition is also seen during the counter-shock phase following exposure to other stressors, this is presumably merely a manifestation of "crossed resistance". Here, as in so many other instances of crossed resistance, the gluco-corticoids appear to play an important rôle; they likewise tend to counteract the tendency to form lung edema and even exert a curative effect in the case of an already formed pneumonia.

The **reticulo-endothelial cells** of the lung, especially the histiocytes which line the alveoli, proliferate actively and become unusually phagocytic during the A-R. This R.E.S. stimulation largely depends upon the integrity of the adrenal-cortex and is presumably mediated through the gluco-corticoids. During the resistant stage the phagocytic cells of the lung return to a comparatively quiescent condition. The increased phagocytic activity during the A-R may represent an effort on the part of the organism to combat the tendency to develop pneumonia as a result of transudation and exudation of blood-constituents into the alveoli. It may also help to free the blood of particulate matter (e.g., bacteria).

Among the pulmonary **diseases of adaptation,** we particularly mentioned *lung edema, pneumonia* (especially "rheumatic pneumonia"), *tuberculosis of the lungs and asthma.* With the possible exception of lung edema, none of these conditions result directly from exposure to stress, but the resistance of the lung to specific pathogens (e.g., allergens, micro-organisms) is greatly dependent upon the G-A-S mechanism and particularly upon adrenal hormones. Hence it largely depends upon the defensive production of corticoids (and to a lesser extent of adrenergic substances) whether a potential pathogen actually produces disease or is tolerated without difficulty.

MUSCULAR SYSTEM

Systemic Stress

A decrease in the muscular tonus and a ready fatigability have long been recognized as **characteristic** manifestations of the shock phase during the A-R.[1] The great lassitude and low muscular efficiency is one of the many points of similarity betwween the shock phase of the A-R and the condition of adrenal insufficiency.

On the other hand, if rats are exposed to sudden but mild variations in **temperature** (cold or heat), their ability to perform muscular exercise is allegedly increased immediately after the recovery period. At this time, they show the fall in the blood-lymphocyte count characteristic of the A-R. In attempting to interpret the mechanism of this response, it has been stated that "one must first of all think of a hyper-activity of the adrenal cortex, due to the development of a general-adaptation-syndrome".[2]

In animals, **anaphylactic reactions** tend to produce granulomatous cellular infiltrations in the skeletal muscles which are not unlike those seen in the heart.[3] These resemble the cardiac lesions caused by stress, LAP, DCA, desoxo-cortisone or the "endocrine kidney" and may be related to the humoral changes of the resistant phase.

Severe **carbon monoxide** intoxication often causes a non-specific type of polymyositis, as well as degenerative lesions and calcification of muscle fibers in man. This is accompanied by skin changes similar to those seen in burns, and renal lesions characteristic of the crush syndrome. Both the cutaneous and the muscle changes are especially severe in regions exposed to mechanical trauma (e.g. pressure).[4] The possible participation of the G-A-S mechanism in this response remains to be explored.

Intense muscular atrophy and weakness is also characteristic of prolonged **starvation** and severe malnutrition in man.[5] It may be accompanied by muscular pain and histologic signs of degeneration (such as hyalin granular disintegration of the cytoplasm, loss of nuclei, calcification) and inflammatory infiltration in the muscle stroma.[6]

It remains to be shown whether the inflammatory and fibrous changes in the skeletal (and cardiac) muscles of **vitamin-E** deficient rabbits[7] are related to the muscle granulomas produced by mineralo-corticoids.

The striated muscle of vertebrates (e.g., frog) shows a progressive, irreversible contraction and loss of excitability following treatment with various stressors such as **drugs** and **ionizing radiations.** This is known as the "Lundsgaard phenomenon".[7a] It is probably the result of a derangement in glucose

[1] Ratsimamanga and Buu-Hoi B33923/47, Selye A9210/38, 36030/36.
[2] Dureuil and Ratsimamanga B28532/48.
[3] Betz B26164/48.
[4] Hedinger B38133/48.
[5] Brozek et al. B23241/46.
[6] Gsell B27611/48, Uehlinger B27612/48.
[7] Bragdon and Levine B44737/49.
[7a] Lecompte B46839/49, B46819/49, Bacq B46824/49, Bacq et al. B46814/49.

metabolism. The fact that so many different agents can elicit this phenomenon suggests that the G-A-S may be involved in its genesis, but further investigations will be necessary to prove this.

Stimuli Influencing the Response of the Muscular System During the G-A-S

Hypophysectomy causes muscular atrophy and weakness in various animal species.[8] In the hypophysectomized rat, there is a decline of the amplitude and area of muscle-action-potential during repetitive indirect stimulation. The decrease of muscle-action-potential parallels the decrease of the magnitude of contraction. "It is inferred that the neuro-muscular fatigue occurring in hypophysectomized animals is due to both a moderate dysfunction of the muscle and a marked dysfunction of the nerve element (either nerve or myoneural junction)".[9]

Crude **anterior-lobe extracts** allegedly increase the muscular efficiency of rats simultaneously with the resulting adrenocortical enlargement. This effect is demonstrable even in certain strains of rats which appear to be resistant to the A-R, in that they do not respond with the usual cortical hypertrophy. It was concluded that a hereditary defect in the stress-response of the pituitary may cause derangements of the A-R, which can be rectified by anterior-lobe extracts.[9a] Since these experiments have been performed on a very small series of animals, they require confirmation.

Adrenalectomy is notoriously conducive to intense muscular weakness and ready fatigability. If rats are previously *trained,* they retain much of their ability to perform intense muscular exercise after their adrenals are removed. "This shows conclusively that it is not the actual presence of adrenal hormones which is needed for the performance of muscular work but that the adrenals are mainly needed during the process of adaptation".[10] Of course, as adrenal insufficiency progresses, even trained animals will eventually suffer from the progressive hypocorticoidism.

Immediately after *unilateral adrenalectomy,* the muscular efficiency of the rat falls, but a few days later it rises above normal. "The increase in the resistance to fatigue which develops a few days after unilateral adrenalectomy, is ascribed to a hyperfunctioning of the other adrenal, comparable to that occasioned by the alarm-reaction".[11]

Under ordinary conditions isolated *removal of the adrenal-medulla* does not noticeably impair the muscular efficiency of the rat[12] or dog.[13] Hence, the emergency secretion of adrenaline by the adrenal-medulla itself is not a very important factor in the maintenance of muscular efficiency.

Nevertheless, both the cortex and the medulla appear to influence muscular contraction as shown by experiments in which extreme fatigue was induced by direct faradic stimulation of the muscles. Here, the work output of adrenal-demedullated rats decreased more rapidly than that of normal controls, and subcutaneous injection of adrenaline significantly improved the rate of work. Under the same conditions, it was noted that in completely adrenalectomized

[8] Selye **94572/49.**
[9] Torda and Wolff B36305/49.
[9a] Nigeon-Dureuil and Ratsimamanga B46555/49.
[10] Selye A8160/36.
[11] Ratsimamanga B30156/47.
[12] Harris and Ingle A34226/40.
[13] Campos et al. B33543/29.

rats, both *gluco-corticoids* and (to a much lesser extent) *adrenaline* improved muscular efficiency, but simultaneous treatment with both these preparations was necessary to obtain optimal results in acute exhaustion.[14] In the case of prolonged work the rôle of adrenaline is probably negligible in comparison to that of the gluco-corticoids.[15] The improvement in work performance by adrenaline is not abolished by complete evisceration, hence it is due to extrahepatic actions of this hormone.[15a]

The ability of rats to perform muscular work in the "swim test" is greatly increased by *calcium pantothenate.*[15b] The muscular effect of the vitamin is therefore not mediated through the hypophysis-adrenocortical mechanism.

In intact rats, even large amounts of a **gluco-corticoid**-containing adrenal extract did not improve muscular efficiency above normal.[16] The work performance of rats kept under reduced *oxygen tension,* was also not improved by cortical extract (or DCA).[17] On the other hand, in rats in which an A-R was produced by exposure to *heat,* the injection of a cortical extract increased muscular efficiency as judged by their ability to swim. It was concluded that "the cortical hormone administered to an organism during the A-R is favorable for the development of the phenomena designated as counter-shock".[18]

Rats chronically overdosed with **mineralo-corticoids** (e.g., DCA) have a greatly reduced muscular efficiency as judged by experiments in the revolving drum.[18a] On the other hand, it has been claimed that patients suffering from various acute infections, exhibit increased muscular efficiency (Mosso's ergograph), when given moderate amounts of DCA.[18b]

Physostigmine allegedly increases the work performance both of normal and of adrenalectomized rats, indeed, even when the sciatic nerve has degenerated after transection. *DFP* has a similar effect in adrenalectomized rats but *prostigmine, acetylcholine* and *adrenaline* were ineffective. "The results suggest that an impaired neuro-muscular transmission, either as the result of impaired acetylcholine metabolism or an abnormal sensitivity to acetylcholine, might be the cause of the asthenia after adrenalectomy".[19]

It must also be kept in mind that certain **testoids** stimulate the growth of the skeletal muscles as shown by observations in the mouse. This property does not run strictly parallel with the renotrophic action, but contributes to the general protein-anabolic effect of such compounds.[20]

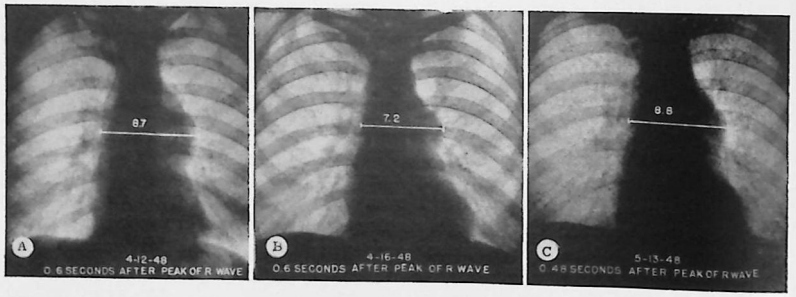
Muscle Diseases of Adaptation

There is some evidence that derangements of the G-A-S mechanism may play a rôle in the pathogenesis of various muscular diseases. Several of these are discussed in other chapters, to which the reader is referred, for instance: **dermatomyositis** (cf. skin), **cellulitis** (cf. rheumatic diseases) and the usually perivascular, **granuloma nodules in skeletal muscles associated with rheumatoid arthritis** (cf. arthritis). It is very probable that these lesions, as well as the so-called **"muscular rheumatism"** are closely related to the granulomas seen in the cardiovascular system throughout the body as part of the hyalinosis

[14] Ingle and Lukens A36631/41.
[15] Ingle and Nezamis B37290/49.
[15a] Ingle and Nezamis B46482/50.
[15b] Dumm and Ralli B47123/50.
[16] Ingle et al. B36859/49.
[17] Dorrance et al. A38460/42.
[18] Dureuil et al. B28531/48.
[18a] Selye 35935/ND.
[18b] Romero-Velasco et al. B46051/49.
[19] Overbeek B36380/49.
[20] Kochakian 98428/47.

and fibroplasia typical of rheumatic-allergic syndromes in general. Allegedly, ATP-treatment is beneficial in various types of muscular rheumatism,[20a] but this requires confirmation.

Myasthenia gravis may also be related to a derangement of the hypophysis-adrenal system. It often occurs in combination with thymus tumors and tends to disappear upon ablation of the thymic neoplasm. In thyrotoxicosis, simultaneously with the proliferation of the thymico-lymphatic apparatus, muscular changes (very similar to myasthenia gravis) have often been noted.[21] After treatment with *ACTH*, the symptoms of myasthenia gravis tend to improve and the characteristic anomalies of the electromyogram may disappear. Simultaneously, there is an increase in the normal ability of serum to support acetylcholine synthesis. The resulting incomplete remissions are often quite long lasting. During the course of ACTH administration, there may be an actual aggravation of the muscular weakness, but this has been ascribed to incidental changes in electrolyte, carbohydrate and glutathione metabolism.[22]



Effect of ACTH upon thymic tumor in myasthenia gravis. Roentgenograms made during diastole. — **A.** Before treatment. — **B.** Immediately after completion of treatment with ACTH. — **C.** Four weeks after discontinuation of treatment. Note that mediastinal mass greatly decreased under the influence of ACTH, but regained its original size within a month after treatment was discontinued. (After Soffer et al. B46442/48.)

Only one myasthenic patient has been treated with *cortisone*. Here there was no definite improvement.[23]

Two patients with **myotonia atrophica** recorded some subjective improvement in symptoms following ACTH administration but this was not accompanied by any increase in muscular function as judged by objective tests.[24]

Two patients with **progressive muscular dystrophy** of the facio-scapulo-humeral type did not appear to benefit from ACTH.[25]

The possible rôle of the G-A-S in the so-called **asthenic adynamic syndrome** has been discussed,[26] but pertinent data do not yet suffice to draw definite conclusions.

[20a] Lövgren B41823/44.
[21] Selye **94572/49.**
[22] Soffer et al. B46442/48. Torda and Wolff B37750/49, B39092/49, B46999/50.
[23] Hench et al. B27892/49.
[24] Milhorat B47000/50.
[25] Milhorat B47000/50.
[26] Bansi and Schwarting B46780/50.

Summary of Observations and Theories Concerning the Participation of the Skeletal Musculature in the G-A-S.

In summary, it may be said that during the A-R (and of course, also in the stage of exhaustion) the morphologic development and functional activity of the musculature are subnormal. Complete **adrenalectomy** produces essentially similar effects, but isolated ablation of the adrenal-medulla has little, if any influence upon muscular structure or activity. Substitution therapy with **corticoids** (especially gluco-corticoids) is highly effective in augmenting the work-capacity of the adrenalectomized animal, but has little if any effect in the presence of normal adrenals. Apparently in healthy individuals, endogenous corticoid production is virtually optimal. There is some suggestion that under stress, corticoid treatment may improve muscular efficiency.

Testoids increase muscular development due to a special musculotrophic effect. The latter is particularly evident if we compare the muscular development and strength of castrate males or females with that of intact males.

All these factors probably influence the response of the muscular system during the G-A-S.

Among the muscle diseases in the pathogenesis of which derailments of the G-A-S mechanism appear to play an important rôle, we mentioned: **dermatomyositis, fibrositis, the granulomatous lesions in skeletal muscles which accompany rheumatoid arthritis** and the clinical syndrome of **"muscle rheumatism"**. The **muscular weakness of hypocorticoidism** and the syndrome of **myasthenia gravis** may also be related.

NERVOUS SYSTEM

The nervous system is particularly sensitive to the effects of systemic stress. During a severe A-R, intense depression of the nervous system is one of the most striking signs of profound shock. Indeed upon more chronic exposure to systemic stress both the central and the autonomic nervous systems show morphologic and functional derangements. These are due to the fact that nervous and mental processes are largely dependent upon the soma and can readily be influenced by many of the biochemical changes which occur during the G-A-S (e.g., muscular paralysis elicited by hypokalemia; psychic disturbances caused by hypoglycemia, sodium depletion, or variations in the B.M.R.).

Conversely, the nervous stimuli elicited by exposure to stress influence the soma and neurogenic stressors (pain, fear, frustrations) are especially potent alarming stimuli. Hence the psychosomatic interrelations are extremely complicated during the G-A-S.[1] It has been suggested that even permanent mental derangements can result from maladaptation to severe systemic stress (cf. Neuropsychiatric Diseases of Adaptation).

It would certainly be a most fascinating task to re-examine certain fields of normal and pathologic neuropsychiatry from the viewpoint of the G-A-S. Among the many nervous and mental derangements that can be elicited by exposure to stress, which are due to specific actions of the evocative agent and which to stress as such, that is to the G-A-S ? Furthermore, among the changes traceable to stress as such, what is due to damage and what to normal or abnormal defense against damage ? To illustrate specific subjects to which we feel this kind of study could be profitably applied, let us mention for instance, the well known effect of "shock" upon conditioned reflexes and schizophrenia, the influence of fatigue and exhaustion (no matter how produced) upon mental processes and the production of such organic changes as vascular damage with edema of the brain by physical or chemical stressors. By demarcating the rôle of mere systemic stress in the genesis of these and cognate phenomena, we could hope to come much closer to a real understanding of many nervous adjustments and maladjustments. This would, in turn, undoubtedly teach us a great deal about ways to make better use of physical and pharmacologic agents in the treatment of psychosomatic derangements.

Unfortunately this aspect of the G-A-S has been badly neglected up to now. Few investigators — and the writer of these pages is certainly not one of them — possess the understanding of biochemical, morphologic and psychologic problems necessary to correlate all these fields. Hence our discussion of pertinent problems will necessarily be patchy and largely based upon scattered observations, most of which have not been interpreted from the viewpoint of the G-A-S by those who described them. Nevertheless, in view of the great practical importance of this subject, we felt that we should attempt at least a preliminary outline of it — no matter how dilettantish it may be.

[1] Selye and Fortier **B41765/49.**

Systemic stress

Characteristic response. — The changes in the nervous system which are characteristic merely of exposure to systemic stress as such, can be logically surveyed only if we keep in mind that they — as all other manifestations of the G-A-S — evolve in three distinct stages: the A-R, the stage of resistance and the stage of exhaustion. During the acute initial period of the **A-R** the most characteristic *functional* changes are tension and excitement if the stress is mild, depression of the central nervous system and shock if it is intense. In either case there is loss of appetite and libido as well as stimulation of the autonomic nerves with a great predominence of the adrenergic system (adrenaline and nor-adrenaline liberation from the medulla and from autonomic nerve endings).

If the stress is severe the functional changes are usually accompanied by manifest *morphologic* lesions such as edema and congestion of the brain, petechial hemorrhages especially in the meninges and degenerative changes in ganglion cells. This is later accompanied by neuroglia proliferation in central and peripheral ganglia, followed by dissolution of ganglion cells through the process of "neuronophagia" or "neuronocytolysis".[2] The permeability of the meninges is also increased and this facilitates the penetration of blood constituents into the cerebrospinal fluid.

During the **stage of resistance** most of these manifestations disappear, although a certain degree of sympathetico-tonus tends to persist. Furthermore, while resistance to the evocative stimulus rises far above normal the adaptability of the nervous system to other agents is greatly diminished. This may lead to maladaptation and psychosomatic disease. The appetite may be normal, but is often increased. Libido is usually subnormal.

Finally, during the **stage of exhaustion,** the changes in the nervous system are mainly characterized by a return of those manifestations which had been present initially during the A-R. However, by this time arteriosclerosis of the brain-vessels has usually developed and further exposure to stress no longer leads to adaptation with resistance but to a final breakdown and death.

Trauma. — In traumatic shock the meninges become congested. Often there are small hemorrhages and brain edema, so that the picture is essentially that which we previously described as characteristic of the shock phase produced by any other severe alarming agent.[3]

Some investigators believe that chromatolysis and other pathologic alterations in ganglion cells are characteristic of shock produced by trauma or other stimuli.[4] Of course any condition causing local anoxia (e.g., circulatory disturbances or compression of the brain by edema), may lead to degenerative changes and even pyknosis in nerve cells, but such lesions must be evaluated with care since they are closely simulated by postmortal autolysis.

Immediately after subtotal pancreatectomy in rats (which had a free choice between various diets) the appetite for a high carbohydrate ration rose and less protein was ingested. However, following recovery from the operation, the appetite for carbohydrate decreased. Hence, the authors considered the possibility that the preference for carbohydrate may have been due to the

[2] Kuntz and Sulkin B44954/47.
[3] Moon **A16304/38.**
[4] Crile and Lower 97296/15.

A-R caused by the intervention, rather than to pancreatic insufficiency [5] as such. Unfortunately no control experiments were done with other types of operations.

Hemorrhage. — After hemorrhage the autonomic readjustments are essentially similar to those elicited by other stressors.[6] The electroencephalographic changes caused by hemorrhage are probably also non-specific and primarily due to brain anoxia.[7]

Burns. — Burns notoriously cause intense, functional nervous derangements such as cramps, extreme excitation or deep apathy and depression. Macroscopically the brain usually exhibits congestion with edema and the intracranial pressure tends to rise. In severe cases there may be signs of a beginning encephalitis with leucocytic infiltrations around the capillaries, degenerative changes in ganglion cells [8] and other lesions which have been interpreted as manifestations of a "serous inflammation".[9] Allegedly the degenerative changes in ganglion cells are most prominent in the hypothalamic nuclei.[10] In order to combat dehydration it is customary to give copious intravenous infusions in burned patients; such therapeutic procedures may also contribute to the characteristic brain edema of such patients.[11]

Congestion, edema and hemorrhages in the brain are often particularly conspicuous in men who died from **heat-stroke.** Acute swelling, shrinkage or pyknosis of cells has also repeatedly been reported, but some investigators regard these as postmortal artefacts. All these changes are so similar to those produced by other types of intense acute stress, that they may well be non-specific manifestations of the G-A-S. Only the great predominance of hemorrhagic lesions (some authors speak of "brain purpura") deserve special mention because of their unusual intensity in the case of exposure to heat. Perhaps they result from the thrombocytopenia, which can cause a severe clotting defect in such patients. If death occurs only after several days, gliaproliferation, with phagocytosis of degenerating nerve cells (e.g., Purkinje's cells) are often prominent. Such morphologic lesions have been held responsible for the acute confusional state and sometimes even permanent damage to the central nervous system, which occur in patients who suffered a severe heat-stroke.[12]

Exposure to **cold** causes essentially similar changes in man, especially hyperemia, edema and hemorrhages.[13]

Since the composition of the diet greatly influences resistance and the development of the G-A-S in general, it is interesting that exposure to extremes of temperature distinctly affects the appetite. Thus in one series of experiments, rats kept in the cold tended to select fat, while those exposed to heat preferred carbohydrates and developed a great appetite for salts. As judged by comparison with rats which were not allowed free food-selection, it appears that the voluntarily chosen foods are actually favorable for resistance to low and high temperatures respectively.[14] Experiments on mice showed that total food consumption increases at low (10°C) and decreases at high (29°C) temperatures. However, here these changes were due almost exclusively to

[5] Covian B31713/48.
[6] Gellhorn **B27006/43.**
[7] Davis et al. B44782/49.
[8] Harkins **82895/42.** Hilgenfeldt **38008/36.**
[9] Eppinger **B37085/49.**
[10] Walker and Shenkin 89895/45.
[11] Humblet and Barac B24102/46.
[12] Haymaker et al. **B37920/47.** Malamud et al. **B18019/46.**
[13] Rewerts B38134/48.
[14] Dugal et al. 93308/45.

an increase or decrease in the intake of carbohydrate. It was suggested that changes in thyroid function may play a rôle in this instance, since exposure to cold augments thyroid hormone formation.[15] The latter view receives support from experiments on thyroxin-overdosed mice which developed the same food selection pattern as those exposed to cold.[16] Since all species do not metabolize large amounts of fat with equal facility it is quite possible that species differences may account for the discrepancies in the above results obtained with rats and mice respectively. In any case the observations show that extremes of temperature exert a pronounced influence upon the appetite and that the resulting changes in food selection are presumably useful for adaptation.

Ionizing radiations. — The central nervous system is singularly resistant to **x-irradiation,** while the autonomic nerve-fibers are somewhat more sensitive.[17] The meninges are rather susceptible to x-ray damage and upon irradiation may exhibit inflammatory lesions with a subsequent increase in cerebrospinal fluid pressure.[18]

In **atomic bomb** casualties meningeal and brain hemorrhages often formed part of the general purpuric syndrome.[19]

Electric injury. — Repeated electro-shock impaired the ability of rats subsequently to learn a "Stone multiple-T" maze.[20] Similarly the performance (judged by an increase in running time and in errors) of rats which had previously learned to find their way through a "Warner-Warden" maze, was impaired by subsequent electro-shock treatment. At the same time the emotionality of the animals increased with the number of shocks (shown by the number of defecations in an open field situation, reaction to noise and audiogenic seizures). "In a second series of experiments designed to study the effects of a high- and low-protein diet on learning and shock sensitivity, similar substantiation was seen for the G-A-S hypothesis" ... "on a high-protein treatment, error scores and activity showed impairment as compared with the control diet group".[21] Incidentally almost the same results were obtained in another experimental group in which the stressors used were audiogenic stimuli and insulin.[22]

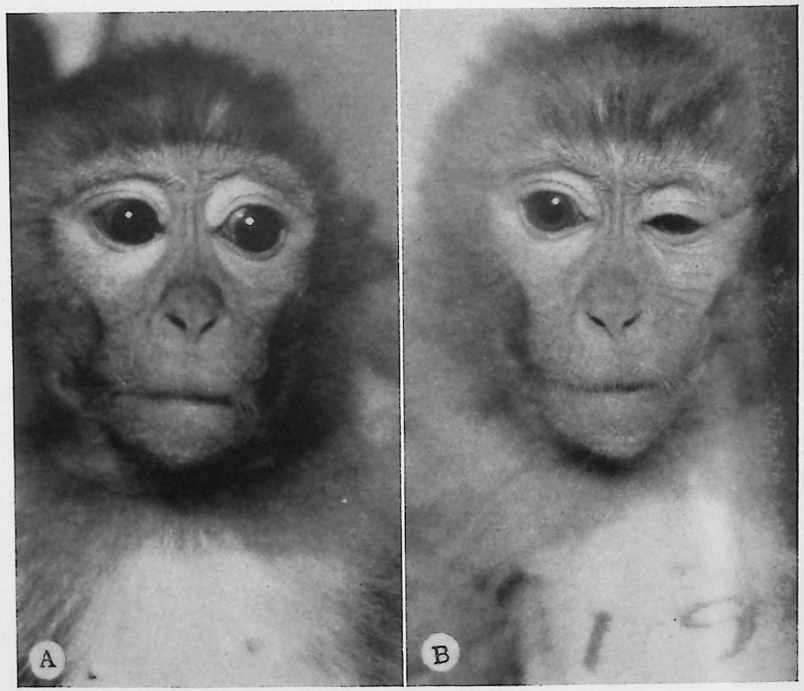
A rather similar experimental investigation revealed "that a controlled series of 25 electroshock convulsions is followed by a significant impairment of learning ability immediately after the shock series and that this impairment is still evident 30 days following treatment. In the latter case, the magnitude of the impairment is not as great as that which is found immediately after the shock series. A decrement in retention also appears 60 days after the convulsive series. This impairment is at least as great as that which was demonstrated immediately after the convulsion". These, and several other similar observations compiled from the literature, were ascribed to the development of a G-A-S and its characteristic three stages.[23]

Nervous stimuli. — The fact that nervous stimuli are particularly effective in eliciting the somatic manifestations of the G-A-S has previously been mentioned in other connections (cf. Stressors, p. 34). Unfortunately little attention has been given to the psychologic disturbances which may result from adapta-

[15] Donhoffer and Vonotzky B1733/47.
[16] Donhoffer and Vonotzky B1734/47.
[17] Ellinger **68685/35.** Prosser et al. B26618/47.
[18] Ellinger **68685/35.**
[19] Liebow et al. **B41902/49.**
[20] Eriksen et al. B37345/48.
[21] Riess B35595/48.
[22] Riess B37365/47.
[23] Braun et al. B35551/49.

tion to systemic stress as such. As we have said in the introductory remarks to the present chapter, this lack of integration is largely due to the fact that comparatively few physiologists, familiar with the somatic aspects of the G-A-S, are sufficiently trained in the methods of the psychologist and vice versa. However, even the few pertinent studies which have been undertaken up to now on the "psychophysiology of stress",[23a] suffice to suggest that this is perhaps one of the most promising fields for the clinical application of the G-A-S concept.

Cannon[24] showed the importance of the **sympathetico-adrenal discharge** in emotion. Many other investigators[25] published evidence indicating that



"Fright reaction" in the monkey. — **A.** Facial expression following section of the left facial nerve. Note the slight deviation of the nostrils away from the side of the paralysis; left palpebral fissure is slightly greater than the right. — **B.** "Fright reaction", that is, contractions in the denervated facial muscles following fright. Note the twisting of the nostrils and mouth to the left, sphincter-like constriction of the palpebral fissure and increased wrinkling of the left side of the face. Similar contractions are obtained by parenteral administration of acetylcholine in the denervated muscles, hence it was suggested that during fright the parasympathetic, as well as the sympathetic, nervous systems discharge their humoral mediators into the blood. (After Bender A34107/38.)

[23a] Darrow and Henry B47919/49.
[24] A19828/29, B14905/39.
[25] Bekhterev B36599/28, Bender A34107/38, B27005/38, v. Bergmann B36600/36, Danielopolu 99409/43, B38202/48, Gellhorn et al, 79539/40, Kling B36598/33.

a **parasympathetic cholinergic discharge** is also a characteristic — though perhaps less important — autonomic response to the nervous stress.

Pertinent data will be found in the section on the "Neuro-psychiatric Diseases of Adaptation" (cf. neuroses, psychoses). Here we shall merely mention a few particularly relevant observations on animals in order to outline the great practical possibilities of this particular aspect of the G-A-S, in the hope that it will encourage further research in this field by the select few whose training enables them to undertake it.

Interestingly, in animals a typical **experimental neurosis** can be produced by nervous stress. In sheep, if conditioned reflex experiments are so arranged that the animal is called upon to solve a problem beyond its capacity (e.g., to distinguish between two closely similar conditioned stimuli) the resulting frustration can lead to an apparently permanent neurosis. This may manifest itself by extreme excitement, uncoöperative behavior and spontaneous, nervous twitching movements.[26] It is particularly interesting from the G-A-S point of view that cortical extract allegedly exerts a therapeutic effect in these experimental neuroses (see below).

It has been shown furthermore in rats that conditioned reactions, which had been inhibited by lack of reinforcement, can be re-established without further training by merely subjecting the animals to electric (or insulin) shock. Such restitution of inhibited conditioned reactions is not accompanied by any change in the response of positively established conditioned reactions: hence it was concluded that electro-shock acts specifically on inhibited conditioned reactions without causing dedifferentiation.[27]

It is extremely difficult to produce intense systemic stress by any alarming stimulus without at the same time causing some nervous stimulation; conversely, no severe nervous or emotional stress fails to elicit somatic manifestations of the G-A-S. For the interpretation of all these neuropsychiatric findings, it would be of the greatest importance to devise methods which would permit us to delimit the specific effects of nervous stimuli from their mere non-specific stress effects.

As judged by **electroencephalographic** studies on animals, the electrical activity of the brain is greatly diminished during spinal shock while the reflexes are abolished.[28] This is probably also largely a non-specific stress effect.

Muscular work. — The effect of muscular exercise upon the nervous system has not yet been studied in relation to the G-A-S. Congestion and sometimes edema of the brain has been noted in rats forced to perform excessive work in a revolving cage.[29] It is perhaps also pertinent that extreme physical exhaustion in athletes may lead to a "cardiovascular syncope" with grave secondary effects upon the nervous system. On occasion this has been known to precipitate epileptic fits, hysteric manifestations, muscle cramps, etc.[30]

Anoxia. — Acute anoxia also produces congestion and edema of the brain, for instance in the rat.[31] In the dog anoxia causes a progressive rise in the cerebrospinal fluid pressure, although the initial rise in blood-pressure is followed by hypotension.[32] The "postanesthetic encephalopathy" of man is probably likewise due to transitory anoxia.[33]

[26] Liddell et al. 62127/35.
[27] Gellhorn B35668/45, B23057/46.
[28] Horsten B37344/48.
[29] Selye 35935/ND.
[30] Jokl B19917/47.
[31] Thorn et al. B335/45.
[32] Scano B37538/47.
[33] Seldon et al. B37818/49.

Extensive studies concerning the functional and morphologic changes produced by anoxia and CO_2-poisoning in animals and man [34] showed that these (edema, hemorrhages, nerve cell degeneration, glia proliferation, liquefaction necrosis, meningeal congestion) are very similar to those elicited by other stressors. Therefore, it is difficult, if not impossible, to state what is specifically due to anoxia and what to the accompanying systemic stress. To answer this it would be imperative to compare the anoxic nervous system not only with the normal control, but also with that of a similar individual exposed to the same intensity and duration of a systemic stress produced by other alarming stimuli.

Diseases. — The frequent occurrence of various neuralgias, especially lumbago, in patients with **focal infections** has repeatedly been emphasized.[35] It is perhaps even more pertinent to the problem of the G-A-S that a so-called "secondary encephalitis" may occur in the course of almost any acute **systemic infectious disease** (particularly the exanthemata such as *chickenpox, scarlet fever, measles*) as well as *mumps* and *pertussis*. This so closely resembles the encephalopathy seen in intoxications with various drugs [36] that its non-specificity is hardly in doubt.

A recent study of patients suffering from *Rocky Mountain spotted fever* showed that, here again, encephalitic manifestations often accompanied by an increased cerebrospinal fluid pressure are common.[37]

In *epidemic typhus* especially severe lesions are frequently found in the hypothalamus and the stalk of the pituitary.[38] Here, as in *typhoid fever*, the very name of the disease ("typhos" means stupor) has been chosen to emphasize the involvement of the central nervous system. The French school sometimes uses the expression "encéphalite a minima" or "typhoid encephalitis" to designate the cerebral changes accompanying this disease in which allegedly the diencephalic and hypothalamic nuclei are again particularly affected.[39]

The pathogenesis of these changes is not known, but their similarity to the brain-lesions produced by corticoid overdosage or the endocrine kidney (cf. below) is rather suggestive (cf. also "Encephalitis" in the section "Neuropsychiatric Diseases of Adaptation").

Considerable emphasis has been placed upon the fact that in acute infections, especially those accompanied by fever, the **permeability of the meninges** is greatly increased. This change is largely non-specific since it also occurs in anaphylactic and peptone shock. It has been suggested that the beneficial action of malaria-therapy in mental disease may be related to this response.[40]

In many infectious diseases (e.g., tuberculosis, pneumonia) of man and in experimental animals treated with diphtheria toxin there is marked hyperplasia of the **neuroglial supporting tissue in autonomic ganglia.** This is often accompanied by dissolution of ganglion cells due to "neuronocytolysis" or neuronophagia by the glia.[41]

Serologic reactions. — An acute allergic disseminated encephalo-myelitis can be produced in various animal species by the injection of brain-antigen

[34] Chornyak B26343/48, **B37366/38,** Gellhorn **B27006/43,** Gellhorn and Heymans B23158/48, v. Lière **B26199/42,** Meessen B38008/47, B37949/48.
[35] **Goia B25571/46.**
[36] Adams and Weinstein B29390/48, Fattovich B41790/47, Musser 88056/45.
[37] Kelsey and Harrell B24821/48, Harrell et al. B24809/47.
[38] Radnay B38067/47.
[39] Tardieu B23845/42.
[40] Eppinger B37085/49.
[41] Kuntz and Sulkin B44954/47.

especially if combined with "adjuvants".[42] This has been compared to human encephalomyelitis, but "in considering these problems, the fact is worth stressing that there are no neuropathologic changes which can be regarded to be specific of allergic reactions".[43] The morphologic changes in the experimental allergic encephalomyelitis have been ascribed to antigen-antibody reactions within the central nervous system itself. However, structurally they resemble the lesions in the central nervous system which are produced by various alarming stimuli, corticoids or the "endocrine kidney", hence it might be rewarding to seek a common denominator.

Drugs. — We have already mentioned that various drugs (e.g., lead, carbon monoxide) may produce an encephalopathy very similar to the "secondary encephalitis" which develops in the course of many infectious diseases.[44] **Arsenicals** are especially effective in this respect.[45]

In connection with "toxic" brain lesions potentially related to the G-A-S, let us add here that in dogs, subcutaneous injection of a **hypertonic NaCl** solution caused congestion and petechial hemorrhages in the meninges and in the brain substance itself. At the same time various, apparently degenerative, changes occurred in the nerve cells, although their significance was questioned "since post-mortem changes occur with great rapidity in tissues of the nervous system". Hypertonic NaCl solutions notoriously cause dehydration with shrinkage of the brain, hence the usual brain-edema, characteristic of exposure to stress, was not manifest in this particular instance.[46]

Diet. — Non-specific damage by inadequate diets undoubtedly also affects the nervous system through reactions which are, at least partly, dependent upon the G-A-S. Special emphasis has been placed upon certain personality changes during **fasting,** which were attributable to mild hypoglycemia such as occurs in the initial phase of the A-R and in the stage of exhaustion. "The minor stages of hypoglycemia then have particular bearing on the problem of fatigue. The individual dislikes to think, to talk, or to move. He has great difficulty in making required decisions, and his mood varies between apathy and irritation, even if fatigue is not specifically reported".[47] As we shall see later, severe hypoglycemia, such as is caused by insulin overdosage, may lead to much more pronounced functional derangements and even to grave morphologic changes in the brain.

In the severely undernourished concentration camp inmates examined during World War II, it has been noted repeatedly that neuritis and certain mental derangements (particularly apathy, melancholia, extreme egocentricity, hallucinations and deliria) tend to develop.[48] In a group of healthy young males, who voluntarily submitted to prolonged semi-starvation, very similar emotional and personality symptoms appeared. These were called "semi-starvation neurosis" in order to emphasize the close relationship to those forms of "experimental neurosis" which can be produced in animals by frustrating conditioned-response experiments.[49] In this group all subjects eventually developed emotional and

[42] Hottle et al. B43454/49, Kabat et al. B41771/47, Koprowski and Jervis B28603/48, Thomas et al. B47901/50.
[43] Jervis and Koprowski B29463/48.
[44] Musser 88056/45.
[45] Byrne B38206/47, Morandini B44529/47.
[46] Davis A37428/41.
[47] Bartley and Chute B34753/47.
[48] Beeck B46648/49, Brozek et al. B23241/46, Gsell **B27611/48.**
[49] Brozek and Erickson B40131/48.

personality symptoms of "semi-starvation neurosis" and some manifested even more severe changes such as hysterical responses and paresthesias, "the situation was essentially similar to the differential response of an apparently homogeneous population to any other stress".[50] "Blackouts" and "light-headedness" on sudden rising, were a universal complaint and occasionally sensations of "faintness" and "dizziness" were reported to occur even without any relationship to postural changes.[51]

Among the neuropsychiatric disturbances caused by under-nutrition the loss of libido and potency — for instance among under-nourished prisoners of war — have already been mentioned in the section on the endocrine organs. It is noteworthy that the classic manifestations of the G-A-S (e.g., adrenal enlargement, thymico-lymphatic atrophy, gastrointestinal ulcers) were always present in undernourished patients who came to autopsy after they developed such neuropsychiatric symptoms.[52]

Experiments on young rats showed that undernourishment delays the myalination of the optic tracts and nerves.[53] This was specifically ascribed to lack of food, but comparative studies with other agents, causing an equal amount of systemic stress, would be necessary to eliminate the possibility of a mere non-specific affect.

Since **sodium** plays such an important rôle in conditioning the hormonal defense mechanism during the G-A-S, it is interesting that these "symptoms of excessive sodium chloride depletion, induced by insufficient salt intake and copious water drinking, are similar to heat-stroke and to Addison's disease and included cramps, fatigue, depression and cardiovascular distress upon exertion". It was concluded that lack of sodium contributes greatly to fatigue and impairment in men.[54]

Stimuli Influencing the Nervous System During the G-A-S

Hypophysis. — Very little is known concerning the mechanism through which systemic stress affects the nervous system. Some observations suggest that during the G-A-S the anterior-hypophysis may exert an important action upon the nervous system through the discharge of ACTH and the subsequent formation of corticoids.

Studies with radio-phosphorus in the rat showed that after **hypophysectomy** phosphorus absorption by the brain is greatly increased and this change can be prevented by pretreatment with ACTH. "It is suggested that the increased rate of P^{32} uptake of the brain in the hypophysectomized animals is connected with increased carbohydrate utilization".[55]

It had been noted some time ago that, in cats, exposure of the brain to air causes swelling and edema due to an increase in the permeability of the cerebral capillaries. This is accompanied by certain electro-encephalographic changes. All of these derangements can be inhibited by pretreatment with **ACTH.**[56]

In patients receiving ACTH, for instance for the alleviation of rheumatoid arthritis, a pronounced euphoria is commonly observed. Sometimes this may

[50] Schiele and Brozek B23185/48.
[51] Keys et al. **B46730/50.**
Taylor et al. B23190/48.
[52] Koecher B37757/49.
Salter et al. B24286/46.
[53] Buchanan and Roberts B28117/48.
[54] Bartley and Chute B34753/47.
[55] Reiss et al. B44858/49.
[56] Prados et al. B39657/45.

result in insomnia and marked excitement.[57] Electroencephalograms taken at this time show an abnormal pattern with the appearance of increasing amounts of slow (5/second) activity. This deviation disappears when the medication is discontinued.[58]

Prolonged treatment with **LAP** may cause brain edema and hemorrhages with manifestations of periarteritis nodosa of the brain such as are produced by corticoid intoxication (cf. below). **Thyrotrophin** probably plays a much less important rôle during systemic stress responses, except for the occasional instance of a hyperthyroidism elicited by exposure to some violent stress (see "Hyperthyroidism"). In any case the actions of thyrotrophin are also indirect and due to the secondary liberation of thyroid-hormone. Only the production of exophthalmos by thyrotrophin is not mediated by the thyroid.

The **gonadotrophins** also have to be considered since their production is decreased during the G-A-S. The resulting secondary gonadal insufficiency probably plays an important rôle in the decrease of libido during stress.[59]

Among the posterior-lobe hormones **vasopressin** is known to affect the hydration of the central nervous system; as a result of this it may even precipitate epileptoid attacks. There is some evidence that during the A-R vasopressin production is increased (cf. Vasopressin Metab., p. 220), but it remains to be shown whether, in the concentrations in which this hormone circulates in the blood during the G-A-S, it plays any important rôle in the genesis of nervous manifestations.[60]

Adrenals. — Adrenalectomy greatly diminishes the general vitality, fighting instinct and libido in several animal species. In man this is associated with a general feeling of weakness and fatigue.[61] Treatment with DCA maintains the fighting instinct of adrenalectomized rats.[62]

The electro-shock threshold of a rat declines rapidly after adrenalectomy but is readily restored by DCA or even NaCl therapy. These and allied observations led to the conclusion "that the electro-shock seizure threshold of the adrenalectomized rat is directly correlated with the plasma sodium level".[63] The susceptibility to audiogenic seizures in predisposed strains of rats is not influenced by adrenalectomy.[63a]

Adrenalectomy (or a functional hypocorticoidism induced by hypophysectomy) greatly raises the sensitivity of the rat to the anesthetic action of steroids (see below). Curiously even DCA exerts a more pronounced anesthetic effect in adrenalectomized than in normal rats, so that the animals are "simultaneously displaying deficiency in, and overdosage with, adrenal cortical hormone".[64] This is even more evident if the water soluble (and hence more rapidly effective) glucoside of desoxycorticosterone is used.[64a]

Observations on intact animals and man show that injection of **adrenaline** closely imitates the "emergency reaction" of Cannon. Indeed this observation

[57] Dutoit and Bauer B46988/50.
Hench et al. B27892/49.
Perera B46972/50.
Spies and Stone B45101/50.
Ragan et al. B43463/49.
Spies and Stone B45101/50.
Taylor and Morris B46977/50.
[58] Hoefer and Glaser B46995/50.
Ragan et al. B43463/49.
[59] Selye **94572/49.**
[60] Selye **94572/49.**
[61] Selye **94572/49.**
[62] Covian B35960/49.
[63] Davenport B36663/49.
[63a] Griffiths B47416/49.
[64] Selye A36210/41.
[64a] Cosmos et al. B46483/50.

and the intense adrenaline discharge noted in situations of systemic stress, form the basis of the theory that the adrenal-medulla plays an important rôle in the response to emotional excitation, painful stimuli and other stressors. The shifting of blood from the abdominal area to the central nervous system and the acceleration of recovery from neuromuscular fatigue are apparently useful defensive functions of adrenaline during emergencies.[65]

This view has been assailed with uncommon vehemence and an analysis of the experimental facts upon which it was based led to the conclusion that "bodily reactions in major emotions can be explained better as consequences of nervous stimuli (chiefly sympathetic) rather than secretory phenomena".[66] The debate was hardly justified. It is now known that both the adrenal-medulla and the sympathetic nerve-endings produce a mixture of adrenaline and noradrenaline in different proportions. There is no doubt that during emergencies both the adrenal-medulla and the sympathetic nerve endings discharge excessive amounts of such "adrenergic" principles and that these greatly influence the activity of the nervous system. Presumably it depends largely on incidental conditioning factors which of these two main sources of adrenergic hormones is more important in any specific case of an emergency response to systemic stress.

Corticoids exert several important actions upon the nervous system and it is not yet clear to what extent these are interdependent. It has been shown in the dog and monkey that heavy overdosage with DCA causes manifestations of intermittent *muscular paralysis* in certain regions of the body. In the dog this is manifest especially in the neck muscles, while in the monkey (in addition to paralysis of the neck) choreiform movements may also appear. We do not know to what extent these derangements are dependent upon muscular or nervous malfunction. However, they are manifestly related to the hypokalemia of DCA-overdosage, since administration of KCl effects an almost instantaneous cure.[67]

Another particularly striking nervous effect of DCA is the production of a reversible depression of the central nervous system. If very large doses of the hormone suddenly enter the blood stream (e.g., following intravenous or intraperitoneal administration) there is a preliminary stage of excitation, followed by deep *anesthesia*. The latter can be so profound, and accompanied by such muscular relaxation, that major operations may be performed on animals under DCA anesthesia. Fish are particularly sensitive to this effect. The mere addition of a few crystals of DCA to the water in which they swim suffices to anesthetize them, but they awaken within a few minutes if transferred to fresh water. Although mammals are less sensitive, such "hormonal anesthesia" can be produced in most laboratory animals (e.g., pigeon, rat, mouse, monkey, cat, dog) and there is ample evidence that animals can tolerate daily DCA-anesthesia during several weeks without developing detectable morphologic or functional derangements. Analeptics, such as metrazol or picrotoxin interrupt this anesthesia. It is noteworthy that other corticoids, and many hormonally active steroids devoid of corticoid potency (e.g., progesterone, testosterone) exert similar effects. Since even some hormonally inactive precursors or degradation products of steroid hormones (e.g., pregnanediol, pregnanedione, etiocholanolones) proved to be potent anesthetics, it is possible that the adrenal-cortex may also depress the central nervous system through steroids other than corticoids.[68]

[65] Cannon **A19828/29**, 57873/14, B37367/11, 35529/11, 40962/19, 10194/31.
Cannon and Hoskins 57883/11.

[66] Rogoff **B28082/45**.

[67] Kuhlmann et al. A31550/39, Selye and Hall A56584/43, A56583/43.

An A-R induced by a variety of stressors increases the anesthetic effect of steroids, perhaps due to "crossed sensitization".[68a]

The anesthetic effect of various hormonal steroids has repeatedly been confirmed,[69] and occasional failures were due either to the use of inadequate dosages or to administration of the compounds in a manner which precluded the rapid uptake of adequate amounts into the blood.[70]

This ability of DCA and of other corticoids to diminish the excitability of the nervous system may be responsible for its reputedly beneficial effect in certain cases of epilepsy.[71] It may also be involved in the elevation of the electro-shock threshold noted after chronic treatment with DCA in rats.[72]

A recent brief preliminary communication confirms that DCA decreases the excitability of the central nervous system, but states that this effect is not shared by ACTH or cortical extract; in fact these latter compounds allegedly inhibit the depressor effect of DCA.[73] This is somewhat reminiscent of the anti-arthritic action of ACTH and gluco-corticoids, as opposed to the production of arthritis by DCA, and may represent another instance of a similar hormone antagonism.

Under certain experimental conditions DCA produces a state of *"experimental catalepsy"* (with or without anesthesia) in rats. This can be interrupted by metrazol.[74] It remains to be seen whether corticoids play any part in the pathogenesis of catalepsy in man.

Chronic treatment with high doses of DCA can cause severe and permanent *brain lesions* in rats, especially after sensitization by unilateral nephrectomy and a high Na-intake. Under these conditions, pronounced hyalinosis of the brain-vessels with subsequent thrombus formation, hemorrhages and liquefaction necrosis may ensue. Frequently there is a diffuse panarteritis of the small and medium-sized brain-vessels and glia proliferation. Inflammatory infiltrations tend to occur in the perivascular spaces and in the meninges. The morphologic characteristics of this lesion are very reminiscent of the so-called "brain rheumatism", "periarteritis nodosa of the brain", certain types of "hypertensive encephalopathy", "toxic", "post-infectious" or "allergic encephalitis" and the cerebral lesions that accompany scleroderma or lupus erythematosus. As we shall see in the corresponding passages of the section on "Neuropsychiatric Diseases of Adaptation" (see: "Encephalitis"), histologically there are no clear-cut differences between these supposedly distinct pathologic entities.

[68] Selye **94572/49**, A35659/41, A35627/41, A35003/41, A35150/41, A36210/41, A36744/42, A36443/42, A37822/42, A36447/42, A39771/43, A55882/43.
Selye and Heard A38070/43,
Selye and Masson A97571/44,
Selye and Stone A67812/44,
Winter A36333/41, A36510/42,
Winter and Selye A35658/41.

[68a] Selye A36210/41.

[69] Beaulieu et al. A56361/42,
Chamorro A57215/42, Clarke A36747/41,
Eichholtz et al. B45516/49,
Friedman A35220/41,
Hartman et al. 99099/47,
v. Koersveld B38414/48,
Leblond 82066/42,
Masson and Beland B344/45.

[70] Hofmann B37368/49,
Vincke and Müller B25879/47.

[71] McQuarrie B37369/46,
McQuarrie et al. A55652/42.

[72] Woodbury and Davenport B37243/49.

[73] Cheng B35910/49.

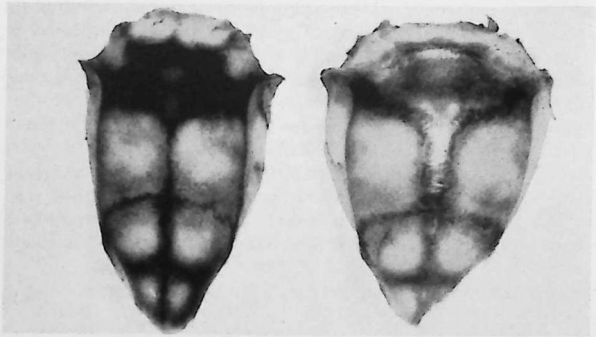
[74] Kerman B33896/47.

It is hardly justified therefore to classify them as cerebral manifestations specific of any one systemic disorder which they may accompany. Functionally the DCA-treated rats at first show an extraordinary hypersensitivity and irritability. They suddenly jump into the air or bite if one attempts to touch them. Later, periodic clonic contractions of the digits of a front paw are often seen, especially when the rats try to walk or are irritated. In more severe cases the head and shoulder muscles undergo rapid contractions; these are often unilateral, causing rather characteristic clonic rotatory movements of the shoulder-girdle and head. Less frequently the contractions are bilateral and lead to sudden backward jerks of the head and shoulders. During these spells the animals tend to salivate profusely, foaming saliva runs down from their mouth and after this, they fall to the floor of their cages in an apparently unconscious state. In this sense the attacks resemble epileptic fits.[75]

In young rats this syndrome of chronic DCA-overdosage is accompanied by extraordinarily pronounced edema of the brain, with an increase in the volume of the hemispheres, narrowing and even obliteration of the sulci, flattening of

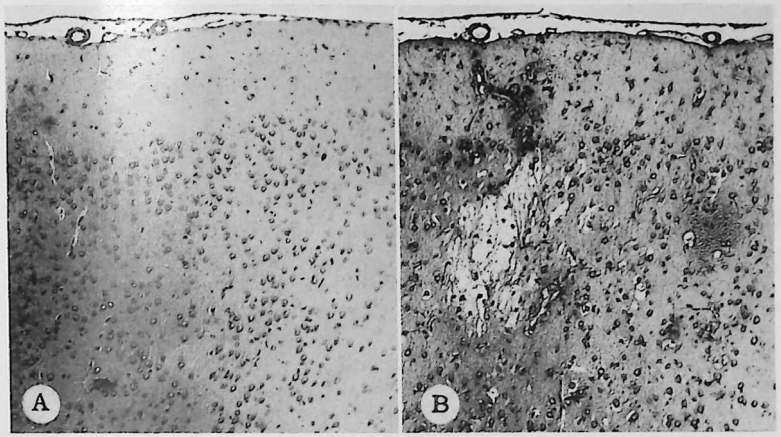


Motor disturbances due to periarteritis nodosa of the brain. — **A.** DCA-treated rat with periarteritis nodosa of the brain, shown during rest between two spells. — **B.** Same rat shown during typical clonic spell with rotation of the shoulder girdle and head towards the left. — **C.** Brain of normal control rat. — **D.** Brain of DCA-treated rat. Note hemorrhages and edema. (Selye B1204/46.)



Effect of DCA upon the skull, in the rat. Calvarium of a normal (left) and chronically DCA-treated (right) rat; both sensitized by unilateral nephrectomy and NaCl. Note that sensitizing procedure itself had no effect, but in DCA-treated animal there was considerable distention of the skull, with separation of the sutures due to pronounced brain edema and increased cerebro-spinal fluid formation. (Selye 35935/ND.)

[75] Beland and Selye A71895/44, Faribault and Haour B19161/49, Selye et al. A71886/44, B3477/48.



Effect of DCA upon the brain, in the rat. Both animals were sensitized by unilateral nephrectomy and 1% NaCl as a drinking fluid. — **A.** Cerebral cortex of otherwise untreated control. — **B.** Corresponding area from the brain of a rat which received 1.25 mg. of DCA/day during 33 days. Note edema and liquefaction necrosis on the left and a small hemorrhage in the right side of the field. A small arteriole near the brain surface is partially hyalinized. (Selye 35935/ND.)

the gyri as well as petechial and occasionally massive hemorrhages. In immature rats — while the bones are still pliable and readily adapt their form to that of the brain — such cerebral lesions lead to a marked enlargement and rounding of the skull. It was noted, in the same experimental series, that young rats survived severe DCA overdosage better than the old ones. This was ascribed to the fact that they are less likely to develop severe intracranial pressure as a result of the above brain changes, because their skulls are still capable of distention. — In adult rats, in which we removed the calvarium surgically before the production of DCA-overdosage, the brain could readily distend when it subsequently became edematous and developed inflammatory infiltrations and hemorrhages. In agreement with expectations these animals survived DCA-treatment longer than intact adult controls.[76]

The fact that removal of the calvarium greatly prolongs the survival time of these DCA-overdosed rats furnishes another example of the great importance of local peripheral factors in the pathogenesis of diseases of adaptation. In this case a peripheral intervention relieved the intracranial pressure. This exerted a life-maintaining effect, although the other manifestations of hypercorticoidism (e.g., periarteritis nodosa, nephrosclerosis, myocardial lesions) remained uninfluenced.

It is noteworthy in connection with the concept of neuropsychiatric diseases of adaptation (cf. p. 671) that other mineralo-corticoids (e.g., desoxocortisone) and even gluco-corticoids (e.g., cortisone) can produce similar functional and structural changes in the rat brain [77] and that even in man DCA-overdosage can lead to the development of such an encephalopathy.[77a]

[76] Timiras et al. B24139/49.
[77] Selye 35935/ND.
[77a] Forster et al. 86960/46.

On the other hand, parenteral injection of an aqueous cortical extract appears to *protect the brain from exposure to edema.*[78] Here there appears to be a certain antagonism between the mineralo-corticoid (DCA) and gluco-corticoid (cortical extract) compounds, since the former increase, the latter diminish the edema tendency of the brain.

Cortical extracts also cause an increase in amplitude and some change in the frequency of the *electroencephalographic* waves, both in animals and in man. It was concluded that adrenal-cortical hormones may play a significant part in the basic physiologic mechanisms of brain activity.[79] The abnormal E.E.G. of addisonians returns to normal under the influence of cortisone therapy.[80]

Studies on *brain metabolism in vitro,* suggest that DCA and allied steroids may cause anesthesia through their effect upon respiratory enzymes.[80a] However, the intimate mechanism of the anesthetic action is still far from being clearly understood.

Pregnenolone, a close derivative of the corticoids, allegedly improves performance in "pursuit meter" tests in men exposed to mental stress or simulated high altitudes.[81] In rats, pregnenolone did not increase the maze-learning ability under basic conditions, but after exposure to cold the performance of pregnenolone-treated animals was slightly superior to that of untreated controls.[82] Because of their practical importance such observations would deserve to be confirmed on a larger experimental material.

The many publications reviewed in the preceding paragraphs clearly indicate that the corticoids exert a very important effect upon the function of the nervous system. Up to now it has been customary to consider almost only adrenaline as a hormone which could be liberated under the influence of systemic stress to condition the response of the nervous system in emergencies. The data reviewed above strongly suggest that corticoids are at least equally as important. However, their effects are more likely to be manifest upon chronic exposure to stress, while the actions of adrenaline are most conspicuous in acute emergencies.

Kidney. — The effect of the kidney upon the nervous system has not received much attention in connection with the G-A-S. Let us merely recall here that a **"hypertensive encephalopathy"** with hyalinization of the brain arterioles is readily produced by the "endocrine kidney" [83] and there is reason to believe that both increased production of renal-pressor-substances and a decrease in their detoxification by the kidney, play a rôle in this as in most other manifestations of the hyalinosis syndrome.[84]

Rats made hypertensive by enclosing their kidneys in latex rubber capsules exhibited a consistent and significant reduction in their **appetite for sodium** salts. It was pointed out that since sodium-depletion prolongs the survival of animals rendered hypertensive by DCA, this observation "adds another item of evidence in favour of some as yet unexplained relation between the hypertensive state and sodium metabolism".[85]

[78] Grenell B2259/47.
Prados et al. B39657/45.
[79] Grenell B2259/47.
[80] Forsham et al. B35919/49.
[80a] Eisenberg et al. B47252/50, B46252/50.
[81] Hoagland B4975/47.
[82] McGinnies B25878/47.
[83] Selye 94572/49.
Selye and Stone 94202/46.
[84] Selye **94572/49.**
[85] Abrams et al. B36304/49.

Other stimuli. — **Insulin** hypoglycemia causes pronounced neuro-psychologic disturbances; hence it is noteworthy that overdosage with this hormone appears to produce a marked discharge of both adrenergic and cholinergic nerves.[86] This may play a rôle in the pathogenesis of tension-depression states [87] and in the mechanism of shock-therapy.[88] In this connection it is also interesting that insulin shock, as well as other intense, acute alarming stimuli, tend to restore conditioned reflexes in animals in which these were lost due to lack of re-enforcement.[89]

A series of experiments in which this effect of insulin was duplicated by metrazol and electric-shock, inspired the remark that: "It appears to be significant for the understanding of the mechanism of shock-therapy to point out that the procedures studied in this paper presumably act on the cortex by removing inhibitory processes".[90]

Certain experiments on rats were expressly performed to examine the rôle of the **diet** in the production of a G-A-S during adaptation to nervous stimuli. These showed that "repeated, intense audiogenic stimulation causes much more nervous and somatic damage in rats kept on a high, than in those receiving a low protein diet". These observations were interpreted to indicate that adjustment to nervous stresses is largely dependent upon the same conditioning factors which regulate the development of a G-A-S in response to other alarming stimuli.[91]

Racial factors also appear to affect the reaction of the nervous system to stress. This is abundantly evident from everyday clinical experience, but it has also been demonstrated under accurately controlled laboratory conditions. Thus certain strains of rats react with epileptoid convulsions when stimulated by sounds of high frequency, while other strains are quite resistant.[91a]

Neuropsychiatric Diseases of Adaptation

A large number of neuropsychiatric disturbances are probably diseases of adaptation, in the sense in which we defined these. Although nervous and emotional stressors are most effective in producing such diseases, essentially similar derangements can be elicited by exposure to a variety of other stressors. Psychosomatic derangements, neuroses and perhaps even psychoses and organic changes in the brain tissue itself, may result from maladaptation to stress. No doubt here derailments along the nervous pathways of the G-A-S are of special importance, but in many instances there is a good deal of evidence to indicate that the hypophysis-adrenal system also plays a prominent rôle.

Psychosomatic derangements, neuroses, neurasthenia and allied conditions. — Several excellent monographs review the literature concerned with the production of **psychosomatic disturbances,** and especially neuroses, as a result of maladaptation to nervous stress.[92] Others list as psychosomatic

[86] Bender and Siegal 78376/40,
Gellhorn B27006/43.
[87] Rennie and Howard B19676/42.
[88] Himwich B23656/44.
[89] Gellhorn B23057/46,
Gellhorn and Minatoya 83860/43, B19653/43,
Gellhorn and Seese 83900/43,
Gellhorn et al. A38112/42.
[90] Gellhorn et al. A38112/42.
[91] Riess B37365/47, B35595/48.
[91a] Griffiths B47416/49.
[92] Dunbar B36276/35,
Grinker and Spiegel B18363/45,
Maier B31227/39,
Masserman B31226/43.

derangements "common to all neurasthenics; slow sedimentation of the blood, increased viscosity of the serum, increased red blood-count, phosphaturia and hyperacidity of the stomach".[93]

Using a convenient standardized technique of painful stimulation [93a] for the study of somatic responses in psychoneurotics exposed to nervous stress "it was concluded that psychiatric patients with somatic complaints tend to manifest increased physiologic responsiveness in the related physiologic system or mechanism, upon exposure to stress. The disturbance appears to be specific to the physiologic system associated with the complaint and can be demonstrated objectively even though the subjective symptom is not experienced at the time of stress".[93b] This may help to understand how specific responses in a predisposed organ system can be elicited by non-specific stress situations.

A change in occupation, or any other nervous strain requiring adaptation may lead to a transient emotional crisis at least in predisposed individuals. This was descriptively termed **"adaptational crisis"** (the "Anpassungskrise" of the German investigators), in order to denote its dependence upon an effort to adjust oneself.[94] More recently, special attention has been called to the close relationship between the somatic manifestations of the G-A-S and many psychosomatic disturbances seen in clinical medicine.[95] A study of the **neurotic reactions to severe combat stress** among aviators during World War II reveals many instructive instances showing that after the initial intense responses to emotional stress a great deal of *resistance* is acquired, but "everyone has a limit to the amount of stress which he can withstand" and eventually *exhaustion* sets in. This has been referred to as "operational fatigue".[96] The striking similarity between these three phases and the corresponding stages of the G-A-S hardly requires much comment.

The "operational fatigue" of combat aviators is probably related to the **"chronic fatigue syndrome"** which tends to develop not only after prolonged nervous strain, but also during various endocrine disorders (e.g., hypocorticoidism, hypothyroidism) and in post-infectious states (e.g., after influenza, undulant fever, dysentery).[97] The adynamy and prostration of the "malignant syndrome" elicited by acute infections, has been regarded as largely due to diencephalo-hypophyseal lesions developing during the A-R.[98]

In this connection a detailed study of the emotional disturbances caused by nervous stress in the civilian population of Austria during World War II also proved very instructive. The usually observed syndrome was described as characterized by the following symptoms: disturbances in the tonus of the blood-vessels, excessive sweating, disturbances in the cardiac rhythm and blood-pressure, paresthesias and diffuse aches and pains, irregularities in the contractility of the iris, dizziness and fainting, hyperthyroidism, loss of libido with impotence in the male, menstrual anomalies in the female, disturbances of micturition, insomnia at night with extreme fatigue and sleepiness during the day, constant fluctuation between profound depression and extreme excitation, derangements in memory and the power of concentration and a particularly

[93] de Courcy and Vollmer B34728/49.
[93a] Malmo et al. B47043/48.
[93b] Malmo and Shagass B47046/49.
[94] v. Bracken B28115/30, B28530/30, B28114/48.
[95] Wolf B26123/48.
[96] Grinker and Spiegel B18363/45.
[97] Bansi and Schwarting B46780/50. Muncie **B44582/41**, Bartley and Chute B34753/47.
[98] Manceaux and Jorda B23176/48.

strong tendency towards self-torture, fear, depression and compulsive thinking at night or whenever the patient is alone.[99] Space does not permit us to discuss all these neuropsychiatric disturbances in detail, but we wanted at least to enumerate them here, since in our opinion they are fairly typical of the response to any long-continued systemic stress.

ACTH did not prove to be useful in patients with various *anxiety states*, although their somatic responses to the hormone may have been slightly abnormal.[99a]

It has been claimed that "acute alcohol poisoning and the repeated alarm stimuli associated with *alcoholism* lead to various stages of adrenal cortex insufficiency." Furthermore, delirium tremens has many points in common with the Addisonian crisis (hypoglycemia, hyponatremia), hence it was concluded that "delirium tremens, which occurs only in chronic alcoholics, is readily explicable in terms of the adaptation syndrome". This led to extensive studies concerning the effect of ACTH in alcoholics. From these it was deduced that "whereas ACE (adrenocortical extract) is effective in Korsakoff psychosis, ACTH is not; both ACE and ACTH are effective in the treatment of acute alcohol intoxication. In this condition ACE is probably preferable because of its greater sedative action. In delirium tremens ACTH is easily the most effective treatment we have used, and is superior to conventional treatment and the use of ACE".[99b]

Preliminary experiments suggest that **DCA** given in combination with ascorbic acid, is beneficial in various types of psychoneuroses (mainly depressive states),[99c] but the brief published statement concerning these observations permits no definite conclusions.

It has already been mentioned that **cortical extracts** allegedly exert a beneficial affect in the prophylaxis and therapy of experimental neuroses in sheep.[100] Similar claims have been made of their utility in various acute "confusional states",[101] psychoneuroses,[102] and chronic alcoholism [103] in man.

It is perhaps also noteworthy in this connection that **ammonium chloride** — which proved so highly effective in counteracting DCA-intoxication in animals — often causes prompt relief of premenstrual *headache* in women in whom this condition is accompanied by sodium retention.[103a]

Psychoses. — The participation of endocrine factors in the pathogenesis of psychoses has long been suspected on the basis of indirect evidence. Allegedly there are histologic changes in various endocrine glands of schizophrenics [104] and diverse types of psychoses tend to be associated with manifold functional endocrine disorders,[105] as well as abnormal somatic reactions to neurogenic stress.[105a]

Special attention has been given in this connection to the anterior-pituitary and the adrenal-cortex. In **Cushing's syndrome** mental derangements are

[99] Kauders B35560/46.
[99a] Cleghorn et al. B46997/50.
[99b] Smith B46998/50.
[99c] Fachini et al. B47924/50, Cranswick and Hall B47397/50.
[100] Liddell et al. 62127/35.
[101] Hoft and Shaby A32900/40.
[102] Huddleson and McFarland A30745/39, Gorrell A36385/40.
[103] Tintera and Lovell B41221/49.
[103a] Fekete B46239/49.
[104] Ariizumi A99212/40, B11342/43, McCartney A11864/29.
[105] Hemphill and Reiss B44863/48, Margolese B18160/48, Sackler et al. B45970/50.
[105a] Malmo and Shagass B47045/49, B47040/50.

quite common and sometimes they even progress to an actual psychosis.[106] Since ACTH production is excessive in Cushing's disease, it is interesting to speculate on the possibility that such mental aberrations might result from an increased endogenous production of this hormone.

In **Addison's disease** depression, melancholia and confusional states are frequently observed and even frank psychoses may develop.[107] In other instances of schizophrenia or acute delirium, histologic changes were observed both in the cortex and in the medulla of the adrenals, although there was no definite evidence of Addison's disease.[108]

Several investigators reported data suggesting some **functional adrenal insufficiency** in psychopaths.[108a] It has been claimed that unlike normal individuals, psychotics do not show hyperglycemia during excitement; indeed they may develop hypoglycemia, presumably because of an increased insulin secretion or a diminished adrenaline discharge during emergencies.[109] The possibility should also be considered that the lack of hyperglycemia in these patients may be related to some functional gluco-corticoid deficiency.

More recently, systematic, comparative studies of the hypophysis-adrenal mechanism have been undertaken in normal and schizophrenic men using several recognized indices of adreno-cortical function, such as: determination in the urine of 17-KS, corticoids, electrolytes, inorganic phosphates, uric acid, and in the blood, of lymphocytes, eosinophils, electrolytes and sugar. Such studies have been made before and after four tests designed to evoke endogenous adreno-cortical activity: 1) glucose administration, 2) pursuit-meter operation, 3) target-ball frustration test, 4) ACTH administration, as well as after treatment with active cortical extract.[110] A synopsis of the many pertinent data led to the conclusion that "of these procedures the target-ball frustration test proved to be least effective in eliciting enduring changes indicative of adreno-cortical activity. Data significantly indicative of adrenal-cortex activation were obtained for the normal men in the glucose-tolerance, pursuit-meter and ACTH tests, while a significant evidence of responsivity in the patients' data occurred only in the lymphocyte response to glucose administration. The behaviour of the indices of adreno-cortical function following ACE (adreno-cortical extract) was similar in the two groups and they could not be significantly differentiated. It is deduced that the responsivity to ACE is similar in the two groups, but that activation of endogenous adreno-cortical secretion generally fails in the psychotic subjects. Evidence is thus provided of a species of hypoadrenalism in the psychotic subjects".[111] However, other investigators,[112] who used insulin-shock, electro-shock and adrenaline injections as stressor agents, noted an essentially normal ACTH discharge in psychotics. They conclude that failure to respond to psychologic stressors (in the work of the above-mentioned investigators) is probably due to the fact that schizophrenics do not respond markedly to this kind of stimulus. Furthermore, the subnormal reaction to

[106] Oldenberg B33916/47, Selye 94572/49.
[107] Gorman and Wortis B33887/47, Loehner A71266/38, Selye **94572/49**, Valenciano 90336/29, 92338/29.
[108] Gibbs 97520/25, de Leo 89967/26, Lingjaerde B29883/41, Mott and Hutton 94776/23.
[108a] Hoagland and Pincus B46996/50, Jaria B46746/49.
[109] Gellhorn et al. 80365/41, A37798/42.
[110] Freeman and Elmadjian B26580/47, Hoagland and Pincus B46996/50, Pincus and Elmadjian B1243/46, Pincus et al. B41235/49.
[111] Pincus et al. **B41833/49.**
[112] Parsons et al. B45571/49.

ACTH which had been reported in schizophrenia [113] has not been observed in involutional melancholia [114] and hence cannot be regarded as characteristic of psychoses in general. Yet, the interesting possibility of interpreting psychoses as diseases of adaptation due to a derangement in the response to the stresses and strains of daily life [115] would deserve further investigation.

Additional data which are compatible with this interpretation, have been derived from observations concerning the *sodium elimination through the sweat.* This was found to be "above the normal range in most psychotic patients, irrespective of their clinical diagnosis, who have been ill for more than three years. Patients ill for shorter periods may show either normal or high values. Elevated sweat sodium concentrations fall to normal during insulin therapy, electro-shock therapy, and spontaneous remissions. These observations suggest that diminished production of hormones controlling the electrolyte balance is frequent in psychosis and that treatment stimulates production of these hormones.[115a]

Pertinent data have also been derived from observations on psychotic patients treated with **corticoids.** Allegedly, in patients suffering from manic-depressive psychosis, the manic phase has responded favourably to *adreno-cortical extract* therapy and beneficial results have also been reported in schizophrenia.[116] However, up to now only a few patients received such treatment.

In patients given fever therapy for syphilis of the nervous system, simultaneous treatment with adreno-cortical extract has yielded favorable results which "suggested that the extract may act upon the central nervous system".[117]

The euphoria caused by *gluco-corticoids* (e.g., cortisone) in man and the encephalopathy caused by severe cortisone overdosage in experimental animals certainly suggest that these hormones exert an important action upon the brain, but it remains to be shown whether this will be of therapeutic value in mental disease.

In a number of psychotics in whom other types of treatment (including shock and psychotherapy) had failed, *DCA* administration allegedly proved to be effective,[118] but here again the number of cases treated is so far very small. Further observation will also be required to verify the allegedly beneficial effect of combined DCA-ascorbic-acid therapy in psychotics.[118a]

In Addisonians receiving large doses of DCA, various nervous symptoms described as neurasthenia, anxiety neurosis or even "persecution mania" have allegedly developed as a result of the treatment.[119] Such complications are undoubtedly quite exceptional, but they are interesting from a theoretic point of view. Here again one is reminded of the encephalopathy caused by DCA in the rat, since it is also conducive to excitement, confusional states and other functional disturbances of the central nervous system.

As regards the therapeutic application of **ACTH** in the treatment of psychoses, available data are still meager and contradictory.[119a] Since an ACTH discharge is a characteristic consequence of various shock-therapies and since this hormone definitely influences mental activity (as shown by the euphoria

[113] Pincus et al. B41833/49.
[114] Altschule et al. B36865/49.
[115] Cranswick and Hall B47397/50, Hoagland B4975/47.
[115a] Altschule and Grunebaum B47852/50.
[116] Loehner A71266/38, A34158/40.
[117] Edelmann et al. A56665/43.
[118] Jens B44448/49.
[118a] Cranswick and Hall B47397/50.
[119] Sarradon B33935/47.
[119a] Altschule and Grunebaum B47852/50.

and depression which it may produce), ACTH was given to a patient with involutional melancholia. Although marked eosinopenia resulted, there was no clinical improvement; subsequent electro-shock therapy produced a definite remission, although it caused a lesser eosinopenic response. From this it was concluded that "increased production of 11-oxysteroids, considered to be responsible for the eosinophilic cell response, is not the cause of clinical remission in patients given electro-convulsive therapy".[120] Yet, another patient with involutional melancholia "was able to go back to work soon after treatment with ACTH and two months later she still is working, although she has had no further therapy".[121] The beneficial results in the latter instance might have been coincidental, but the possibility must also be kept in mind that the therapeutic effect of ACTH may depend upon hitherto unidentified conditioning factors. The inadequacy of ACTH in patients in whom electro-shock is effective may likewise depend upon the fact that, in addition to the ACTH discharge, shock-therapy causes several metabolic changes which may condition the effectiveness of the hormone. (Cf. also "shock-therapy" on page 106). The urinary elimination of gluco-corticoids is markedly increased in psychotics who respond favourably to electro-shock therapy.[121a]

Non-specific encephalitis and allied encephalopathies. — In the experimental section of this chapter we described in detail those structural changes in the brain which occur in animals receiving excessive amounts of **mineralocorticoids** (e.g., DCA, desoxocortisone), **gluco-corticoids** (e.g., cortisone), or **LAP.** These lesions are strikingly similar among themselves and also resemble those which develop in man under the influence of a variety of stressors, such as infections or drugs, known respectively as *"post-infectious encephalopathy"* or *"toxic encephalopathy"* (cf. above). Very similar changes in the brain have been described furthermore in hypertensives as *"hypertensive encephalopathy"*,[122] in nephritics as *"edematous necrosis of the brain"*,[123] in patients with periarteritis as *"periarteritis nodosa of the brain"*,[124] and in rheumatic fever as *"rheumatic encephalopathy"* or *"brain rheumatism"*.[125] In all these instances the brain lesions have received different names because it was tacitly assumed that these are essentially distinct nosologic entities. It is important to realize, however, that all the above-mentioned encephalopathies are essentially characterized by vascular lesions of the non-specific "hyalinosis" and panarteritis type, which lead to hemorrhages, an increase in the permeability of the capillairies, edema formation, and subsequently to non-specific nutritional disturbances in the brain; these are in turn followed by glia proliferation. Whether the lesions present themselves as multiple small foci, or as extensive hemorrhagic and necrotic patches, depends largely upon the caliber of the vessels involved. Incidental conditioning factors may also influence the resulting morphologic changes. Thus, a high blood-pressure or a clotting defect will augment the tendency to form brain hemorrhages in the presence of vascular damage, and in chronic lesions, glia proliferation and healing will be more prominent than in the acutely fatal types. Nevertheless, it must be kept in mind that all these

[120] Altschule et al. B36865/49.
[121] Spies et al. B45105/49.
[121a] Ashby B46594/49.
[122] Alajouanine B44526/47, Scheinker B37903/48, B26942/48, B26943/48.
[123] Beckmann B38015/47.
[124] Antonin B43911/48.
[125] Benda B41789/47, Bruetsch B436/44, B2313/47, B44527/47, Chavez B42350/48, van der Horst B44503/48, Neubuerger B37968/47, Warren and Chornyak B45563/47.

different names refer to essentially the same non-specific morphologic lesions and that these can be accurately reproduced by overdosage with exogenous corticoids and by stimuli which increase endogenous corticoid production.

It is particularly instructive to note, in this connection, that an essentially similar encephalopathy may also occur in man following treatment with large doses of **ACTH** [126] or DCA.[127]

On the basis of these data we consider it highly probable that this non-specific type of encephalopathy is a disease of adaptation.

Polyneuritis. — It is a well established fact that polyneuritis may develop following a number of infections and intoxications, especially after diphtheria [128] and treatment with sulfonamides [129] or other compounds causing allergy. In these cases it is frequently accompanied by cardiovascular and renal changes similar to those produced by corticoid overdosage. Sometimes animals receiving large amounts of mineralo-corticoids also exhibit inflammatory changes in the peripheral nerves.[130]

Poliomyelitis. — It has been mentioned in connection with the phenomenon of crossed resistance that "the effect of stress factors in preventing the development of lesions is beautifully illustrated in the epidemiology of poliomyelitis and in experimental studies of the infection in monkeys. There is the time-honored observation that the disease affects only the healthiest children in the community; the incidence is heavy in country districts and light in the towns; heavy in suburbs and light in the slums; heavy in the well-cared for children of countries with low infantile mortality and negligible in undernourished tropical children; higher in American whites than negroes; higher in officers than in men; higher in the autumn when food and vitamins are more plentiful, than in the spring, the season of scarcity, of pellagra and rickets. Experimentally, various forms of trauma and malnutrition lower the incidence of the disease or give complete protection." ... "The agents which Selye used to provoke an alarm-reaction in rats are all obviously potent in the prevention of poliomyelitis." [131] Yet up to the present **ACTH** proved ineffective in the treatment of poliomyelitis in man.[132]

The fact that those muscle groups which are particularly exposed to fatigue tend to be most seriously affected in poliomyelitis may well be due to the phenomenon of neuronic exhaustion which will be discussed below in connection with neurosyphilis.

Neurosyphilis. — It had long been recognized that in tabes the loss of tone and sense of position affect first those muscle groups which are most intensely in use. This led to the formulation of the *"exhaustion theory"* of tabes.[133] Subsequent animal experiments showed that in the neurosyphilis of the rabbit it is possible to induce the first nervous manifestations in the pupil by intermittent exposure to light and dark, so that an Argyl-Robertson sign develops rapidly. "It seems reasonable to suppose that if a cell is not getting proper nutrition and yet continues to function, the catabolic changes will gradually overbalance the anabolic ones, and that the cell will sooner or later reach a condition of exhaustion".[134]

[126] Elkinton et al. B45107/49.
[127] Forster et al. 86960/46.
[128] Gore B38112/48, Reisner B45567/47.
[129] Bodinova-Smelâ B38204/47, Lovskin and Kernohan B45303/48.
[130] Selye 35935/ND.
[131] Hughes B44427/49.
[132] Coriell et al. B45575/50, B47734/50.
[133] Edinger B45572/05.
[134] Russel B41274/12.

In this sense, the systemic metabolic manifestations of the G-A-S may influence the course of neuro-syphilis while local factors act as "conditioning agents".

Even general paresis can be precipitated by an emotional shock [135] and it would be interesting to determine whether the G-A-S mechanism participates in this response.

Effort syndrome, neuro-circulatory asthenia or Da Costa's syndrome. — This syndrome is characterized by manifestations which greatly limit the subjects' capacity for effort. The cardinal symptoms and signs are breathlessness, palpitations, fatigue, left thoracic pain and dizziness, with functional disturbances of the respiratory, vasomotor, muscular and sweat gland systems. The syndrome is usually classified with the neurasthenias and has been defined thus: "neuro-circulatory asthenia is a condition characterized by instability of the nervous and vasomotor systems, with clinical manifestations of fatigue, dyspnœa, palpitation and precordial pain".[136] In spite of a considerable literature on this subject,[137] we know very little about the pathogenesis of this syndrome. It has been related to hypoglycemia or excessive adrenaline secretion [138] and it was pointed out that patients affected by the effort syndrome usually exhibit signs of constitutional physical and nervous weakness, exhaustion by exposure or continuous hard work, delayed convalescence from acute illnesses (such as rheumatic fever, pneumonia, pleurisy, dysentery, influenza or tonsillitis). Many of them suffer from unrecognized infections (e.g., incipient tuberculosis, focal abscesses, etc.).[139] All these observations suggest some relationship to the diseases of adaptation.

"Shock disease". — This is a disease which periodically decimates the snowshoe hare in the U.S.A. by the sudden development of fatal hypoglycemia. The cause for the periodicity of the mortality from this disease is unknown. It is interesting, however, that "during the period of decline, the hares of the Lake Alexander area and throughout Minnesota in general, became unable to survive for more than a short time when held in captivity and many died in live-traps almost immediately after they were caught. They appeared to be abnormal, suffering from a condition that caused them to succumb when subjected to stress".[140] Morphologically, the outstanding manifestation of "shock phase" is a peculiar and ill-defined degeneration of the liver with disappearance of hepatic glycogen. Here we are undoubtedly dealing with a disease of adaptation in the sense that the malady particularly impedes resistance to any kind of stress, but it has not yet been established exactly how the G-A-S mechanism is deranged.

Other neuropsychiatric disturbances. — In one relatively early case of **multiple sclerosis**, and a rapidly progressive case of **amyotrophic lateral sclerosis**, ACTH may have caused some slight improvement, but treatment was continued for a few days only and hence it is too early to draw definite conclusions.[141]

Special attention has been given to the development of the G-A-S in **paraplegic** patients. The conclusion was drawn that "the physical and emotional stress, to which the paraplegic must constantly adapt himself, might be a factor leading to the increase of 11-OCS (gluco-corticoid) excretion according to the 'adaptation concept' of Selye".[142]

[135] Martimor and Cornuche B41546/42.
[136] Cecil A63152/43.
[137] Anonymous B2423/45, Donati B45762/47, Wood B318/41.
[138] Greene B696/44.
[139] Grant A34252/40.
[140] Green et al. A33357/39.
[141] Randt et al. B47001/50.

Theories and Summary of Observations Concerning the Participation of the Nervous System in the G-A-S

It has been mentioned in other connections that emotional and **nervous stressors** are particularly effective in eliciting the G-A-S, both as regards the manifestations of damage (e.g., shock, gastric ulcers, etc.) and of defense (e.g., liberation of ACTH, corticoids, adrenaline). Hence sedation, anesthesia or deafferentiation of directly injured areas diminish the intensity of traumatic shock, although they do not abolish it completely since humoral factors are likewise involved (cf. pp. 138, 166).

The liberation of adrenergic substances by the adrenal medulla depends almost entirely upon its secretory, **splanchnic** nerve supply. The discharge of vasopressin by the posterior-lobe becomes impossible following transection of the **hypophyseal stalk** since this intervention causes an atrophy of the entire posterior-lobe. On the other hand, stalk-transection does not interfere with the discharge of ACTH during the A-R (cf. page 570). Presumably the latter response is largely, if not entirely, dependent upon humoral factors.

Stress itself, and certain hormones produced during the G-A-S especially **ACTH** and the **corticoids**, can even produce severe morphologic changes in the nervous system. Among these, edema of the brain, hyalinization of its vessels, nutritional disturbances (liquefaction necrosis, hemorrhages) and subsequent neuroglia proliferation are particularly prominent. Frequently this is preceded or accompanied by increased formation of cerebrospinal fluid and a rise in intracranial pressure. This type of encephalopathy may result in epileptoid attacks, acute excitation and confusional states or, in severe cases, pronounced depression and even coma.

Several neuropsychiatric derangements have been interpreted as **diseases of adaptation** primarily due to derangements of the G-A-S mechanism. Most important among these are certain *neuroses* and *psychoses*. Several investigators claim to have obtained beneficial results with corticoid or ACTH therapy in experimental neuroses, as well as in certain neuroses and psychoses of man, but pertinent data do not yet permit definite conclusions. It is certain, however, that in man, a state of euphoria, sometimes followed by severe depression, can be induced by the administration of cortisone or ACTH. These functional changes, as well as the well-known anesthetic effect of corticoids, show that the ACTH-adrenal mechanism can influence mental activity.

Certain *encephalopathies* of man (e.g., the so-called hypertensive, toxic, allergic, rheumatic and post-infectious encephalitis) resemble the brain lesions produced by ACTH or corticoid overdosage. It is tempting to assume that here again we are dealing with a disease of adaptation in the pathogenesis of which increased ACTH and corticoids play a prominent part.

[142] Staub et al. B47699/50.

SENSE ORGANS

Eye. — It has long been known that during the A-R (produced by cold, formaldehyde, spinal shock, adrenaline, atropine, morphine, etc.) there may be a temporary clouding of the **lens**, which tends to vanish rapidly when the animal recovers from the shock phase.[1] Subsequent investigators repeatedly confirmed this in animals severely damaged by acute anoxia [2] or adrenaline overdosage [3] and also interpreted the change as due to the shock-phase of the A-R.

Allegedly, this clouding of the lens may be the immediate consequence of derangements in carbohydrate metabolism during the A-R. It is interesting therefore that similar changes have been noted in man not only during diabetic coma but also after other conditions of dehydration.[4]

The contractility of the **pupil** is severely deranged during traumatic shock in man; it may be excessively contracted, dilated or immobilized.[5] "This failure of the pupillary reaction points to a block of the nerve impulses along the reflex path involved in the reaction and is further indication of injury to the nervous elements".[6]

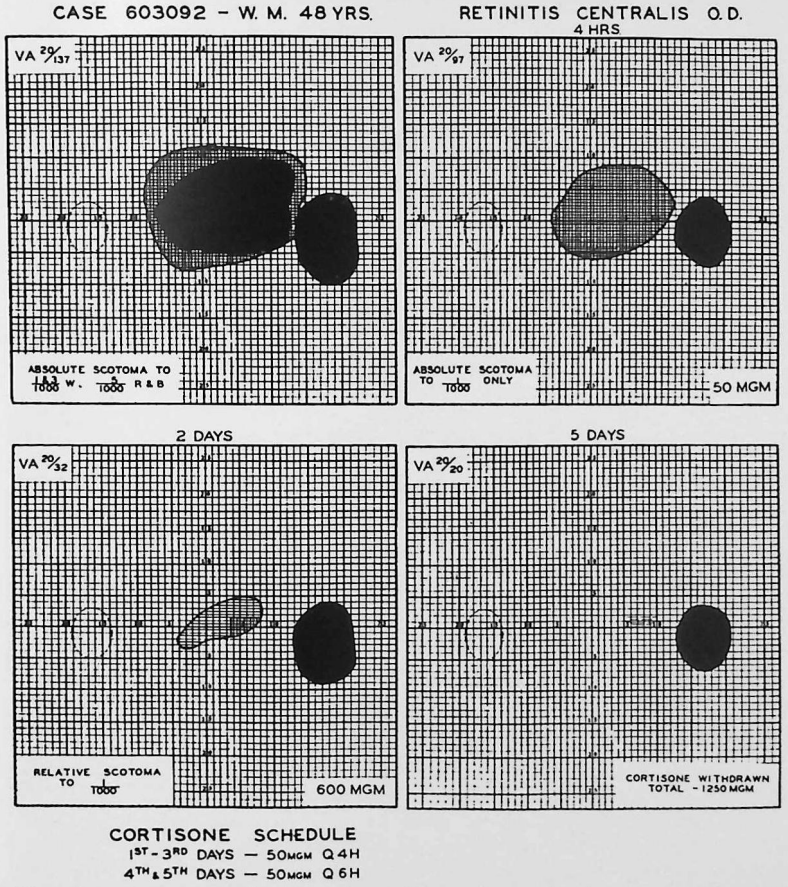
It is not within the scope of this volume to discuss the many aspects of what has been termed **"allergy of the eye and its adnexa"**. Let us merely refer the reader to the excellent monographs [7] which, in reviewing the extensive literature on this subject, came to the conclusion that many of the pertinent changes are undoubtedly due to deranged homeostatic mechanisms. Their precise relationship to the G-A-S has not yet been examined.

Various inflammatory diseases of the eye can be successfully treated with artificial fever or parenteral foreign protein therapy. It has been suggested that here again the benefit is largely due to the G-A-S mechanism and particularly to the endogenous liberation of ACTH and gluco-corticoids.[7a] On this rationale cortisone or ACTH have been administered in such varied conditions as luetic keratitis, keratitis with anterior uveitis, plastic iritis and retinitis centralis, with most satisfactory results. Indeed cortisone proved to be effective even upon local application to the eye,[7b] choroiditis, anterior and posterior uveitis, retinitis pigmentosa, choroideremia, optic neuritis and retrobulbar neuritis, while in four cases of glaucoma secondary to severe uveitis, the results were not striking.[7c] The fact that such a wide variety of ophthalmic conditions is improved by ACTH or cortisone clearly shows the non-specificity of this therapy (cf. also illustrations on pp. 681-685).

The so-called **rheumatic diseases of the eye** [8] should also be considered in this connection. Here, the fundamental histologic lesions are very similar

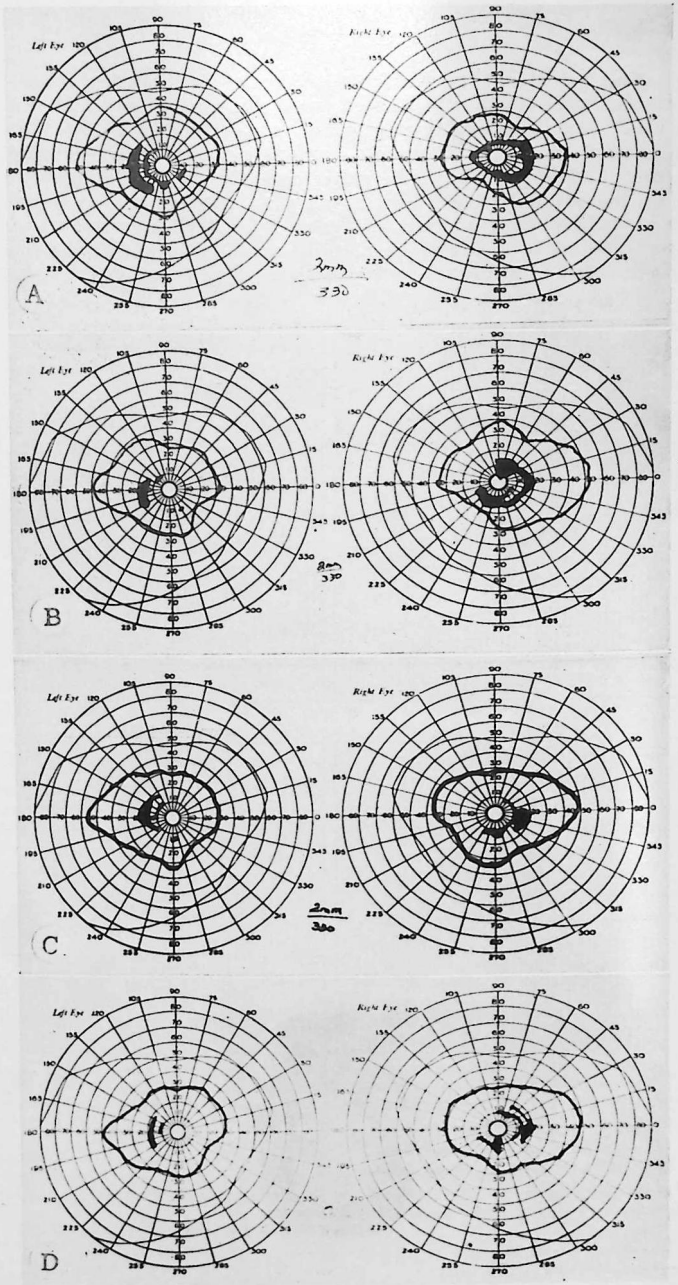
[1] Selye 36031/36, 38798/37.
[2] Barbour and Seevers 84296/43, Bellows and Nelson A63319/43.
[3] Suden A34989/40, Suden and Wyman A34582/40.
[4] Lawrence et al. 85593/42.
[5] La Croix A32640/18.
[6] Cannon and Cattel 13334/22.
[7] Duggan **92782/45. 92784/43.**
[7a] Steffensen et al. B47620/50.
[7b] Steffensen et al. B47620/50, Olson et al. B47733/50.
[7c] Gordon and McLean B47732/50, B47737/ND.
[8] Franceschetti B42309/46.

to those observed in other mesenchymal organs and ACTH or cortisone appear to be spectacularly effective in pertinent types of iritis, iridocyclitis, uveitis and choroiditis.[8a] It becomes increasingly more obvious, however, that the separation of "rheumatic" from other inflammatory lesions of unknown origin is of little value in ophthalmology. In either case the principal culprit is not the pathogen, but the host, and treatment is more effective if it succeeds in rectifying faulty host-reactions to local stress (ACTH, cortisone, non-specific therapy), than if it is aimed specifically against the unidentified pathogen (specific antisera, antibiotics, sulfa-drugs).



Effect of cortisone upon retinitis centralis. — Tangent screens showing the spectacular and rapid improvement obtained with gluco-corticoid therapy.
(Courtesy of Dr. E. H. Steffensen, Henry Ford Hospital, Detroit.)

[8a] Mann and Markson B47801/50.



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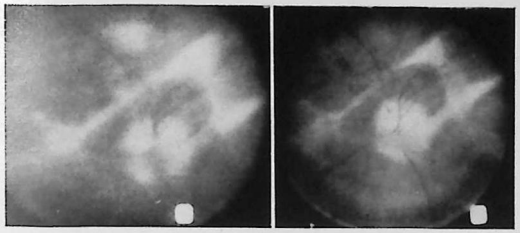
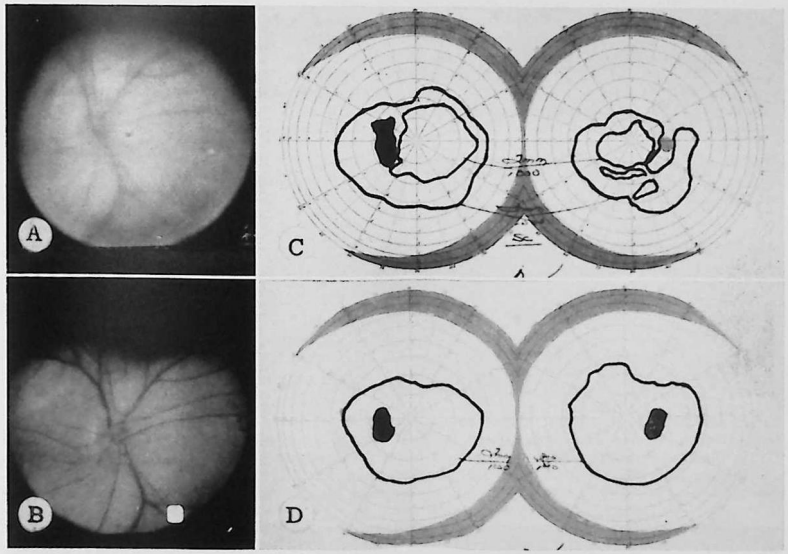


Non-diabetic retinitis proliferans treated with ACTH. — **A.** Before treatment. Vision 2/200. Vitreous extremely cloudy, fundus barely visible with opththalmoscope. — After 9 days of ACTH (approximately 80 mg./day). Vision 6/200 +. Vitreous has cleared considerably and since it is now less hazy, the fibrous bands are more visible.

(Courtesy of Dr. D. M. Gordon, New York.)



Optic neuritis treated with ACTH. — **A.** Optic neuritis of 18 months duration before ACTH treatment. — **B.** After 16 days of ACTH treatment (about 70mg./day), discs almost normal in appearance and vitreous clear. — **C.** Visual fields corresponding to Fig. A. Central fields taken with 2 and 3 mm. targets at 1 m. Note extreme restriction of fields with the 2 mm. target and large blind spot on the left with 3 mm; failure of right field with 3 mm. target to encircle the blind spot completely ("breaking through of blind spot"). — **D.** After 13 days of ACTH treatment note that fields are almost normal with but slight enlargement of the blind spot. Vision became practically normal.

(Courtesy of Dr. D. M. Gordon, New York.)

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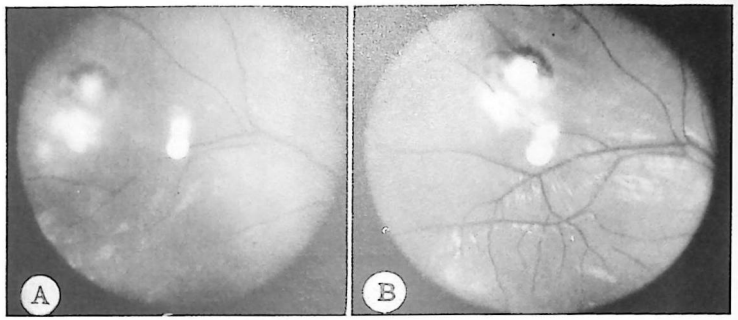
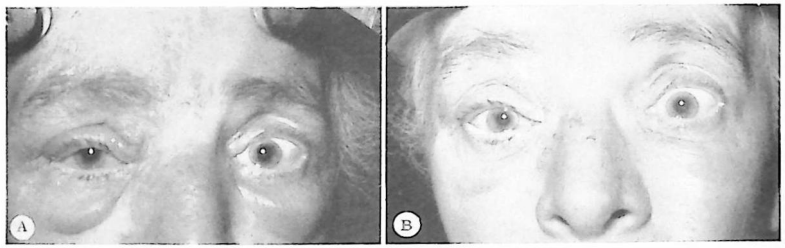
Effect of ACTH upon retinitis pigmentosa. — **A.** Before treatment. Note the complete ring scotoma in right eye and incomplete double ring in left. — **B.** After 9 days of ACTH vision improved from 20/50 + 2 (right) and 20/30 — 2 (left) to 20/30 + (right) and 20/20 (left). Here shown two days after cessation treatment. Note the improvement in ring scotomata, especially on right. — **C.** Two months after cessation of treatment vision still good. — **D.** Three months after treatment vision still good, although now his dark adaptation is slower.

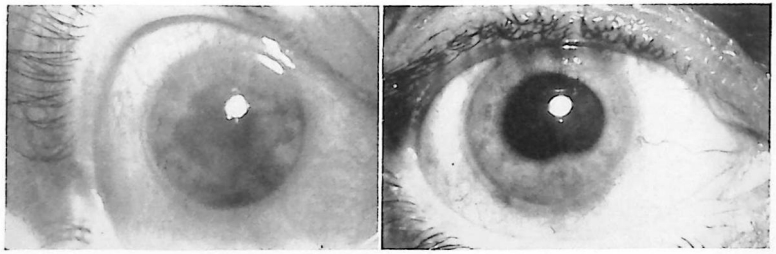
(Courtesy of Dr. D. M. Gordon, New York.)



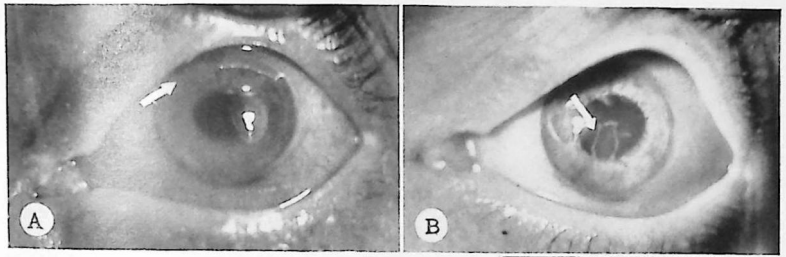
Acute exudative chorioretinitis treated with ACTH. — **A.** Two weeks after beginning of chorioretinitis. (Patient had received penicillin, sulfadiazine, aureomycin by another ophthalmologist). Four distinct exudative lesions near the upper left corner of the field, with marked retinal edema and cellular infiltration of vitreous body, as seen with slit-lamp biomicroscope. (Two bright spots in center are reflections of arc-lamp carbons.) Vision at this time 20/40. — **B.** Four weeks after continuous treatment with ACTH. Beginning dosage 80 mg./day gradually reduced to 2 mg./day. Retinal edema subsided in 24 hours, lowermost exudative areas absorbed after 6 days of ACTH. Finally (as shown here) topmost area heals with pigment proliferation. Formerly large exudative lesions on vessel have shrunken and are largely absorbed. Vision 20/15. (Courtesy of Dr. H. E. Thorpe, Pittsburgh.)

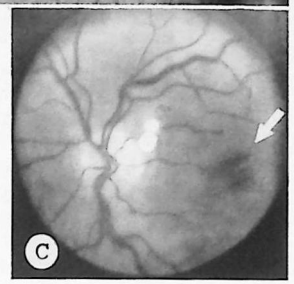


Effect of ACTH in herpes zoster ophthalmicus. 61-year-old woman with herpes zoster ophthalmicus. — **A.** Before treatment. — **B.** 24 hours after initiation of ACTH treatment. She received a total of 800 mg. over a period of 10 days and during this time improvement continued. The spectacular efficacy of the therapy is already quite obvious, however, after 24 hours as seen in this picture. (Courtesy of Dr. E. H. Steffensen, Henry Ford Hospital, Detroit.)

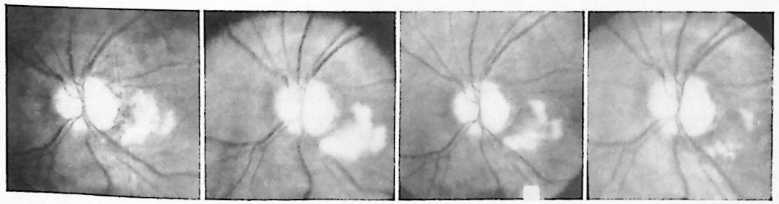


Effect of ACTH in plastic iritis. 63-year-old male with severe plastic iritis. Before (left) and four days after he had received 220 mg. of ACTH in divided doses. He was eventually given a total of 460 mg. of ACTH and cleared completely in eight days. When seen eight weeks after discontinuation of therapy, there was still no evidence of recurrence.
(Courtesy of Dr. E. H. Steffensen, Henry Ford Hospital, Detroit.)





Effects of ACTH upon hypopyon keratitis. — **A.** Left eye of a 64-year-old male with acute hypopyon keratitis. The eye is painful and inflamed, the cornea infiltrated and stains with fluorescein. There is extensive fibrinocellular exudate (to level of arrow) in the anterior chamber and acute iridocyclitis. Iris markings are extremely hazy due to this exudate. No fundus deflex could be seen. Vision = shadows only. The condition developed after trauma to the left eye by a stone. Patient was treated with antibiotics and non-specific protein therapy without avail. Pneumococcus isolated on culture from corneal ulcer. — **B.** Same eye after 140 mg. of ACTH in divided doses given during 48 hours. The pain subsided within 12 hours after initiation of ACTH and redness was much reduced. The exudate in the anterior chamber about 90% concentrically absorbed (see arrow). Iris markings much clearer. Fundus reflex now visible. — **C.** After 12 days of ACTH (total amount 450 mg.), fundus readily seen and could even be photographed. Vision now 10/30. The arrow indicates macular changes of traumatic origin.
(Courtesy of Dr. H. E. Thorpe, Pittsburgh.)



Acute choroiditis treated with ACTH. — **A.** Before beginning of treatment. — **B.** After 14 days of Δ5-pregnenolone treatment. Note that lesions become actually denser and larger. — **C.** After 11 days of ACTH. Healing has begun. — **D.** 18 days after discontinuation of ACTH. Note that lesion has considerably fragmented. This patient also has Buerger's disease, which showed great improvement during ACTH-treatment, with partial relapse shortly after discontinuing the injections. (Courtesy of Dr. D. M. Gordon, New York.)



Effect of ACTH in vernal conjunctivitis. 20-year-old boy with severe vernal conjunctivitis. Before (left) and after treatment with 1320 mg. of ACTH over a period of 15 days. The condition regressed even further after cessation of treatment.
(Courtesy of Dr. E. H. Steffensen, Henry Ford Hospital, Detroit.)

It is also pertinent to this discussion that psychosomatic factors appear to play an important rôle in the pathogenesis of some cases of chronic **conjunctivitis** and chronic **blepharitis.**[8b]

Observations on severely undernourished prisoners of war suggest that prolonged **fasting** may also cause disturbances of vision. These are characterized by annular scotomas and ophthalmoscopic changes suggestive of vascular lesions in the choroid and retinal membranes.[9] Too little is known about these lesions to justify more than their brief mention here.

The **exophthalmos** of Grave's disease is generally attributed to an increased production of thyrotrophin,[10] but perhaps other hormones of the anterior-lobe are also involved. In any case, administration of ACTH or DCA to guinea-pigs failed to produce exophthalmos,[11] while in man ACTH is often spectacularly effective in ameliorating the course of the exophthalmos in hyperthyroidism.

It is particularly instructive that in intact guinea-pigs, thyrotrophin produces only mild and transitory exophthalmos, while after thyroidectomy this response is much more pronounced and persistent.[11a] The development of experimental exophthalmos in the guinea-pig largely depends upon the accumulation of much intercellular ground substance and water in the connective tissue of the orbit. This is evidenced by the presence of metachromatic material, of which hyaluronic acid is an important constituent. The hexosamine content of these tissues is likewise increased. This is "similar to the changes of myxedema in man and suggests a common mechanism for the two conditions". Since mucopolysaccharides are extremely hydrophilic, the accumulation of these substances in themselves may explain the increased water retention in the orbital cavity.[11b]

Nose. — The fact that various allergic reactions of the nasal mucous membrane are influenced by stress is too well known to deserve much comment. Recent investigations showed, however, that "nasal hyperfunction characterized by varying degrees of hyperemia, swelling and hypersecretion of the membranes, as well as eosinophilia in the nasal secretions and circulating blood, occurred in all subjects, 'sensitive' or 'normal', exposed to mixed ragweed pollen when the circumstances were appropriate." ... From pertinent observations "it was concluded that 'sensitive' individuals differ from normals only in degree, but pollen or stressful life situations may induce nasal hyperfunction in either, with associated local and circulating eosinophilia and symptoms of rhinitis".[12] Here the rôle played by the G-A-S is not yet clear but it is interesting that ACTH frequently causes an improvement in the appearance of those large edematous nasal polyps, with mucopurulent discharge, which tend to occur in certain allergic patients.[13] This hormone also proved very effective in some cases of vasomotor rhinitis [14] and allergic rhinitis.[15] In this connection it is interesting that, much before the advent of ACTH or cortisone therapy, vasomotor rhinitis has been considered to be an allergic phenomenon frequently elicited by emotional stress factors. "In many of the

[8b] Halliday B44599/43, B46202/47.
[9] Koecher B37757/49.
[10] Selye 94572/49.
[11] Jefferies B41087/49.
[11a] Selye 94572/49.
[11b] Ludewig et al. B46258/50.
[12] Holmes et al. B33418/49.
[13] Bordley et al. B44913/49, Rose B46991/50.
[14] Randolph and Rollins B46990/50.
[15] Astwood et al. B47853/50.

patients with vasomotor rhinitis, especially of the non-seasonal variety, it was possible to correlate most of their episodes of nasal disease with periods of considerable emotional conflict".[16] Furthermore, the histologic structure of nasal polyps indicates that an allergic inflammation with abundant fibrin deposition in the stroma is eventually conducive to organization by "fibro-capillary tissue".[17]

Since elsewhere in this book we gave considerable attention to the syndrome of hunger edema, it is noteworthy that undernourished concentration camp inmates were often afflicted with "dripping nose", shortly before they developed widespread nutritional water retention. After onset of the generalized edema the dripping continued and, when the diet improved, it disappeared together with the other manifestations of hunger edema. In these instances there was no evidence of actual rhinitis.[18]

Summary. — In the **eye,** during the A-R, clouding of the lens and derangements in the contractility of the pupil are quite common.

Certain inflammatory, allergic or rheumatic changes of the eye, such as conjunctivitis, blepharitis, sympathetic ophthalmia, iritis, iridocyclitis, uveitis and choroiditis may perhaps be interpreted as ocular diseases of adaptation, since they can apparently be elicited by a variety of stressors and at least some of them proved to be highly amenable to ACTH and cortisone therapy.

The exophthalmos of Grave's disease is only one manifestation of thyrotoxicosis. The latter has been discussed elsewhere as possibly belonging to the group of the diseases of adaptation, but it is relevant to mention here, that ACTH can cause remissions of exophthalmos.

Various types of allergic reactions in the **nasal** mucous membrane exhibit characteristics of the diseases of adaptation and proved to be amenable to ACTH therapy.

[16] Wolf B26123/48.
[17] Kline B37972/48.
[18] Van der Hal B45589/47.

GASTROINTESTINAL SYSTEM

The gastrointestinal tract is extremely sensitive to any kind of stress and strain. This subject has been extensively discussed in pertinent monographs.[1] Indeed as early as 1833, Beaumont [2] saw, by direct inspection, the reddening of the mucosa during emotional upsets in the stomach of a man with a traumatic gastric fistula. The predominantly adrenergic stimulation of the gastrointestinal vessels and musculature during the "emergency reaction" [3] is another frequently cited pertinent observation.

Systemic Stress

Characteristic response. — When the A-R concept was formulated it immediately became evident that the production of acute gastric and duodenal **hyperemia** and **erosions,** sometimes with hemorrhage into the stomach, are very constant and characteristic manifestations of this first stage in the G-A-S. The formation of an erosion is usually preceded by a period of stasis and hyperemia. Subsequently the mucosa becomes edematous and the resulting derangement in tissue nutrition gradually leads to the breakdown of the lining cells, which are exposed to the highly destructive gastric juice. Essentially the same type of lesion is produced by a variety of drugs, traumatic injuries, burns, excessive muscular exercise, cold and other alarming stimuli, hence its non-specific nature can hardly be in doubt.[4] Although these ulcers disappear at the beginning of the resistant stage they re-appear during the stage of exhaustion.[5]

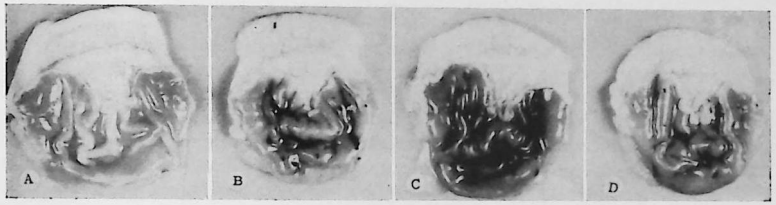
The healing of the gastric erosions caused by an A-R is very rapid; in the rat it is usually far advanced as soon as 24 hours after cessation of exposure to the alarming stimulus.[6] The exact relationship between the acute gastroduodenal erosions of the A-R and the chronic peptic ulcer of man has not yet been clarified, but probably all these gastrointestinal lesions are interrelated to some extent. Presumably the ulcers are largely due to the intense autonomic discharge which occurs in the splanchnic area during exposure to systemic stress and also elicits marked **peristaltic, vasomotor** and **secretory reactions.**

During the A-R and the exhaustion phases of the G-A-S, erosions may also occur in other parts of the alimentary tract, expecially in the upper small intestine. At the same time **Peyer's patches** disintegrate, as part of the general caryoclastic reaction of lymphatic tissue. Not infrequently, this is accompanied by intense **diarrhea** or **constipation** and in certain species (including man) by **nausea** and **vomiting.**[7]

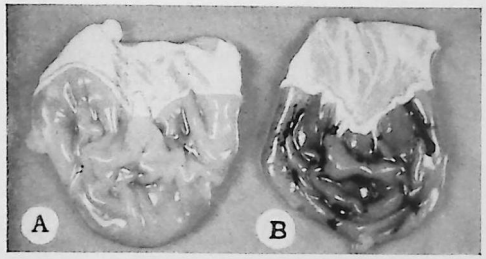
Particularly acute and severe damage in rats may specifically affect that part of the cecum which in this species corresponds to the **appendix.** In such cases this part of the gut shows hemorrhagic edema similar to that observed

[1] Babkin **B123/44.** Pavlov B37648/10. Selye et al. 58020/36.
[2] B37370/833. [5] Selye A8406/38.
[3] Cannon A19828/29. [6] Dalton A35629/41.
[4] Selye 36031/36, 36032/36, 38798/37, [7] Selye 36032/36, 38798/37, 66642/36.

during the first stages of acute appendicitis in man. It has been suspected that certain cases of acute clinical appendicitis are perhaps also due to similar systemic rather than local causes. Since some investigators believe that the liberation from tissues of histamine-like metabolites is the basic cause of shock-symptoms, it is of particular interest that intravenous administration of histamine proved especially effective in eliciting such acute appendicular lesions. It is also noteworthy that previous exposure to a mild alarming stimulus tends to prevent the production of appendicitis by subsequent exposure either to histamine or to any other kind of systemic stress.[8] It has been claimed, though not proven, that the appendicular lesions of the A-R result from local neurovascular derangements in this part of the gut.[9]



Acute gastric ulcers during the A-R. in the rat. — **A.** Normal appearance of the stomach in an untreated control rat. In the other three animals an A-R was produced by: — **B.** high spinal cord transection, — **C.** exposure to a temperature of +2°C, — **D.** repeated forced muscular exercise during a period of 48 hours, while food was withheld. Note considerable hyperemia of the gastric mucosa, with the appearance of many blood-covered erosions. The gastric contents also contained much free blood. The proventriculus (upper part of the stomach), which is not covered by gastric mucosa but by a stratified epithelium, is not subject to ulcer formation during the A-R. (Selye 35935/ND.)



Gastric ulcers during the exhaustion phase of the G-A-S, in the rat. — **A.** Normal gastric mucosa of control. — **B.** Hyperemia of the gastric mucosa, with numerous deep blood-covered ulcers, following 30 days of exposure to cold. Note similarity of these lesions to those seen in the A-R. (Selye 35935/ND.)

Trauma. — Following extensive muscle trauma in dogs, congestion, hemorrhages and sometimes small erosions appear in the upper gastrointestinal tract and the descending colon.[10] Using the heart-lung-dog preparation (in which venous pressure and cardiac output can be maintained at a steady level irrespective of systemic circulatory changes) it was found that such gastrointestinal hemorrhages and erosions are independent of venous flow and cardiac output; they appear even in this preparation as soon as spontaneous shock develops. The fundamental factor responsible for this type of irreversible circulatory failure was a decrease in total peripheral resistance, which

[8] Selye 66642/36, 68819/37, B1204/46. [10] Cleghorn B2573/46.
[9] Oertel B37053/37.

enabled the animal to store quantities of blood equal to about five times its normal blood-volume. "Autopsy revealed no storage depots other than the mucosa of the upper intestines which was always edematous, intensely congested and often hemorrhagic".[11] This intense congestion of the splanchnic viscera in profound shock is in sharp contrast with the abdominal vasoconstriction characteristic of the "emergency reaction" to milder stimuli.

Vomiting, diarrhea or constipation may also develop as a consequence of traumatic injuries; they are particularly frequent after surgical interventions in the abdomen.[12]

Hemorrhage. — Following severe hemorrhages, acute gastric erosions occur in animals [13] and man; [14] here again these lesions are accompanied by other manifestations of the A-R.

Burns. — Curling [15] was among the first to describe duodenal ulcers in severely burned patients and hence these are often referred to as "Curling's ulcers". It has subsequently been shown that they are frequently accompanied by hemorrhages or even necrosis in the suprarenal glands as well as many other manifestations of the A-R.[16] Esophagitis or esophageal ulceration likewise tend to occur and frequently the gastric mucosa is intensely congested. Here acute erosions may also be seen, but more often blood merely oozes through an almost intact gastric surface lining.[17]

Similar gastrointestinal lesions have been produced by burns in the dog.[18] While both in man and in the dog duodenal ulcers are most common, in the rat burns — as well as other alarming agents — more frequently tend to cause acute gastric erosions.[19]

Allegedly, hemoconcentration plays an important part in the causation of the mucosal necrosis which precedes the gastric and duodenal ulcerations; avoidance of hemoconcentration prevents the formation of such erosions in burned dogs.[20] It must be kept in mind, however, that the motility of the stomach and the acidity of its digestive secretion are also increased under the influence of burns as shown by observations in the dog.[21]

Temperature. — The production by exposure to **cold,** of an A-R with acute gastric erosions in the rat has long been a standard laboratory technique in the study of the G-A-S.[22] Interestingly compounds which are normally not, or only poorly, absorbed upon oral ingestion (e.g., adrenaline, histamine, allergenic proteins) readily enter the blood-stream from the wound surfaces of these gastrointestinal ulcers and thus cause signs of an intoxication. This may have a bearing upon the pathogenesis of some manifestations of the A-R, since it indicates that toxic, but normally not absorbable, substances may enter the blood from the alimentary tract during the shock-phase and thus aggravate the systemic damage.[23]

[11] Wegria et al. A56861/43.
[12] Adams B10543/37.
[13] Price et al. B26011/41.
[14] Blalock B37650/34.
[15] B37649/842.
[16] McLaughlin 92906/33.
[17] Braithwaite and Beales B46046/49, Erb et al. A57594/43, Ficarra and Naclerio B808/44, Harris 90255/29, Hilgenfeldt **38008/36,** McLaughlin 92906/46.
[18] Behrmann et al. B4278/46, Hartman 93230/46, McLaughlin **92906/33.**
[19] Selye B1204/46.
[20] Friesen and Wangensteen B37558/47.
[21] Necheles et al. B2321/46.
[22] Selye A8052/38, B1204/46, 36032/36.
[23] Eppinger B37085/49. Karady B44929/41. Selye **A8052/38.**

Essentially similar gastrointestinal changes — particularly edema, congestion, and hemorrhages — were found in men who died from **heat-stroke** [24] and in guinea-pigs exposed to lethal **solar radiation.**[25]

Ionizing radiations. — Treatment with ionizing radiations causes particularly pronounced lesions in the gastrointestinal tract, such as: necrosis of the surface epithelium, edema and congestion of the submucosa and severe hemorrhages into the lumen. The hemorrhagic tendency is especially manifest because of the vasotoxic action and the occasionally demonstrable clotting defect produced by such rays. These structural changes are accompanied by anorexia, nausea, vomiting and diarrhea. The gastrointestinal lesions caused by x-irradiation and those elicited by the rays of the atomic bomb are essentially the same. This was shown in man and in various experimental animals.[26]

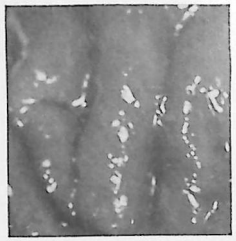
Isolated irradiation of the upper abdomen causes particularly severe necrotic lesions in the stomach only.[27]. This shows that such changes are not entirely due to the A-R but partly caused by the direct effects of the rays. The extraordinary intensity of the gastrointestinal lesions produced by ionizing rays also suggests a specific component in their pathogenesis. The lesions in the gut are probably further accentuated because these rays exert a specific and direct destructive effect upon lymphatic structures (disintegration of Peyer's plaques) as well as upon vascular endothelia and the blood-clotting mechanism (purpuric manifestations).

Repeated injections of *foreign protein* combined with isolated gastric irradiation, in otherwise harmless dosages, causes pronounced ulceration in the stomach of the rabbit. This has been interpreted as showing that ulcers are the consequence of an allergic (hyperergic) condition, the effects of which can be localized in the stomach through the direct actions of the rays.[28] As we shall see later the presence in the stomach of food (especially carbohydrate) or of buffer solutions (e.g., aluminum hydroxide) has an opposite effect; it prevents the production of gastric ulcers by various alarming stimuli. These observations give further support to the view that individual manifestations of the G-A-S can be inhibited or aggravated by local conditioning factors.

Electric injury. — Repeated exposure of rats to electro-shock caused accumulation of phagocytes in the submucosa of the stomach and the small intestine. This was accompanied by multiple small hemorrhages and in animals which survived longer than the A-R period, occasionally by vascular changes "reminiscent of periarteritis nodosa".[29]

Nervous stimuli. — It is common knowledge that nervous and emotional stress can cause intense gastrointestinal disturbances such as nausea, vomiting or diarrhea. Furthermore, on empirical grounds, it has long been suspected that even chronic peptic ulcers tend to develop, especially among patients continuously exposed to intense nervous stress.[30]

[24] Malamud et al. B18019/46.
[25] Pinner and Margulis 37822/36.
[26] Anonymous B26330/48, B28192/48, Bloom **B31225/48,** De Coursey B38048/48, Cronkite B24042/48, B24051/48, Ellinger **68685/35,** Liebow et al. **B41902/49,** Moon et al. A31861/40, Prosser et al. B26618/47, Tullis B27010/48.
[27] Betz B26312/47.
[28] Betz B26312/47. B38084/47.
[29] Hirsch B33742/49.
[30] Grinker and Spiegel B18363/45, Palmer **95299/46.**



A. Normal Mucosal Folds during circumstances of security and contentment. (Approx. actual size)

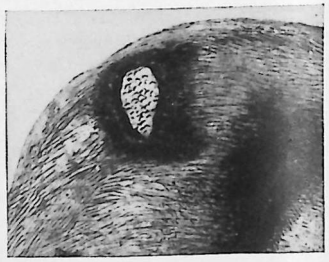


B. Same folds during hyperaemia and engorgement of gastric mucosa associated with emotional conflict involving hostility and resentment. (Approx. actual size)



C. Small mucosal erosion covered by blood-stained flake of opaque mucus occurring in engorged hyperactive stomach. (Approx. actual size)



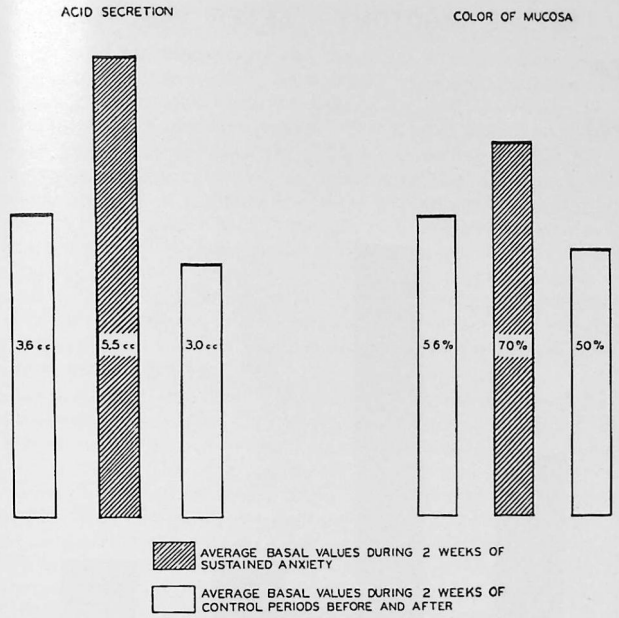


D. Small punched-out ulceration induced by the action of gastric juice on an area inadequately protected by mucus. (Approx. actual size)

E. Drawing of ulcer (of D.) enlarged approximately 2½ times.

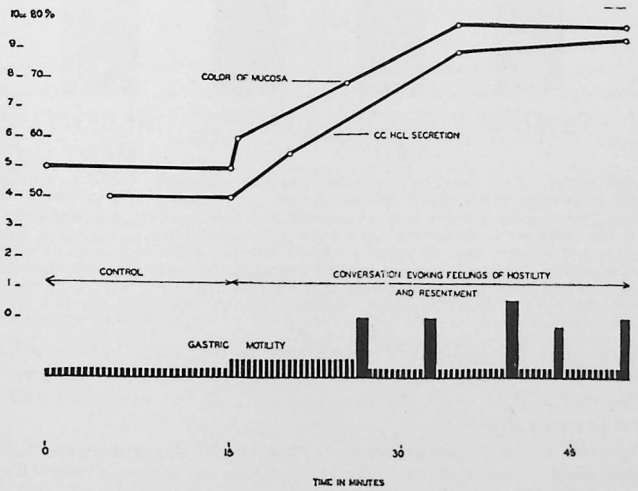
Observations concerning the pathogenesis of gastric ulcer, made on a patient with a gastric fistula. — **A, B** and **C** illustrate that intense, prolonged acceleration of acid secretion in the stomach (here induced by emotional conflict), results in hyperemia and engorgement of the mucous membrane resembling hypertrophic gastritis. In this state, the mucosa is unusually susceptible to injury and even trifling traumas result in hemorrhages and small erosions. However, ordinarily the mucosa is protected from further injury by an effective coating of mucus. — **D.** and **E.** Loss of this protection by removal of the mucus exposes the lining to the acid gastric juice and permits a minor erosion to progress towards ulcer formation.

(Wolf and Wolff B46202/48.)



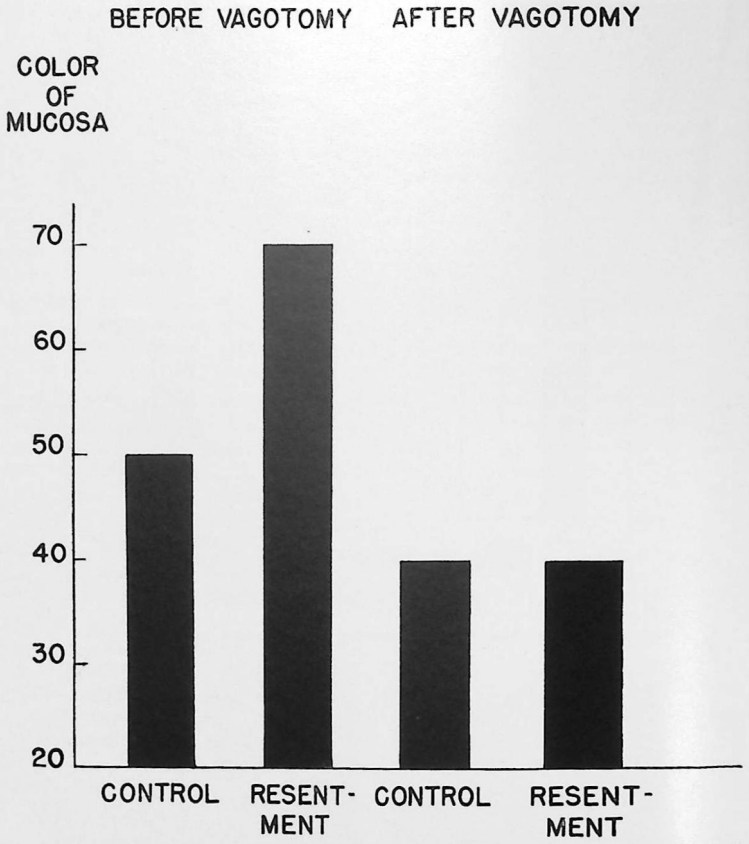
Sustained acceleration of gastric function during chronic emotional conflict.

(After Wolf and Wolff B46202/48.)



Increased motility accompanying hyperemia and hyperacidity in association with hostility and resentment.

(After Wolf and Wolff B46202/48.)



Variations in color of the gastric mucosa before and after vagotomy. Based on data obtained by direct observation of the gastric mucosa, through a cystoscope, in a patient in whom a gastric fistula was made prior to surgical removal of a carcinoma of the esophagus, during which it was necessary to section the vagus nerves. Note that, prior to vagotomy, resentment (induced by conversation about an irritating subject) induced marked hyperemia of the mucosa. The latter became so turgid that the minor traumas, incident to instrumentation with the cystoscope, caused bleeding. Simultaneously there was flushing of the face. Conversely, after vagotomy, the gastric changes no longer occurred, although flushing of the face was again elicited by the resentment. (After Wolf and Wolff B46431/48.)

The so-called *"air-raid ulcers"*, which have so frequently been noted during the second World War among civilians in heavily bombed cities, are presumably also due to the A-R — in this case produced by the emotional excitement incident to aerial attacks.[31]

In men whose gastric mucosa could be observed by direct inspection through a gastric fistula, two distinctly different patterns of response were observed

[31] Selye A56386/43.

to occur under the influence of *emotional* irritation. The first type, gastric hyperfunction, is characterized by hyperemia of the mucosa with the appearance of scattered bleeding-points and sometimes even erosions. At the same time the titratable acidity of the gastric juice increased, there was heartburn and epigastric pain which could be relieved by milk or sodium bicarbonate. This was called the "aggressive pattern". It was often accompanied by flushing of the skin and occurred when the patient was willing to fight his troubles. Conversely, gastric hypofunction is characterized by pallor and flatness of the mucosa, as well as a diminution of its acid-secretion and motility. This was found to be associated with "emotions such as fear and sadness in which there was a desire on the part of the subject to withdraw or reject a situation rather than to come to grips with it".[32] This dual response reminds us of the counter-shock and shock phases of the A-R, representing passive damage and active defense respectively. It remains to be seen whether these gastric changes correspond to those cutaneous vascular reactions which make some people pale, others flush with anger.[33]

In another subject, who also bore a gastric fistula, the mucosa of the stomach could be observed before and after *vagotomy*. Here it was found that emotional stimuli, which caused gastric hyperemia, engorgement and hypermotility before transection of the vagus, no longer produced such effects after the operation, although the other manifestations of anger and resentment remained the same.[33a] This admittedly does not prove that the gastric response to stress is solely mediated by the vagus, "the evidence is highly suggestive however, especially when considered in company with the clinical results of the treatment of peptic ulcer by vagotomy".[34] It is also pertinent that both in cats [35] and in dogs,[36] peptic ulcers can be produced by prolonged *vagus stimulation*.

Various **surgical lesions of the nervous system** may lead to severe gastrointestinal changes. Thus a perforated, acute peptic ulcer was noted in a patient after an *operation for a cerebellar tumor*.[37] Electric *stimulation of the hypothalamic region* in animals was found to cause increased peristalsis of the stomach and patches of hyperemia, all of which could be prevented by previous vagotomy.[38] *Transection of the upper spinal cord* in rats is routinely used to produce an A-R with acute gastric erosions, especially in fasting animals; this is usually conducive to massive hemorrhages into the stomach.[39]

Muscular work. — Excessive muscular exercise is one of the most commonly used alarming stimuli. In fasting animals it is known to produce gastric hyperemia, hemorrhages and erosions with great rapidity; this is always accompanied by other manifestations of the A-R.[40]

In the fasting rat striking changes can be seen as soon as 30 minutes after initiation of heavy exercise. First there is dilatation and congestion of the capillary loops immediately beneath the surface lining, a decrease in the pepsinogen granules of the chief cells and of the mucinogen granules in the mucous cells. The parietal cells remain singularly unaffected. Later the stroma becomes edematous and there is degeneration with sloughing of the surface epithelium

[32] Wolf B26123/48, Wolf and Wolf B26155/47.
[33] Card B37400/49.
[33a] Wolf and Wolff B46431/48.
[34] Wolf and Andrus B26053/47.
[35] Stahnke 21250/24.
[36] Manning et al. B37652/37.
[37] Cushing B37651/32.
[38] Beattie 4673/32.
[39] Frank A34171/40, Selye 38798/37, Selye and MacLean A75010/44.
[40] Selye 36031/36, 38798/37.

and hemorrhage. Eventually deep erosions are formed in the gastric mucosa, but curiously within 24 hours the repair of the surface damage is already considerable due to intense mitotic proliferation of the epithelium. "These changes are in no way specific to the agents used and it should be emphasized that non-specific damage must always be considered as the most likely primary cause of acute gastric ulcers induced by whatever experimental intervention".[41]

The intestinal absorption of various toxic substances which are normally not damaging when administered by mouth, has also been demonstrated in animals with gastric ulcers produced by excessive muscular exercise.[42]

In the dog, muscular fatigue depresses the gastric secretion of HCl, although even in this species it increases the tendency to form gastric or duodenal ulcers. It has been concluded therefore that fatigue exerts some effect upon the gastric mucosa (probably by changing its blood-supply), which renders it more vulnerable to the digestive action of the acid-pepsin mixture.[43]

Other stressors. — The gastrointestinal changes which we have described as characteristic of the A-R, have also been noted to occur in animals and man under the influence of **anoxia,**[44] various spontaneous **diseases** conducive to "medical shock" [45] and a variety of **drugs** which caused marked systemic damage such as *colchicine,*[46] *allyl-formiate,*[47] *hypertonic NaCl solution,*[48] *formaldehyde,*[49] *nitrogen and sulfur mustards,*[50] *curare,*[51] various *bacterial toxins,*[52] *morphine, atropine, adrenaline,* etc.[53] The comparable actions of *histamine* and various *hormones* will be discussed below in the passage dealing with stimuli influencing the response of gastrointestinal tract during the G-A-S.

The effect of the **diet** deserves special attention. We have repeatedly mentioned that *fasting* animals are exceedingly sensitive to the gastric ulcer-producing action of the A-R.

As we shall see below certain food constituents (especially glucose or buffer substances which neutralize the gastric acid) are especially effective in preventing the formation of gastrointestinal ulcers during the A-R. It is common clinical knowledge furthermore that the diet also exerts an important influence upon the course of peptic ulcers in man.[54]

During and immediately following the second World War numerous informative pertinent observations were made on concentration-camp inmates and among the civilian populations of impoverished occupied territories. Here, the incidence of various gastric dyspepsias and of gastric and duodenal ulcers was found to have risen considerably during the period of malnutrition.[55] Chronic diarrhea, edema of the gastrointestinal tract (and perhaps also the disintegration of Peyer's patches) predisposes severely starved individuals to a variety of intestinal infections, such as dysentery, typhoid and paratyphoid, to which they easily fall prey.[56]

[41] Dalton A35629/41.
[42] Selye A8052/38.
[43] Lillehei and Wangensteen B18000/48.
[44] van Liere **B26199/42.**
van Liere et al. B26763/48,
Reynolds and Phillips B4516/47.
[45] Meessen B23957/47.
[46] Dustin 94160/41.
[47] Eppinger B37085/49.
[48] Davis A37428/41.
[49] Selye and MacLean A75410/44.
[50] Graef et al. B39006/48,
Karnofsky et al. B37880/48.
[51] Cole et al. B38679/47.
[52] Jona B41768/47,
Penner and Bernheim B37656/42.
[53] Selye 36031/36, 36032/36.
[54] Palmer **95299/46.**
[55] Brull B23116/47,
Brull and Lambrechts B26140/45,
Dumon-Ruyters B3032/45,
Gsell **B27611/48.** Uehlinger **B27612/48.**
[56] Uehlinger B27612/48.

In experimental animals certain qualitatively inadequate diets proved to cause gastric and duodenal ulcers. Here again the non-specificity of the response is clearly indicated by the fact that deficiency in such varied food constituents as *calcium, thiamine* and *pantothenic acid* produced essentially similar lesions.[57]

Stimuli Influencing the Response of the Gastrointestinal Tract During the G-A-S

Hypophysis. — The hypophysis-adrenal discharge is not responsible for the production of gastrointestinal lesions during the G-A-S. Indeed, in **hypophysectomized** animals alarming stimuli produce gastric ulcers even more readily than in intact controls and treatment with crude anterior-pituitary extracts tends to restore the resistance of the gastrointestinal mucosa towards normal.[58]

Following administration of various **anterior-pituitary extracts** to intact animals, no characteristic changes are found in the gastrointestinal tract, at least none that coud be related to the G-A-S.[59] Nevertheless there is some evidence that *ACTH* exerts a specific effect upon the gastric mucosa in that treatment with this hormone causes a markedly increased urinary elimination of "uropepsin". This proteolytic enzyme is normally present in human urine and may be derived from the secretion of pepsinogen (by the peptic cells) directly into the blood-stream. Significantly, the effect of ACTH upon uropepsin excretion is absent in patients with pernicious anemia and after total gastrectomy. ACTH also increases pepsin secretion into the gastric juice; it appears to stimulate both the endocrine and the exocrine activity of the gastric mucosa.[59a]

Conversely, vasopressor **posterior-lobe extracts** produce severe hemorrhagic lesions in the acid-bearing area of the stomach. It has been claimed that even chronic ulcers may be produced in this manner. The causative principle has been suspected to be a true **"gastrotoxic hormone"** of the posterior-lobe, which allegedly also participates in the regulation of hemopoiesis.[60]

The above changes are accompanied by the usual adreno-cortical stimulation, thymico-lymphatic atrophy and other manifestations of the A-R, hence they may not be related to any specific principle but rather to the systemic stress effect of these highly toxic preparations. In any case it is unnecessary to invoke a hypothetical new hormone, since similar gastric lesions are produced by purified *vasopressin.*[61] Yet vasoconstriction is known to sensitize the gastric mucosa to ulcer-formation during the A-R, hence the specific vasopressor action of this posterior-lobe hormone may act as a conditioning factor. This would explain the unusual intensity of the gastric manifestations which it produces.

Vasopressin is also useful in combating postoperative constipation and ileus,[62] but there is no proof that the disturbances in gastrointestinal motility during the G-A-S are due to a diminished production of this hormone.

Adrenals. — **Adrenalectomy** frequently results in gastric and duodenal ulcer formation in various experimental animals.[63] Immediately after ablation

[57] Berg et al. **B37735/49.**
[58] Selye 38798/37, B1204/46.
[59] Selye **94572/49.**
[59a] Gray et al. B46965/50.
[60] Dodds and Noble 54523/35, 55669/34.
[61] Selye et al. 58020/36.
[62] Adams B10543/37, Selye **94572/49.**
[63] Elliot 33473/14,
Mann 32971/16, 33376/16,
Stewart and Rogoff 22415/29.

of the suprarenals, when ulcers have not yet formed, exposure to systemic stress produces them with particular ease.[64]

In experiments with vesicants (which are rapidly detoxified in the body) it was shown that if the circulation to portions of the intestine is occluded during and a few minutes after intravenous administration of the drug, the clamped segment is protected from ulceration. Adrenalectomy affords no protection. Hence here we must regard the lesions as due to a direct peripheral action of these toxic substances.[65]

Thus the presence of the adrenals is certainly not necessary for the production of this particular manifestation of the A-R; indeed the decreased vitality of an adrenalectomized animal predisposes it to the formation of gastrointestinal ulcers during stress. This effect of hypocorticoidism upon gastrointestinal ulcer formation during the A-R is similar to that exerted by a lack of cortical hormones upon the development of most other signs of shock or damage (e.g., hypoglycemia, hyperkalemia, hypothermia, hemoconcentration). In the absence of a defensive corticoid production these manifestations of "relative hypocorticoidism" are greatly accentuated. In agreement with this interpretation, suitable substitution therapy with corticoids diminishes the tendency of the adrenalectomized rat to develop gastrointestinal ulcers under the influence of such alarming stimuli as cold, muscular exercise or trauma.[66]

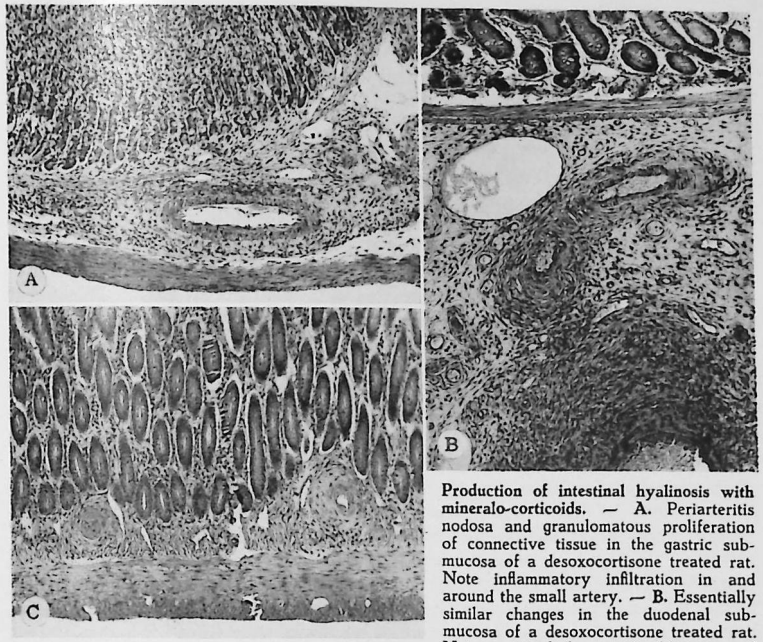
It has been claimed that adrenalectomy causes a pronounced depletion of the blood vitamin-K content in dogs and that the resulting hemorrhagic tendency is responsible for the formation of bleeding gastrointestinal ulcers,[67] but this interpretation requires further confirmation.

Overdosage with **adrenaline** also tends to cause gastrointestinal lesions similar to those described as characteristic of the A-R. Perhaps these are somewhat more intense than could be expected merely on the basis of the resulting systemic stress, but here — as in the case of vasopressin — the specific vasoconstrictor effects of the hormone may be superimposed upon the A-R and thus accentuate this particular manifestation of it. Vascular disturbances in the gastrointestinal mucosa notoriously sensitize it to exulceration.[68] It has also been noted that although upon adrenaline injection intestinal motility is initially depressed, this is soon followed by a period of increased motility, both in experimental animals and in man.[68a] Hence, perhaps the adrenergic discharge also participates in the alterations of gastrointestinal motility during the G-A-S.

Overdosage with **corticoids** induces no very characteristic changes in the gastrointestinal tract. Yet, in the rat after severe DCA intoxication, there is a remarkable tendency for the formation of gastric edema. This may be related to the NaCl-regulating action of this mineralo-corticoid, since the gastric mucosa is an important portal for Cl-elimination. Upon chronic treatment with DCA or desoxocortisone, periarteritis nodosa of the gastric vessels may lead to local circulatory disturbances; these however, are merely one manifestation of the generalized vascular hyalinosis syndrome.[69]

RPS may also affect the intestinal tract. Following partial constriction of a renal artery young dogs frequently develop intussusception.[69a]

[64] Selye 36032/36. B1204/46.
[65] Karnofsky et al. B37880/48.
[66] Selye 35935/ND.
[67] Constantinescu and Vasiliu B19797/43.
[68] Selye 36032/36. B1204/46.
[68a] Dreyer and Zauder B42280/49.
[69] Selye B1204/46. B43385/50.
[69a] Selye 94572/49.



Production of intestinal hyalinosis with mineralo-corticoids. — **A.** Periarteritis nodosa and granulomatous proliferation of connective tissue in the gastric submucosa of a desoxocortisone treated rat. Note inflammatory infiltration in and around the small artery. — **B.** Essentially similar changes in the duodenal submucosa of a desoxocortisone treated rat. Note particularly great dilatation of lymph vessels in upper left corner underneath the muscularis mucosae and thick hyalin deposit underneath the intima of the large artery near lower edge of the field. — **C.** Intense hyalinization of the blood-vessels and the surrounding mucosal collagen in the jejunum of a DCA treated rat. After Selye B43385/50 and35935/ND.)



Intussusception following constricting ligature of one renal artery. Young female dog in which the left renal artery was constricted by a partial ligature in order to produce hypertension. Note two intussusceptions in this loop of small intestine. This is a frequent complication in very young dogs following the Goldblatt operation, but the mechanism of the change is not yet known. (After Selye 94572/49.)

Other hormones and hormone-like substances. — Several clinicians have claimed that **folliculoids** may have a beneficial effect in the therapy of peptic ulcer, but in animals, overdosage with estrone [70] or stilbestrol [71] actually produces gastric erosions, conjointly with other manifestations of the A-R. Here again, as with most alarming stimuli, the ulcers were more readily obtainable in hypophysectomized or adrenalectomized than in intact animals.

Insulin-overdosage (as so many procedures which cause severe hypoglycemia, e.g., adrenalectomy, fasting, partial hepatectomy) is particularly prone to cause severe gastric erosions in the rat.[72] Since glucose administration selectively counteracts ulcer-production during the A-R (see below) it is possible that here the hypoglycemia acted as a "conditioning factor" specifically sensitizing the gastric mucosa to this manifestation of the A-R.

Histamine strongly stimulates the secretion of HCl by the stomach and continuous excessive secretion of a highly acid gastric juice is an important factor in the pathogenesis of peptic ulcers. Hence it appeared logical to suspect that the endogenous production of histamine (or some similar metabolite) may be involved in the production of gastrointestinal ulcers during the A-R. Experimental gastric or duodenal ulcers can be readily produced by histamine administration in various currently used animal species, particularly if the compound is administered so as to act continuously for a long time (e.g., continuous intravenous infusions, histamine mixed with beeswax). If in such experiments the rate of continuous histamine administration is raised above the level which produces maximal gastric secretion, the severity and rapidity of ulcer formation is further augmented. This was taken to show that histamine "exerts some additional action to decrease the resistance of the intestinal mucosa to the destructive effect of the gastric juice".[73]

It is probable that histamine is produced endogenously in the stomach during the normal secretory process "and is, so to speak, a part of the normal secretory mechanism". This agrees with the view that histamine-liberation could represent the common pathway in the production of gastric ulcers by various agents.[74] Histamine also causes a prolonged stasis in the gastric mucosa and this probably contributes to its ulcer-producing effect, since the tissue thus devitalized readily undergoes self-digestion by the gastric juice. We already have had occasion to mention that transection of the vagi tends to prevent the formation of gastric ulcers and to expedite their healing in man, while vagal stimulation can produce gastrointestinal erosions in animals. It has been suggested that histamine is liberated in the gastric mucosa by *acetylcholine* and hence the question was asked "would not acetylcholine, if produced in unusually large amounts by the action of the vagus nerves, mobilize in its turn an excess of histamine which might disturb the blood circulation in certain regions of the gastric mucosa?" [75] This interpretation, if proven correct, would help to clarify the interrelations between vagus stimulation and histamine liberation in the pathogenesis of peptic ulcers.

It has already been mentioned that in the rat an acute phlegmonous appendicitis (or more precisely an inflammation of that region in the cecum which corresponds to the human appendix) can be produced by intravenous administration of histamine. This lesion is similar to that occasionally observed

[70] Selye et al. 38815/36.
[71] Selye A18206/39.
[72] Selye et al. 58020/36.
[73] Hanson et al. **B36389/48.**
[74] Babkin B123/44.
[75] Babkin B123/44.

during an A-R elicited by other very acutely damaging stressors.[76] In the rat, prolonged treatment with large doses of histamine can even produce inflammatory lesions throughout the gastrointestinal tract with severe diarrhea.[77] If an excessive amount of histamine is really produced during the G-A-S, it may therefore play a rôle even in the pathogenesis of gastrointestinal lesions other than peptic ulcers and appendicitis.

When an animal is protected against the acute lethal effects of histamine, by simultaneous treatment with *anti-histaminics* the production of peptic ulcers is greatly facilitated. This is due to the fact that the action of histamine upon the gastric mucosa is not significantly influenced by such compounds, while most of its other toxic effects are abolished. In this manner very large doses of histamine can be given without endangering life and thus the ulcer-producing action is brought out selectively.[78] In this manner it was possible to improve greatly the technique of experimental ulcer production by histamine. Recent observations show however, that at least certain anti-histaminics (e.g., tagathen) inhibit even the ulcer-producing action of histamine if they are given in large quantities. This may have practical applications in the therapy of peptic ulcers.[79]

Dogs can be locally sensitized by the *topical injection of antigens* into the stomach or duodenum, so that a subsequent systemic administration of the same antigen causes a marked local reaction with edema at the site of pretreatment. Such a gastrointestinal edema acts as a conditioning factor favoring the production of ulcers by histamine.[80]

Several alarming stimuli such as *muscular exercise*,[81] *hemorrhages* [82] and *burns* [83] have been shown to increase the ulcer-producing effect of histamine administration. *Nitroglycerine* [84] and slowly absorbable preparations of *adrenaline* or *vasopressin* in beeswax exert a similar effect,[85] perhaps due to their direct action upon the gastrointestinal blood-supply.

From our point of view the great interest of all these observations lies in the fact that they clearly illustrate the possibility of sensitizing the organism specifically to certain manifestations of the A-R. This "selective conditioning" of certain targets helps us to understand why systemic stress can produce some "diseases of adaptation" without necessarily producing them all.

Certain so-called **gastrointestinal hormones** (e.g., enterogastrone, urogastrone and anthelone) inhibit gastric secretion and tend to prevent the formation of peptic ulcers after various interventions. The possible relationship between these substances and the hormones produced by endocrine glands has been reviewed elsewhere.[86] Hypophysectomy allegedly diminishes the urogastrone content of the urine.[87] If confirmed, this would suggest that gastrointestinal hormones also participate in the pathogenesis of ulcers during the A-R.

Nervous stimuli. — We have already mentioned data which lead us to believe that nervous stimuli play an important rôle in the pathogenesis of gastro-

[76] Selye 66642/36, 68819/37.
[77] Selye A8425/38.
[78] Halpern and Hamburger B23153/48, Vallery-Radot et al. B1901/47, Winter and Mushett B17782/48.
[79] van Meter and Oleson B36932/49.
[80] Friesen et al. B38058/48.
[81] Lillehei and Wangensteen B18000/48.
[82] Lillehie et al. B19862/48.
[83] Friesen and Wangensteen 95355/46.
[84] Baronofsky and Wangensteen B1321/46.
[85] McCorriston et al. B34774/49.
[86] Baronofsky and Wangensteen B37653/45. Kaulbersz et al. B23086/45.
[87] Selye **94572/49.** Kaulbersz et al. B23086/45.

intestinal ulcers during exposure to systemic stress (see above). Nervous stimuli can not only elicit gastric ulcers but may also participate in their production by other alarming stimuli. Thus, the particularly severe gastric ulcers, normally produced in the rabbit by the combined action of histamine and nitroglycerine, are at least partially inhibited by subdiaphragmatic bilateral *vagotomy*.[88] On the other hand post-ganglionic *sympathectomy* of the gastrointestinal tract potentiates the susceptibility to histamine-induced ulcers in dogs.[89] The production of acute hemorrhage or ulceration in the pylorus and duodenum by burns to the hind-legs was not noticeably influenced by low *spinal-cord transection* in cats, although in the same animals such elimination of the nervous factor decreased the resulting hemoconcentration.[90]

Diet and drugs. — Dietary factors and drugs likewise modify the gastrointestinal response during the G-A-S. "Experiments on albino rats indicate that the gastric ulcers which appear in the course of a severe alarm-reaction (produced by high spinal-cord transection) may be prevented by the prophylactic administration of various **food** substances, **aluminium-hydroxide gel** and especially by comparatively small doses of **dextrose.** Dextrose is effective when given either per os or intravenously. It prevents gastric ulcer formation even in doses insufficient to raise the glucose content of blood above the normal level for the duration of the experiment. The prophylactic effect of dextrose is non-specific in the sense that the compound prevents the formation of gastric ulcers by a variety of widely different damaging agents such as formaldehyde injections, exposure to cold or spinal-cord transection".[91]

The acute gastric erosions, noted in rats following ligature of the pylorus are likewise aggravated by quantitatively insufficient diets. They are particularly pronounced in rats which had previously been rendered **thiamine**-deficient,[92] but are inhibited by **salicylates** [93] and **T.E.A.** [94]

In the dog, **atropine** completely suppresses the hypermotility of the stomach, but does not affect the increase in its secretion normally induced by burns. It was concluded that the "gastric motility of burns may be due to a cholinergic mechanism, and gastric secretion of burns may be due to a histaminic mechanism"... "If these findings can be applied to the human being, atropine and an antacid are recommended in cases of burns in order to prevent vomiting, gastrointestinal hemorrhages and the formation of ulcers.[95]

Penicillin diminishes, or even prevents the formation of gastric and duodenal ulcers in the burned dog.[96] Hence it was concluded that "since penicillin-treated animals did not develop ulceration in spite of elevated blood-histamine values, there is further indication that blood-histamine does not enter into the pathogenesis of Curling's ulcer.[97] We do not feel that this deduction is entirely justified. There is ample evidence (see above) that during the A-R, factors directly damaging the gastrointestinal tract (e.g., x-irradiation, high acidity, vascular disturbances) may greatly increase susceptibility to ulcer-formation. It is possible that penicillin exerted its beneficial effect in burns only because it interfered with the destruction of the mucosa due to its antihistaminic and

[88] McCorriston et al. B34774/49.
[89] Lillehei and Wangensteen B26420/48.
[90] Kabat and Hedin 83643/42.
[91] Selye and MacLean A75010/44.
[92] Shay et al. 93231/46.
[93] Pauls et al. B38086/48.
[94] Maxwell et al. B38085/47.
[95] Necheles et al. B2321/46.
[96] Hartman 93230/46.
[97] Behrmann et al. B4278/46.

antibacterial actions. The above observation thus seems to prove merely that under the particular circumstances of this experimental arrangement, a moderately high blood-histamine-level did not in itself suffice to produce erosions.

Gastrointestinal Diseases of Adaptation

Gastrointestinal ulcers. — The importance of the stress factor in the pathogenesis of gastroduodenal ulcers has been emphasized by most reviewers of this subject [98] and it is rather significant that peptic ulcer has variously been designated as a "stress disease",[99] or even an "endocrine disease".[100] A relationship to stress is fairly well established for the chronic types of gastric and duodenal ulcers, but it is even more obvious in the acute gastrointestinal erosions such as "Curling's ulcer" or the "air-raid ulcers" (cf. above). Extensive systematic studies were undertaken to elucidate the rôle of the G-A-S in the production of gastrointestinal ulcers [101] and it has been concluded concerning the acute type that "such ulcerations can complicate very diverse pathologic states in patients, especially: sub-acute or chronic infections, burns, surgical interventions, more or less sudden endocranial processes, intense emotional shock, anaphylactic shock, etc., all conditions which are particularly effective in eliciting an alarm-reaction".[102]

Undoubtedly in man **emotional tension** is the most common stressor agent involved in the pathogenesis of both the acute gastrointestinal erosions of the A-R and the chronic peptic ulcer. Statistical studies have shown that certain *occupations* which involve a great deal of mental stress and tension, predispose to the development of peptic ulcers and "there is much to suggest that the increase in duodenal ulcers may be due to the increase in the stresses and strains of modern life".[103]

Of course *"constitutional" factors* are largely responsible for the equanimity or excitement with which we respond to a potential stressor. Certain "personality traits are easily noted and are stressed by most observers, tenseness, unusual and perhaps ineffectual drive, continuous nervous haste with the tendency to non-completion of any task, an unrealizable compensatory tendency to be self-sufficient, independent, distant and, perhaps, critical and obstinate, individualism, tendency to be overly conscientious and painstaking in performing ordinary duties but not consistently profound, tendency to worry continually but to repress outward signs of emotion, hypersensitivity, and of a peculiar instability withal".[104] The personality features and emotional reactions of patients with peptic ulcer, gastritis and duodenitis have been carefully analyzed from the psychiatric point of view and there remains no doubt that in the vast majority of the cases these can be regarded as psychosomatic disorders.[105]

Statistical studies have shown, furthermore, that during times of *war* — presumably as a result of psychic strain — the incidence of peptic ulcer increases in various countries.[106] Of course the personnel of the armed forces, being

[98] Brown **B36454/46**, Card **B37400/49**, Wolf and Wolff **B46313/47.**
[99] Ogilvie B36284/49.
[100] Crabb B39720/43.
[101] Firket and Betz B39208/49, Selye B1204/46.
[102] Firket and Betz B39210/49.
[103] Doll and Jones **B37398/49.**
[104] Wilensky B2566/46.
[105] Halliday B44599/43, Mittelmann and Wolff B322/42.
[106] Dumont-Ruyters 95583/44, Henning and Stadler B45309/49, Saksela B45646/47, Vartiainen B39569/46, De Witte B44383/46.

exposed to particularly severe nervous stress, is even more subject to peptic ulcer in war time.[107] Hunger further augments this tendency [108] in man just as it does in animal experiments concerning the G-A-S (cf. above).

Perhaps the most convincing observations showing the importance of emotional factors in the genesis of acute gastric ulcers were derived from patients with a gastric fistula. Here it was possible to follow the actual development of morphologic changes in the gastric mucosa under the influence of *sudden emotional stress*. From such studies "it appears likely, that the chain of events which begins with anxiety and conflict and their associated overactivity of the stomach, and ends with hemorrhage or perforation, is that which is involved in the natural history of peptic ulcer in human beings".[109]

The relationship between peptic ulcer and other diseases of adaptation is further emphasized by the fact that *local vascular changes* (hyalinization, endarteritis obliterans and periarteritic lesions) are frequently seen in the gastric and duodenal mucosa of patients with gastroduodenal ulcers.[110] These lesions resemble those artificially produced by mineralo-corticoids;[111] they tend to be accompanied by hypertension and by hyalinization of vessels even outside the gastrointestinal tract. It is probable that nutritional disturbances resulting from partial vascular occlusions predispose the mucosa of the digestive tract to ulceration, and inhibit the healing of an already formed erosion.

Acute erosions of the gastric mucosa are particularly common among patients with *organic brain disease*, especially liquefaction necrosis or hemorrhages. This is reminiscent of the fulminating hemorrhagic gastric erosions produced by experimental interventions on the central nervous system (especially the hypothalamus) of animals. In all these instances the basic mechanism was assumed to be a derailment of the G-A-S.[112]

The *glucose tolerance curve* is frequently abnormal in patients suffering from gastric ulcer, but there is some disagreement concerning the type of anomaly characteristic of this disease and its possible pathogenic significance.[112a]

The *gluco-corticoid excretion* is often subnormal in ulcer patients.[112b]

The **therapeutic** value of *vagotomy* in the treatment of peptic ulcers [113] furnishes further proof of the important part player by nervous factors in the pathogenesis of this disease.

Because of the prominent rôle of hypophyseal and steroid hormones in defense against stress, attempts have been made to use *corticoids*,[114] *folliculoids*,[115] *testoids* [116] and even *posterior-pituitary* preparations [117] for the therapy of peptic ulcer. Up to now the results have been variable but large doses of the highly active ACTH and gluco-corticoid preparations have not yet been used. In dogs *ACTH* appears to inhibit the development of the "Mann-Williamson type" of experimental ulcer.[117a]

[107] Gunther B44280/48, Masini B44454/46.
[108] Dauwe B44712/48.
[109] Wolf and Wolff A56485/42.
[110] Betz B26164/48, B39209/49, de Navasquez and French B37961/47.
[111] Selye B43385/50.
[112] Betz B39209/49.
[112a] Goldschmied B45475/48, Briesendorp B45829/48.
[112b] Sandweiss B46301/49.
[113] Hollander B33232/46, Kirsner et al. B37500/47, Walters B37426/49, Walters and Fahey B39570/49.
[114] Bastenie et al. B44661/49, Gunther B32087/46, Hassanein B40866/47, Piccinini B43771/48, Sadek B42868/47.
[115] Beer and Thalmann B45310/49, Larizza B38402/49, Wagner B43772/48.
[116] Larizza B38402/49.
[117] Kobulniczky and Bunyor B36582/48.
[117a] Sandweiss B46301/49.

Ulcerative colitis, mucous colitis. — Emotional factors, similar to those mentioned in connection with the development of peptic ulcer, undoubtedly play a rôle in the pathogenesis of mucous and ulcerative colitis and frequently this disease is amenable to psychotherapy.[118] In many instances ulcerative colitis is accompanied by a polyarthritis and sometimes it responds well to non-specific vaccine therapy.[119] All these facts suggest some relationship to the diseases of adaptation. In this connection it is particularly noteworthy that in a limited number of cases ACTH proved to cause marked remissions in ulcerative colitis.[120] During pregnancy, ulcerative colitis likewise often improves,[120a] but it remains to be seen whether this is the result of increased gluco-corticoid production.

The *lysozyme* of the stools is usually greatly augmented in patients with chronic ulcerative colitis and in dogs similar intestinal lesions may be produced by the administration of this enzyme.[120b] Presumably it acts by removing the protective mucous from the surface of the intestinal lining and thus renders it more susceptible to proteolytic digestion by the bacterial flora of the colon. Preliminary observations suggest that ACTH diminishes the lysozyme content of the stools. (Cf. p. 247.)

Celiac disease. — For the discussion of this condition the reader is referred to pages 127 and 189.

Gastrointestinal allergy. — Derailments of the G-A-S probably participate in the pathogenesis of various so-called gastrointestinal allergies. These are generally characterized by inflammatory lesions in the gastrointestinal mucous membrane, with edema and hyper- or hypo-motility of the muscular coat. They often respond very favorably to adrenaline.[120c]

Necrotizing enteritis. — This allegedly new disease has frequently been reported during the last few years, especially in the undernourished population of occupied Germany. The clinical picture is characterized by sudden onset of colicky abdominal pain and bloody diarrhea. Morphologic examination reveals hemorrhagic necrosis of the intestinal villi, severe hemorrhagic edema of the submucosa, hyalin degeneration of the arteriolar walls and an inflammatory infiltration with numerous eosinophils. As the nutritional changes in the gut progress, eventually large portions of the intestine may become necrotic. Some infectious etiology has been suspected, but could never be proven and most students of this disease assign a considerable rôle in its pathogenesis to starvation, anxiety and allergic reactions.[121]

Appendicitis. — It has already been mentioned that appendicitis-like changes can be produced in animals by exposure to various acute alarming stimuli.[122] The appendix contains a great deal of lymphatic tissue and, as we have repeatedly stated, the lymphatic organs are particularly sensitive to non-specific damage, because the gluco-corticoids liberated during the G-A-S cause lymphocyte disintegration. This may perhaps create a "locus minoris resistentiae" in the appendix and explain the development of appendicitis in patients

[118] Almy and Tulin B45648/47, Daniels B26776/48, B24034/48, Halliday B44599/43, West B37499/46.
[119] Kirshen B33748/47.
[120] Bauer B45576/49, Dutoit B47864/50, Dutoit and Bauer B46988/50.
[120a] Felsen and Wolarsky B45830/48.
[120b] Meyer et al. B45707/48, B46081/49.
[120c] Rudolph and Sage B45511/48.
[121] Koch B44154/48, Schoen B44153/48.
[122] Selye 68819/37.

suffering from a variety of contagious diseases.[123] In this sense certain types of appendicitis have also been classified as diseases of adaptation.[124] The so-called "allergic appendicitis" probably likewise belongs to this group.[124a]

Tonsillitis. — The acute tonsillitis often noted after exposure to cold, following burns, radiation damage and other types of non-specific injuries may also find its explanation in a derailment of the G-A-S. As in the case of appendicitis, it is probable that the gluco-corticoids, produced during stress, could diminish local resistance to microbial development in the tonsils as a result of lymphocyte disintegration.[125] While this may apply to most kinds of common tonsillitis, particularly extensive investigations concerning the so-called allergic tonsillitis, especially that accompanying erythema nodosum, led to the conclusion that this is also a disease of adaptation.[126]

Theories and Summary of Observations Concerning the Participation of the Gastrointestinal Tract in G-A-S

During the G-A-S, particularly in the A-R period, the gastrointestinal tract exhibits certain rather **characteristic** reactions. Among these are hyperemia with the formation of bleeding erosions in the stomach and the upper intestinal mucosa. Presumably these ulcers are largely due to the intense autonomic discharge which occurs in the splanchnic area during exposure to stress and elicits marked peristaltic, vasomotor and secretory reactions in the gastrointestinal tract. Almost simultaneously there is lympholysis in Peyer's plaques and the appendix. Often this syndrome is accompanied by diarrhea or constipation, nausea and vomiting. — All these changes tend to disappear during the resistant phase but may reappear in the stage of exhaustion.

Special emphasis has been laid upon the fact that unlike the lympholysis in the Peyer's plaques and appendix (which are presumably mediated by gluco-corticoids) the other gastrointestinal changes, especially the erosions, are not the result of **ACTH** and **corticoid** discharge and indeed are aggravated by hypophysectomy or adrenalectomy.

Vasopressin and **histamine** have a certain tendency to cause gastric ulcers in experimental animals; hence endogenous production of such hormones may play a rôle in the pathogenesis of the ulcers occasioned by stress itself. The particular ulcer-producing potency of these compounds is ascribed to certain specific conditioning factors, namely, the vasoconstrictor action of the posterior-lobe hormone and the gastric secretion-stimulating effect of histamine, respectively.

The **vagus** undoubtedly also plays an important rôle in the pathogenesis of gastrointestinal ulcers since vagotomy tends to prevent their development in animals during the A-R and often exerts a curative effect in the peptic ulcers of man. Conversely, prolonged vagus stimulation can in itself cause gastric ulcers in animals. It remains to be shown whether this is due to "histaminergic" stimulation.

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[123] Avancini B37993/48, Calvy B42367/48, Goodman and Silverman A58035/43, Sédallian and Monnet B45579/47.
[124] Ehrich B46789/50, Selye B1204/46.
[124a] Kline B37972/48, Rudolph and Sage B45511/48.
[125] Selye B1204/46.
[126] Ehrich B45789/50, Lucherini and Cecchi B35563/48.

Among the gastrointestinal **diseases of adaptation,** we listed *acute gastrointestinal erosions* ("Curling's ulcers", "air-raid ulcers", the gastrointestinal erosions of acute infections, intoxications, etc.) and the *chronic peptic ulcer.*

Like peptic ulcers, *mucous or ulcerative colitis* tend to occur in high-strung nervous individuals and can frequently be related to stress. In the latter conditions ACTH appears to have a beneficial effect.

Inflammatory changes in the lymphoid organs attached to the gastrointestinal tract, particularly *tonsillitis* and *appendicitis* may perhaps also develop as diseases of adaptation elicited by exposure to a variety of non-specific stressors. Here the acute disintegration of lymphatic structures apparently diminishes local resistance to otherwise non-pathogenic micro-organisms.

LIVER

The liver plays a very important rôle in most of the systemic stress reactions in which the whole organism is involved. Whenever systemic homeostasis is endangered, the prodigious adaptive powers of the hepatic cells are called upon. By regulating intermediate metabolism the liver can perform many important chemical reactions through its specific enzyme systems. It also acts as one of the major stores of proteins and carbohydrates. Furthermore, it is usually through the liver that depot-fat is made available for utilization by other cells. After being discharged from the adipose tissue during the catabolic phase of the A-R, fat is temporarily deposited in the hepatic cells, whence it is removed for combustion as needed.

The liver also stimulates erythrocyte formation through the production of a hemopoietic substance and through the destruction of damaged erythrocytes by its abundantly developed, reticulo-endothelial Kupffer cells. The liver produces several of the components of the blood-clotting system as well as the proteins (e.g., γ-globulins) from which serologic antibodies are formed. Its spacious venous sinuses can store a large amount of blood and make it available when emergency necessitates it. By the production of hypertensinogen the liver participates in the regulation of blood-pressure. It raises resistance to chemical poisons by destroying them, or by reducing their toxicity (e.g., through conjugation). Through the bile it helps to eliminate numerous, undesirable degradation products, at the same time facilitating the absorption of food from the intestine. These manifold activities of hepatic tissue have long been recognized as playing a prominent part in the maintenance of the normal body temperature, the chemical and cellular composition of the blood, the blood-volume, etc.

In view of these facts it is surprising at first sight, that so little is known about hepatic changes characteristic of the G-A-S. However, our ignorance concerning this point probably finds its explanation in that almost all the hepatic changes which ensue upon exposure to non-specific systemic stress, are largely dependent upon specific conditioning factors such as age, heredity, diet and previous exposure to stress. It is for this reason that the hepatic lesions, produced by diverse alarming stimuli, lack that uniformity which is so characteristic of the response of many other organs, for instance the thymus or the adrenals.

In pharmacology and especially in endocrinology we have learned to distinguish between "overt" and "masked" actions; the former are evident under all ordinary conditions of observation, while the latter are readily inhibited or modified by conditioning circumstances. The atrophy of the thymus following treatment with folliculoids or the enlargement of the seminal vesicles after testoid administration are examples of overt or manifest actions; the production of coma with insulin (which depends on the availability of sugar), or the induction of vaginal cornification with folliculoids (which is inhibited by progesterone), are examples of conditional or inhibitible hormone effects. This distinction must be clearly kept in mind in our consideration of the hepatic

changes characteristic of the G-A-S. The liver, as the "central chemical laboratory and depot" of the organism, is extremely versatile in its capacity of maintaining the homeostasis of the body as a whole, but it is even more efficient in maintaining its own structural integrity. This is clearly shown after surgical ablation of large portions of the hepatic parenchyme and manifests itself by an extremely rapid morphologic and functional repair. Such unusual regenerative powers could not fail to efface many of the hepatic changes caused by the G-A-S, unless we take special precautions to unmask them.

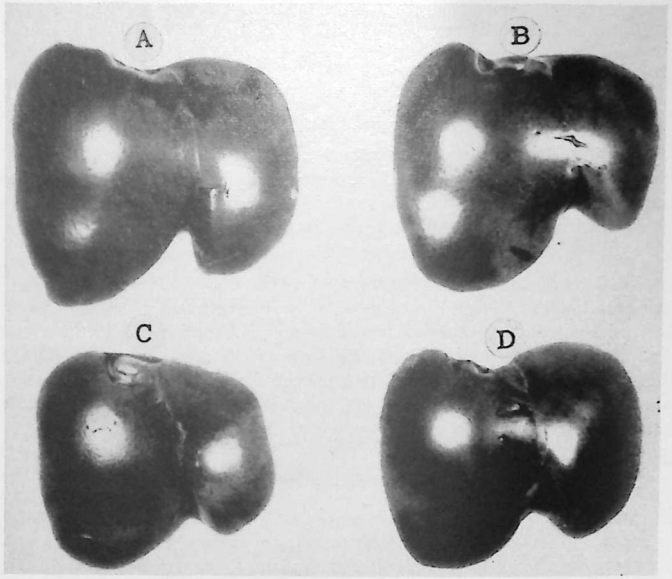
Clarification of this complex subject would be well worth while. Even a fully compensated (and hence "masked") change presumably has its functional implications since compensation is usually accomplished at a cost. Furthermore, a clear understanding of the hepatic response to systemic stress and of the factors which modify their development, would probably teach us a great deal about the pathogenesis of certain "idiopathic" liver diseases (cf. Hepatic Diseases of Adaptation).

Systemic Stress

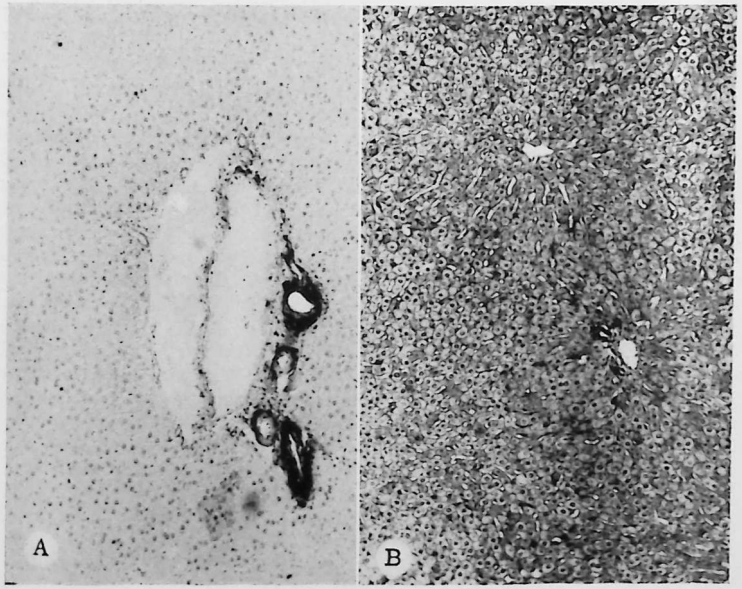
Characteristic response. — In animals, the following hepatic changes appear to be most characteristic of the A-R, inasmuch as they are most constant irrespective of the kind of alarming stimulus used: cloudy swelling, pyknoses, distension of Disse's spaces with edema of the stroma (especially around the gallbladder) and a decrease in the size of the liver. The latter may partly be accounted for by the diminished blood-content of the hepatic veins.[1] Sometimes the liver undergoes fatty infiltration, severe atrophy, focal necrosis and leucocytic infiltration.[2] In the course of the stage of resistance intense mitotic proliferation may compensate for the initial loss of hepatic tissue and the liver resumes its normal size. During the stage of exhaustion the involution of the liver becomes particularly severe again and there may be some cirrhosis. Cellular pyknosis or even extensive necrosis are even more common than during the A-R.[3]

In men who died from diverse types of shock-producing lesions (trauma, hemorrhage, infections, anesthesia, burns, intoxications, etc.) and who showed various other manifestations of the A-R, "hepatic degeneration and necrosis were regular features, but their degree and distribution were inconstant. Degeneration tended to be diffuse and the degree varied from granular cytoplasm and vesicular nuclei to necrosis. Absence of nuclei, pyknosis, and disintergrating cells were the criteria for necrosis. Frequently this involved only scattered group of cells; when the groups were large focal necrosis was seen. Occasionally, as after burns, heatstroke, or death from low atmospheric pressure, extensive necrosis involved the centers of the lobules and resembled that produced by poisons".[4] Usually these changes are initiated by a transudation into the capillary spaces and other manifestations of "serous inflammation".[5] It has been claimed that fluid accumulation in the interstitial spaces between the hepatic parenchyme and the endothelium of the sinusoids occurs only as an agonal or post-mortal change and that hence, serous inflam-

[1] Selye 38798/37, 35935/ND.
[2] Foglia and Selye A8424/38. Leblond et al. A18194/39. Selye 36031/36, 36030/36.
[3] Selye 35935/ND.
[4] Moon B19951/48.
[5] Eppinger B37085/49.



The liver during the A-R in the rat. — **A.** Control for B, C and D, in which an A-R was produced by exposure during 48 hours to the stressor effect of: — **B.** spinal cord transection at the height of the 7th cervical vertebra, — **C.** exposure to cold (+2°C), — **D.** repeated forced muscular exercise while food was withdrawn. Note great decrease in the size of the liver with varying degrees of fatty infiltration. (After Selye 35935/ND.)



Liver phosphatase during A-R. in the rat. — **A.** Liver of a normal control (incubated during 12 hours with glycerophosphate). The enzyme is located principally in the perithelial cells of the vessels and the bile canaliculi. Some reaction occurs also in the nuclei and particularly in the nucleoli of the hepatic cells. No reaction is observed in the cytoplasm. — **B.** Liver during A-R produced with formalin. The increase in the enzyme involves the nuclei, nucleoli, and the cytoplasm of the hepatic cells. (After Herlant and Timiras B41763/ND.)

Legend →

mation does not exist.[5a] In view of the extensive literature to the contrary, this claim requires confirmation.

The functional derangements of the liver during shock, and the part played by the hepatic tissue in the production of the shock-syndrome have been extensively reviewed elsewhere.[6] Hence we need not discuss them in detail, especially since in this book they have also been mentioned in the corresponding chapters of the section on metabolism (e.g., in connection with carbohydrate, lipid and protein metabolism, VDM, fibrinogen, etc.). Suffice it to add here that functional hepatic damage has been regarded as the principle factor in the pathogenesis of the so-called "exaggeration phenomena" (the sudden exaggeration of various pre-existing symptoms by an alarming stimulus).[7]

Trauma. — Traumatic injuries in dogs were found to cause congestion of the hepatic sinusoids, with degenerative changes in the parenchymal cells especially around the central vein.[8] In man the hepatic changes caused by severe trauma are essentially similar.[9] Liver function-tests performed on men immediately after surgical operations, revealed a considerable hepatic impairment, which slowly returns to normal after about five days. These changes were especially severe in patients who developed complications with infections of the wound or of the respiratory tract. A high-caloric diet, especially one containing much protein, and moderate muscular exercise after the operation, were found to exert a beneficial effect upon liver-function.[10]

Hemorrhage. — In dogs, hemorrhagic shock produces hepatic changes similar to those caused by traumatic injuries. Although this was not specifically mentioned in the description of the pertinent experiments, the illustrations show that Disse's spaces, around the hepatic sinusoids, were greatly distended with fluid.[11] This is very characteristic of the so-called "serous inflammation" of the liver.

The importance of the hepatic changes in the pathogenesis of the whole hemorrhagic shock syndrome has been demonstrated with particular clarity in dogs. The blood-supply of the liver was maintained at an approximately normal level by cross-circulation with a healthy donor dog, while the remainder of the organism was subjected to the consequences of a severe hemorrhage. Here, selective maintainance of the blood-flow through the liver effectively combatted the development of "irreversibility". Significantly in control dogs (which received the same amount of donor-blood as the experimental animals, but through the jugular instead of the splenic vein) the transfusion gave no effective protection against the development of irreversible hemorrhagic shock.[12]

Burns. — Extensive skin burns in man cause typical "serous inflammation" of the liver. There is degeneration and pyknosis of hepatic cells, disintegration

[5a] Popper B45820/48.
[6] Anonymous B36916/46, Wilhelmi **B18793/48.**
[7] Wilensky B3270/46.
[8] Cleghorn B2573/46.
[9] Moon B19951/48.
[10] Keeton et al. B36903/47.
[11] Cleghorn B2573/46.
[12] Frank et al. 93252/46.

of the lobular pattern especially around the central veins, as well as distension of Disse's spaces and the lymphatic vessels by albuminous plasma-fluid. The frequently mentioned edema of the gall-bladder wall and of the surrounding connective tissue, is probably a consequence of increased lymph-flow since there are close relations between the hepatic lymph-vessels and the connective tissue surrounding the gall-bladder.[13] In very severely burned patients this "serous inflammation" of the liver is accompanied by extensive focal necrosis, marked swelling of the Kupffer cells and sometimes by renal changes typical of the "crush syndrome".[14] Judged by liver-function tests in man the hepatic tissue appears to be most seriously afflicted at about the third to sixth day after the burn.[15]

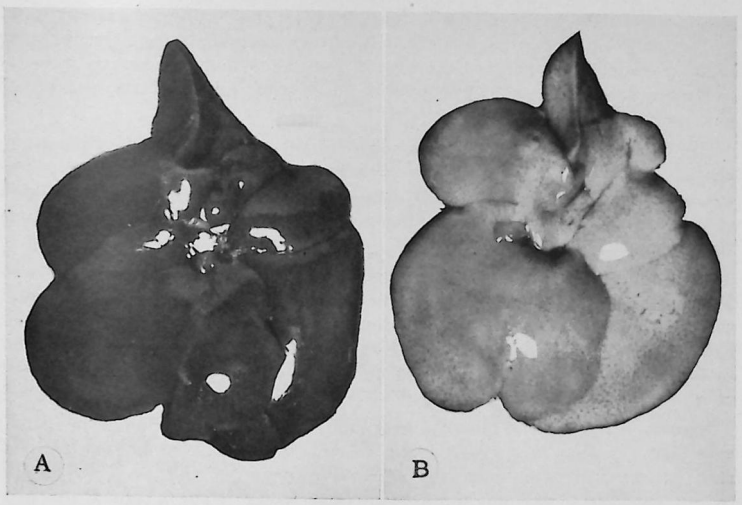
A careful survey of the experimental and clinical literature on burns reveals that, under certain conditions, eosinophilic infiltration (reminiscent of an anaphylactic reaction) and fatty degeneration of the hepatic cells may become prominent.[16] The intensity of the hepatic changes is aggravated by secondary infections, or after intoxications. This has been shown particularly for tannic acid which is often used in the local treatment of the injured areas.[17] Yet, all the above-mentioned characteristic lesions can develop in the liver without such complicating factors; hence it is justified to regard them as caused by the burn itself.[18] In the light of the G-A-S concept it is to be expected that the additional stress of an infection or intoxication would be superimposed upon any non-specific effect of the burn and may thus aggravate its effects.

Temperature. — Exposure to **heat** (diatherm or radiotherm) causes congestion, parenchymatous and fatty degeneration and often scattered areas of patchy focal necrosis in the rabbit. The necrotic areas are usually located around the central veins of the lobules and consist of acidophilic, hyalinized cellular debris, invaded by leucocytes and macrophages.[19] In men who die from heat-stroke, the liver is usually also congested although occasionally it may be ischemic. Frequently there is parenchymatous degeneration or centrolobular necrosis,[20] sometimes jaundice and "lower-nephron nephrosis" accompany the hepatic changes.[21] It has been emphasized that in man, as in animals, the effects of excessive heat upon the liver resemble those caused by other alarming stimuli and are accompanied by extra-hepatic manifestations of the A-R.[22]

Observations on mice, exposed to extremes of temperature, lead to the conclusion that in this species heat does not alter the fat-content of the liver although **cold** causes marked fatty infiltration of the hepatic parenchyme. The fat-deposition produced by cold was ascribed to stress and thought to be mediated by the pituitary-adrenal system. The simultaneous enlargement of the liver was of such magnitude that it could not be due exclusively to this accumulation of fat.[23] Perhaps it was caused by plasma-imbibition in the sense of a "serous inflammation". As we have said in the introductory paragraphs of this chapter, during the A-R, fat-deposition occurs in the liver only under

[13] Eppinger **B37085/49**, Zinck **B37654/40**.
[14] Buis and Hartman A36295/41, Erb et al. A57594/43, Harkins **82895/42**, Moon **B19951/48**, Walker and Shenkin 89895/45, Zinck B33768/40.
[15] Rae and Wilkinson B26861/44.
[16] Harkins **82895/42**.
[17] Hartman B38623/47, Prior B37994/48.
[18] Harkins 82895/42.
[19] v. Haam and Frost A30282/39.
[20] Gore and Isaacson B41903/49.
[21] Malamud et al. B18019/46.
[22] Moon B19951/48.
[23] Levin B32877/49.

certain conditions; in any case it tends to disappear immediately after the A-R phase of the G-A-S. Hence, in the above experiment, the failure to obtain fatty livers at a certain time after exposure to heat should not lead us to doubt that this is a characteristic feature of the A-R. Several other investigators who noted fatty infiltration following exposure to cold in rats [24] and guinea-pigs [25] considered this change as typical of the A-R.



Liver during A-R. in the rat. — **A.** Normal liver. — **B.** Naked eye view of the liver in a rat in which an A-R was elicited by exposure to cold. Note the light color of the hepatic parenchyme, due to marked fatty infiltration. The conditioning factors responsible for this change are not yet completely understood, but steatosis of the liver is quite variable and inconstant during the A-R. (After Selye B1204/46.)

The deposition of fat in hepatic cells, as well as changes in the total weight of the organ, are clear-cut examples of G-A-S changes which depend largely upon conditioning influences such as the diet, genetic constitution, or the availability of glycogen stores. It has been found for instance that in rats, in which an A-R was produced by cold while they were completely deprived of food, the liver underwent a considerable decrease in weight, despite fat storage.[26]

Ionizing radiations. — A detailed survey of the pertinent literature shows that the liver is rather sensitive to **x-irradiation.** Judged by clinical observations, even after moderate exposure, the hepatic function is rapidly impaired, while bile-flow and the urinary excretion of urobilinogen are augmented. Upon severe irradiation extensive hepatic necrosis may ensue. Animal experiments revealed a hyperglycemia, accompanied by a diminution of the hepatic glycogen stores; this latter reaction was tentatively ascribed to an emergency

[24] Leblond et al. A18194/39.
[25] Foglia and Selye A8424/38.
[26] Leduc and Guillemin B27410/49.

discharge of adrenaline.[27] Both in mice [28] and in rats [29] moderate x-irradiation suffices to cause pronounced fatty infiltration of the liver, presumably through the pituitary-adrenal system. In man and animals exposed to the **rays of the atomic bomb** the hepatic lesions were essentially the same as those caused by severe x-irradiation.[30]

Nervous stimuli. — In patients with "free anxiety" the hippuric-acid excretion after administration of sodium benzoate is significantly increased. This was ascribed to a change in hepatic function; it reverts to normal concurrently with a reduction of the free anxiety. "It may be postulated that the increase in the conjugating property of the liver of patients with free anxiety, belongs to the general category of changes which ensue when an organism is exposed to a situation which induces fear".[30a]

Ultraviolet rays. — Intense ultraviolet irradiation of the skin, sufficient to produce an erythema, also causes marked fatty infiltration of the liver in the mouse. From this it was concluded that the action must be mediated through some blood-borne principle since ultraviolet rays penetrate the skin only to a depth of about 0.5 mm.[31]

Muscular work. — Intense forced muscular exercise also causes marked fat deposition in the liver only in certain species, such as the guinea-pig [32] and mouse.[33] In the rat this is less pronounced but usually accompanied by marked hypertrophy of the Kupffer cells.[34] Here again this change was accompanied by the classical syndrome of the A-R and was interpreted as an essential part of it.

Anoxia. — Exposure to severe anoxia, induced by low atmospheric pressure, also causes degenerative changes and centrolobular necrosis in the liver of man, concurrently with other typical manifestations of the A-R.[35] Under certain conditions mice do not develop fatty livers when exposed to low barometric pressure,[36] but as we have said above, this should not prevent us from considering the change as typical of the A-R, since we are dealing with a highly conditional reaction. Widespread focal necrosis of the liver has also been noted in various species exposed to excess CO_2.[37] In the cat anoxia may cause serous hepatitis.[37a] In men who died from drowning similar changes are found, sometimes in conjunction with edema of the gall-bladder.[37b]

Diseases. — Many spontaneous diseases of man are known to cause more or less pronounced functional or even morphologic liver damage. The relationship between these lesions and the G-A-S will be discussed in connection with the diseases of adaptation (cf. Hepatitis, Liver cirrhosis). Here we merely wish to emphasize that "serous inflammation" of the liver,[38] as well as various degenerative lesions and even focal necrosis, are common accompaniments of all those diseases (especially the acute infections and intoxications) which elicit the syndrome of "medical shock".[39]

[27] Ellinger **68685/35.**
[28] Ellinger B24015/48.
[29] Leblond and Segal 82724/42, Leblond et al. A18194/39.
[30] Liebow et al. B41902/49.
[30a] Persky et al. B45379/50.
[31] Ellinger 87108/45.
[32] Foglia and Selye A8424/38.
[33] Levin B32877/49.
[34] Selye A15667/39.
[35] Moon B19951/48.
[36] Levin B32877/49.
[37] Meessen B38008/47, B37949/48.
[37a] Altmann B46049/49.
[37b] Rusakov B46050/49.
[38] Eppinger **B37085/49**, Winter B38059/47.
[39] Meessen B23957/47.

In hamsters bearing transplantable mixed-cell sarcomas, extramedullary hemopoiesis was particularly intense in the periportal connective tissue of the liver.[40] This is mentioned because LAP, as well as various tumor-extracts and tumor-transplants, tend to cause similar ectopic hemopoiesis in rats. As we have said elsewhere, this is especially common in the liver, the adrenal cortex and the connective tissue of the renal pelvis.

Serologic reactions. — It is difficult to appraise the hepatic changes during anaphylactic and allergic reactions. Serologic responses exert intense specific changes upon the liver, which differ widely in various species and, being superimposed upon the manifestations of the G-A-S, tend to obliterate the latter.

Drugs. — A variety of drugs are known to cause congestion, degenerative changes (especially fatty infiltration), gall-bladder-edema and focal necrosis in the liver of animals [41] and man.[42] These lesions have been considered to depend largely upon the resulting A-R or "serous inflammation".[43] However, here again, specific hepatotoxic actions may be superimposed, since many drugs (e.g., chloroform, CCl_4) exert a specific toxic effect upon the hepatic parenchyme.[44] The hepatotoxic action of vesicants appears to be non-specific.[45]

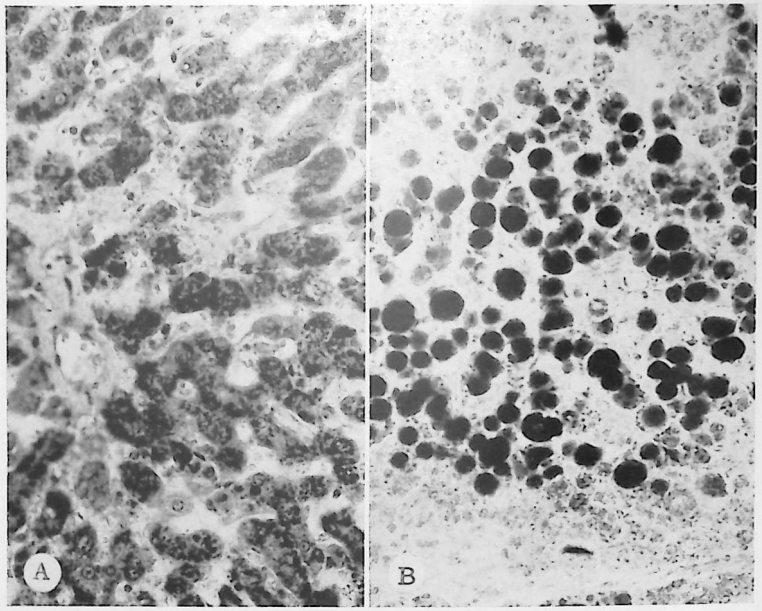
Diet. — The diet is a very important factor in conditioning the response of the liver to systemic stress (cf. below). However, malnutrition may in itself act as an alarming stimulus and elicit the typical hepatic manifestations of the A-R. For instance, complete starvation causes intense fatty infiltration of the liver especially in certain species (guinea-pig, mouse) and, characteristically, the fat-content of the hepatic cells diminishes rapidly as the animal progresses from the A-R to the resistant stage.[46]

In the livers of guinea-pigs fed on corn, round-cell infiltrations in the portal triangles and pronounced proliferation of the Kupffer cells have been described as a characteristic finding.[47] This was not specifically related to the G-A-S (which at the time of these observations had not yet been described), but it is noteworthy that the same animals showed marked thymico-lymphatic atrophy, gastric ulcers, adrenal stimulation and other typical manifestations of the A-R.

Among the malnourished inmates of concentration camps, fatty infiltration of the liver, congestion, dilatation of Disse's spaces, accumulation of brown "wear and tear pigment", lymphocytic infiltrations of the periportal spaces, hemosiderosis, loss of glycogen and severe liver atrophy often occur in association with clinical signs of deranged hepatic function. These changes have been regarded as quite characteristic of the "hunger disease" and more particularly of protein deprivation.[48]

Certain amino-acids (e.g., glycine) are known to exert rather specific hepatotoxic effects and can cause extensive liver necrosis.[49] This as well as the changes produced by many other hepatotoxic diets (e.g., deficiency in lipotropic factors, certain amino-acids or vitamins) are largely specific lesions; although close interrelations appear to exist between these specific hepatic changes and those characteristic of the G-A-S. It would be difficult to assess the rôle of the former during exposure to systemic stress.

[40] Kelsall and Crabb B18013/47.
[41] Eppinger B37085/49, Foglia and Selye A8424/38.
[42] Moon B19951/48.
[43] Eppinger **B37085/49**, Terbrüggen and Deneke B38040/47.
[44] Cabot B37879/48, Sellers et al. B38060/48.
[45] Dekanski B37985/48.
[46] Selye 35935/ND.
[47] Rondoni and Montagnani B23143/15.
[48] Gsell B27611/48, Overzier B45391/48, Schmengler B41796/48, Uehlinger B27612/48.
[49] Hay 93491/47.



Fatty infiltration of the liver during starvation, in man. — **A.** Numerous, medium sized fat droplets in the central portion of a liver lobule, in a 57-year-old, starving, female concentration-camp inmate. — **B.** Infiltration with very large fat droplets in a 39-year-old man suffering from severe undernourishment. (After Uehlinger B27612/48.)

Stimuli Influencing the Response of the Liver During the G-A-S

Unlike some of the organs discussed in previous chapters of this book, the liver responds to so many stimuli that it is difficult to single out those of sufficient interest to deserve special mention in connection with the G-A-S. This great responsiveness of the liver to diverse agents is the cause of the repeatedly mentioned fact that hepatic responses during the G-A-S depend so much upon incidental conditioning factors.

Hypophysis. — **Hypophysectomy** causes a pronounced atrophy of the liver in all mammals.[50] This is largely due to diminution of metabolism and especially of food intake. It was shown, for instance, that the usual changes in hepatic weight and composition are almost completely prevented in hypophysectomized rats force-fed quantities of food approximately isocaloric with the amounts voluntarily consumed by normal controls.[51]

We said above that the transposition of fat from the adipose tissue depôts into the liver is a rather characteristic change during the A-R. This transfer becomes particularly obvious if the total amount of liver tissue is reduced by *partial hepatectomy*. It is interesting therefore that in the starved rat, hypophysectomy inhibits the fat deposition in the liver which would normally occur upon partial ablation of this organ. Significantly, even a small residue of

[50] Selye 94572/49.

[51] Levin A71832/44.

anterior-pituitary (accidentally left behind at the time of hypophysectomy) suffices for the formation of fatty livers under those same conditions, hence the conclusion was inescapable that some anterior-lobe hormone is responsible for this effect. Apparently the organism must be completely depleted of circulating ACTH before this reaction is inhibited. Hypophysectomy performed simultaneously with the partial hepatectomy did not prevent the formation of fatty livers in the rat although this response never occurred if the pituitary was removed long before the hepatic intervention.[52] The rate of hepatic regeneration is also diminished by hypophysectomy in the rat.[53]

Purified *growth hormone* causes no disproportionate hepatic enlargement in the hypophysectomized rat.[54]

Treatment with **anterior lobe extracts** causes a disproportionate increase in liver-weight.[55] Thus in rats treated with a crude, alkaline, beef-pituitary extract, the average body-weight rose from 150 to 200 gm. and the liver-weight from 7 to 14 gm. during 2 months of treatment. From this it was concluded that certain anterior-pituitary extracts selectively stimulate hepatic growth and that the hepatotrophic effect is not merely due to the growth hormone.[56] This view received further confirmation by subsequent experiments in which it was shown that thyroxine greatly potentiates this hepatotrophic effect in the rat, hence probably the thyrotrophin content of the crude extracts added to their hepatotrophic potency.[57] It is noteworthy that anterior-pituitary extracts not only increase the size of the liver but produce extreme polymorphism of its nuclei with an outburst of mitotic divisions, some of which are abnormal and conducive to the formation of large polynuclear giant cells. In addition crude LAP may cause infiltration of the hepatic stroma with hemopoietic cells and megakaryocytes.[58] Such marked hepatotrophic actions could not fail to influence the regenerative power of the liver, which is so often called upon during the G-A-S.

Curiously in intact (unlike in hypophysectomized) rats, purified *growth-hormone* produces a considerable disproportionate liver enlargement. It was suspected that somatotrophin could act through the intermediary of the hypophysis causing it to secrete a hepatotrophic principle.[59]

Pure growth-hormone causes a rather pronounced diminution of the liver-fat in the rat.[60] Allegedly, in the mouse, partially purified growth-hormone preparations may exhibit a slight fatty-liver-forming ability,[61] but this could be due to contaminating substances, especially since this species is extremely sensitive to any agent causing hepatic steatosis.

The fatty infiltration of the hepatic parenchyme is presumably dependent upon *ACTH* and the subsequent production of corticoids. Steatosis of the liver has been produced in force-fed rats by treatment with pure ACTH.[62] The production of fatty livers by ACTH has repeatedly been confirmed in the mouse.[63] Yet in guinea-pigs its activity was much less marked than that of

[52] Collip et al. 36231/35, Selye et al. 32783/35.
[53] Canzanelli et al. B37729/49.
[54] Li and Evans B29320/48.
[55] Selye 94572/49.
[56] Selye and Nielsen 84644/44.
[57] Selye et al. B124/45.
[58] Selye A75044/44.
[59] Li and Evans B29320/48.
[60] Li and Evans B29320/48.
[61] Payne B32809/49.
[62] Baker et al. B26490/48, Li et al. B34773/49.
[63] Levin B35913/49, B32877/49, Payne B32809/49.

impure anterior-lobe extracts. It was concluded that ACTH is not likely to account for the entire fatty-liver effect of anterior-lobe preparations.[64]

We attach particular importance to recent observations in rats, indicating that threshold doses of LAP, which cause no significant hepatic enlargement in themselves, become intensely hepatotrophic if ACTH is simultaneously administered. This is all the more striking, since the size of other organs (and of the animal as a whole) is diminished, as a result of its catabolic effect. Similar preparations of other tissues (e.g., lyophilized liver) do not cause hepatic enlargement when given conjointly with ACTH.[64a] It is possible that the component of the LAP responsible for this hepatotrophic effect, is identical with that which changes the gluco-corticotrophic effect of ACTH into a mineralo-corticotrophic potency. It will be recalled that mineralo-corticoids (e.g., DCA) likewise possess some hepatotrophic effect (cf. below).

The production of fatty livers by purified corticotrophin is prevented by *adrenalectomy*.[65] This agrees with the opinion that the effect is mediated by the adrenal cortex.

Adrenals. — **Adrenalectomy** interferes with hepatic function and structure in many ways. The liver of adrenalectomized animals is usually small and poor in glycogen, protein and fat; it can be restored approximately to normal by adequate corticoid therapy.[66]

Immediately following *partial hepatectomy* the regeneration of the liver-remnant is greatly inhibited, if not completely prevented, in adrenalectomized rats. This manifests itself by the absence of the usual hyperplastic and hypertrophic phenomena, as well as by the deposition of protein.[67] Eventually, however, regeneration occurs even in the absence of the adrenals.[68] The hepatic steatosis, which normally occurs in fasting rats after partial hepatectomy is also prevented by adrenalectomy.[69] Conversely, the large quantities of fat deposited in the livers of *over-fed* rats disappears more rapidly during a subsequent fasting period if the adrenals be removed.[70]

It is particularly interesting in connection with the G-A-S that in rats, the fatty infiltration of the liver, normally seen during an A-R caused by *cold, colchicine* or *fasting*, can be completely prevented by adrenalectomy.[71] These observations have subsequently been confirmed with a number of other alarming stimuli, such as *x-irradiation* [72] and *muscular exercise*.[73]

There is convincing evidence that the inhibition of fat-transfer into the liver of adrenalectomized animals is due to a lack of *corticoids*. Replacement therapy with 17-hydroxycorticosterone, 11-dehydrocorticosterone or DCA enables adrenalectomized mice to deposit fat in their liver during fasting.[74] The gluco-corticoids appear to be more active in this respect than DCA. Cortical extracts, unlike DCA, also restore the ability of the adrenalectomized rat to respond with active hepatic regeneration, after partial hepatectomy. In these experiments, the ability to form fatty livers, was also partially restored by DCA.[75] In prolonged experiments in which hepatic regeneration occurred

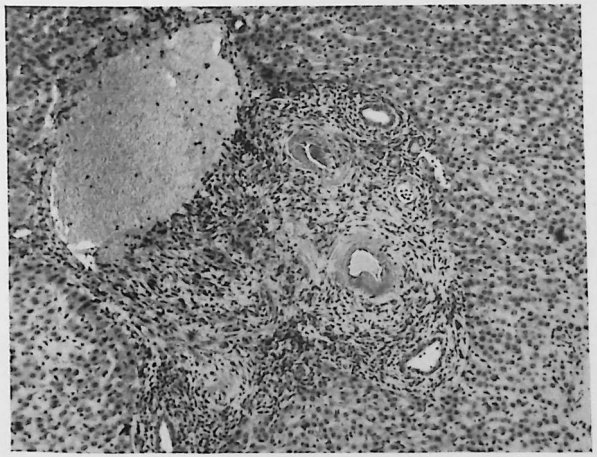
[64] Jefferies B41087/49.
[64a] Selye 35935/ND.
[65] Levin B35913/49, Payne B32809/49.
[66] Selye **94572/49.**
[67] Berman et al. 97700/47.
[68] Canzanelli et al. B37729/49.
[69] Berman et al. 97700/47.
MacKay and Carne A14767/38.
Selye et al. 32783/35.
[70] MacKay A9146/37.
[71] Leblond et al. A18194/39.
[72] Leblond and Segal 82724/42.
[73] Levin B35913/49.
[74] Levin B35913/49.
[75] Berman et al. 97700/47.

despite adrenalectomy, cortical extracts had no detectable effect upon the liver remnant.[76]

A not yet identified fraction of the adrenal cortex, the "fat hormone", is claimed to be especially effective in sustaining the ability of adrenalectomized rats to deposit liver fat. This compound can be separated from other steroids by chromatographic absorption, and has been found much more effective than any other cortical steroid so far examined for this "lipocorticoid" activity.[77] On the other hand it was shown in mice, that Kendall's compounds "A" and "B" greatly augment the fat-content of the body as a whole. Here, the liver-fat was not separately estimated, but it is possible that some relationship exists between these latter steroids and the corticoids responsible for fat-tranfer into the liver during systemic stress.[78]

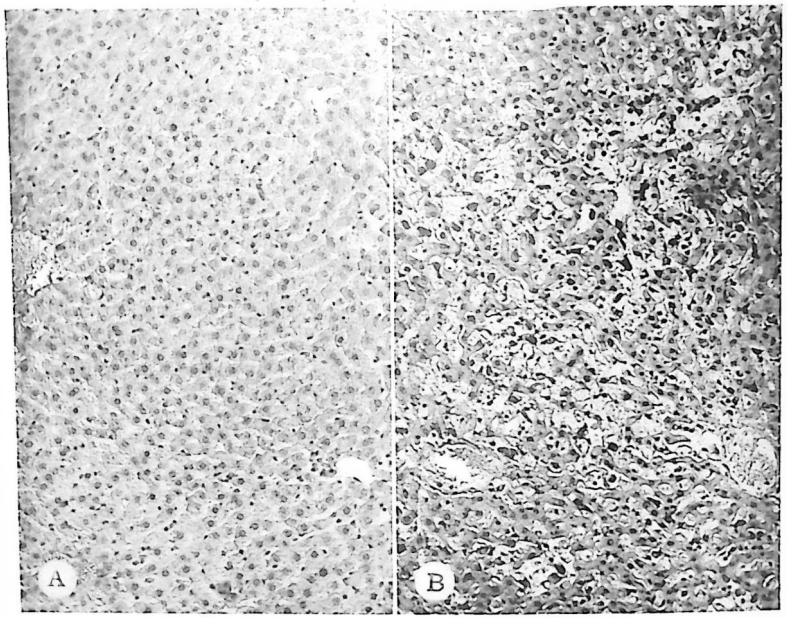
It is obvious from all these observations that the transfer of lipids and proteins from other tissues into the liver is largely regulated by corticoids. Such transfer is presumably a prerequisite for the subsequent utilization of the lipids and proteins mobilized during the catabolic phase of the A-R. Hence these actions are probably of the greatest importance in the regulation of intermediate metabolism at times when the body is exposed to systemic stress. (Cf. also Metabolism, p. 110 ff.)

In the intact animal **corticoids** also exert important actions upon hepatic structure. For instance in the fowl [79] and rat [80] *DCA* causes hypertrophy and hyperplasia of the liver. This is all the more remarkable since after adrenalectomy, DCA is singularly ineffective in promoting hepatic regeneration after



Periarteritis nodosa of the liver following DCA treatment, in the rat. Note that although hepatic parenchyme is essentially normal, the arterioles in the portal spaces are hyalinized and infiltrated by inflammatory granuloma cells. (After Selye 35935/ND.)

[76] Canzanelli et al. B37729/49.
[77] Hartman et al. B2191/47, 98749/47.
[78] Kendall B3002/45.
[79] Selye A56607/43.
[80] Berman et al. 97700/47.



Liver following overdosage with cortisone in the rat. Both animals were sensitized by unilateral nephrectomy and 1% NaCl as drinking fluid. — **A.** Liver of otherwise untreated normal control. — **B.** Liver of rat which received 1.25 mg./day of cortisone during 33 days. Note marked hyperemia, accompanied by "serous inflammation"; the interstitial spaces, between the endothelia and the hepatic trabeculae, are filled with fluid. Note also atrophy of hepatic cell columns (presumably due to venous congestion) and marked enlargement of Kupffer cells, which are loaded with dark blood-pigment derivatives. (After Selye 35935/ND.)

partial hepatectomy. Conversely, heavy overdosage with *cortisone* causes involution and sometimes even focal necrosis of hepatic tissue in the rat,[81] and mouse.[81a]

Unilateral *nephrectomy*, which sensitizes the rat to some (but not to all) actions of DCA, very markedly increases its ability to enlarge the liver.[82] Experiments on mice suggest that overdosage with DCA can actually prevent the fatty infiltration of the liver normally produced by *x-irradiation*.[83] Perhaps this is due to the compensatory atrophy of the adrenal cortex, which would diminish its ability to secrete the more active "lipo-corticoids" e.g., 11-dehydro-corticosterone.

Other stimuli. — High doses of **thyroxine** may cause functional and occasionally even structural hepatic damage in various animal species and even in man.[84] It is of particular interest in connection with the G-A-S that in thyroxine-pretreated rats, exposure to *anoxia* produces especially pronounced degenerative changes.[85] Furthermore sterile inflammation of the subcutaneous tissue,

[81] Selye 35935/ND.
[81a] Antopol B47052/50.
[82] Selye and Pentz A59789/43.
[83] Ellinger B24015/48.
[84] Selye **94572/49.**
[85] McIver and Winter B33399/43.

induced by staphylococcus toxin, causes necrosis of the liver in hyperthyroid rabbits.[85a] This suggests that hyperthyroidism may specifically sensitize hepatic tissue to the damaging effects of systemic stress. However, the fat-tranfer into hepatic cells which occurs under the influence of systemic stress, is not prevented by *thiouracil* overdosage. This was regarded as evidence that "thyroidal activity is not necessary for liver-fat mobilization".[86] In agreement with this view it was noted that in the mouse, the ability of anterior-lobe extracts to cause fat deposition in the liver is likewise not prevented by thyroidectomy or propylthiouracil.[87]

Thyroidectomy reduces and thyroxin increases the rate of hepatic regeneration in *partially hepatectomized* rats, but the intense inhibition of liver growth occasioned by hypophysectomy is not wholly due to hypothyroidism.[88]

Heavy overdosage with natural or artificial folliculoids may cause enlargement of the liver, hepatitis and hepatic necroses and even death with severe icterus in certain strains of mice.[89] However, neither stilbestrol nor testosterone or progesterone produce any significant degree of fatty infiltration in the mouse.[90]

The production of fatty livers by **partial hepatectomy** is greatly facilitated by simultaneous exposure to a variety of stresses such as withdrawal of drinking water, hemorrhage, or intravenous injection of saline.[91]

It is common clinical knowledge that the diet exerts a particularly marked effect upon the response of the liver to various damaging agents. Thus, for instance, the functional hepatic damage demonstrable in patients who underwent surgical operations (especially if complicated by infection) is effectively counteracted by *high-protein* and *high-caloric* feedings.[92] Allegedly certain *amino-acids*, such as methionine, are especially effective in this respect and hence commonly used in clinical practice.

It is more specifically pertinent to our problem that food, particularly *carbohydrates*, are most effective in preventing fatty infiltration of the liver remnant following partial hepatectomy.[93] Furthermore, experiments on mice treated with ACTH or an alarming stimulus such as cold or muscular exercise, revealed that "parenteral administration of glucose during exposure to an otherwise effective stress, or during treatment with pituitary extract, prevents most of the liver-fat increase".[94]

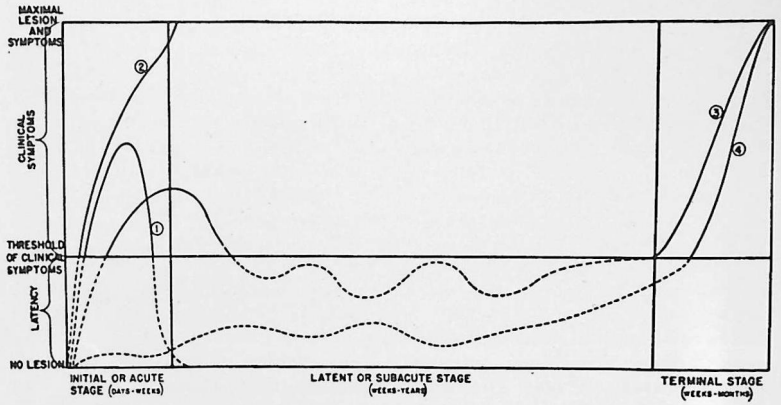
The hepatic cirrhosis produced in rats by CCl_4 is effectively inhibited by such *lipotropic* food-factors as choline or methionine.[95] It would be interesting to examine the effect of such dietary constituents upon the hepatic changes caused by stress.

Hepatic Diseases of Adaptation

The largest group of liver diseases is constituted by diffuse non-suppurative inflammatory or degenerative lesions. Although many pertinent types have been described as distinct nosologic entities, it is interesting that one of the most experienced students of this field attempted their correlation into a single

[85a] Sealy and Lyons B46719/49.
[86] Levin B35913/49.
[87] Payne B32809/49.
[88] Canzanelli et al. B37729/49.
[89] Selye A18206/39.
[90] Payne B32809/49.
[91] Collip et al. 36231/35, Selye et al. 32783/35.
[92] Keeton et al. B36903/47.
[93] Collip et al. 36231/35, Selye et al. 32783/35.
[94] Levin B32877/49.
[95] Sellers et al. B38060/48.

group and states "the process may be violent and rapidly fatal as in 'acute yellow atrophy' or there may be prompt and complete healing such as occurs in most instances of hepatitis (infectious jaundice, catarrhal jaundice). In other cases the early stages are perhaps entirely latent and the disorder only emerges into clinical prominence in a terminal stage (cirrhosis). It seems highly advisable in the interest of orderly thinking to try, tentatively at least, to correlate these various pictures as has been done so well with nephritis in which an analogous state of affairs seems to exist".[96] In attempting to arrange these various hepatic derangements according to their chronologic progress, it is significant that — without thinking of any possible relationship with the G-A-S — the typical triphasic pattern of the latter appears to emerge.



Three stages in the development of hepatitis in man. — 1. Acute hepatitis (toxic or infectious) with complete recovery (catarrhal or infectious jaundice). — 2. Acute hepatitis (toxic or infectious) with death (including acute yellow atrophy). — 3. Acute hepatitis which, after an initial stage, progresses slowly below threshold of clinical symptoms with termination, perhaps after years, with cirrhosis. The initial stage may be entirely subclinical (4). Various other possibilities suggest themselves.

(After A. L. Bloomfield in Musser's "Internal Medicine", 88056/45. Courtesy of Lea and Febiger.)

It is also striking that **acute yellow atrophy,** as well as the various types of acute, sub-acute or chronic **hepatitis** and hepatic **cirrhosis** do not appear to be related to any one pathogenic agent. The acute stages of hepatitis represent a rather typical example of that "serous inflammation" which may be elicited by diverse alarming stimuli such as microbes, drugs, exposure to cold or ionizing radiations. Some stressors (e.g., syphilis, CCl_4, alcohol) are undoubtedly more likely to affect the liver than others, perhaps because in addition to their stress effect they also exert specific actions upon the hepatic tissue and thus condition the response to the former. Nevertheless, it is obvious that even here the G-A-S mechanism is superimposed upon the specific hepatic damage. Hence, it will often depend as much upon the efficacy of systemic defense, as upon the specific hepatotoxic action of the stressors, whether in the final analysis liver disease ensues, and if so, whether it will progress to the grave types of yellow atrophy or chronic cirrhosis.[97] The experimental and

[96] Musser 88056/45.

[97] Eppinger **B37085/49.**

clinical observations indicating that malnutrition and other types of damage increase the susceptibility to infectious hepatitis,[98] further emphasize the importance of the stress-factor in the development of liver disease.

The connection between hepatic damage and the endocrine system is further emphasized by the frequent occurrence of hormonal derangements in patients suffering from liver cirrhosis, malnutrition and other types of systemic stress particularly damaging to hepatic cells. These hormonal derangements have been discussed in other connections, but to remind the reader of the type of change that occurs, let us merely enumerate those which were most common in a large series of patients with Laënnec's cirrhosis: loss of libido and potency, decrease in axillary hair, testicular atrophy, gynecomastia, diminished 17-KS excretion without rise in urinary gonadotrophins, derangements of the menstrual cycle and a marked decrease in adreno-cortical lipids.[99]

Up to now the possible value of *ACTH* treatment has been studied in a few pertinent cases only. Preliminary observations suggest that in hepatic cirrhosis, as well as in certain types of hepatitis, liver function improved under the influence of ACTH. In cirrhosis, biopsy specimens taken before and after administration of the hormone indicate a diminution in the amount of fibrous tissue.[99a] This agrees with many other observations showing that ACTH and gluco-corticoids tend to diminish fibroplasia in various tissues.

The possible rôle of stress in the production of **cholecystitis** has not yet been examined. Pertinent studies would be highly desirable since the lymphatic vessels of the gall-bladder are closely integrated with those of hepatic tissue in general and "serous inflammation" is frequently accompanied by marked gall-bladder edema, occasionally conducive to actual inflammation.[100] The "allergic cholecystitis" [100a] may also be interpreted as a disease of adaptation.

Theories and Summary of Observations Concerning the Participation of the Liver in the G-A-S

As one of the most important regulators of metabolism **the liver plays a prominent rôle in the G-A-S and the diseases of adaptation.** Apart from its participation in assuring the homeostasis of intermediate metabolism, it also regulates blood-clotting, hemopoiesis, and the detoxification of many noxious compounds. Through its well developed R.E.S. it aids phagocytosis and through the formation of bile, it helps to eliminate certain damaging agents and to absorb some substances from the alimentary tract. By virtue of all these actions, the liver participates in the G-A-S mechanism.

Conversely, systemic **stress can produce marked structural and functional changes in the liver.** During the A-R, involution of the hepatic parenchyme, frequently accompanied by a transitory fat-storage, are especially prominent. The hepatic changes of the resistant and exhaustion phase have not yet been systematically studied.

Hypophysectomy or **adrenalectomy** prevent the temporary fat-deposition which otherwise occurs in the liver during the A-R, while certain **corticoids**

[98] Schmengler B41796/48.
[99] Lloyd and Williams B24306/48.
[99] Dohan et al. B47867/50, Lloyd and Williams B24306/48.
[99a] Bluemle et al. B46992/50. Bongiovanni et al. B47856/50.
[100] Eppinger **B37085/49.**
[100a] Kline B37972/48.

(especially the gluco-corticoids, and perhaps even more actively, the still hypothetical "lipocorticoids") restore this ability even in hypophysectomized or adrenalectomized individuals. Presumably the temporary transposition of fat from depots into the liver is regulated by corticoids, which thus make lipids available for emergency use by extra-hepatic cells.

Certain **anterior-pituitary extracts** exert a definite hepatotrophic effect in that they stimulate mitosis and hypertrophy of hepatic cells. Purified growth hormone and ACTH do not appear to account fully for this action. It may depend upon a combination of pituitary hormones or a hitherto not yet identified component of the anterior-lobe.

Among the hepatic derangements which appear to be largely **diseases of adaptation,** we mentioned *acute yellow atrophy,* the various types of acute, sub-acute and chronic *hepatitis* as well as liver *cirrhosis.* In all these instances, a variety of stressors can act as eliciting pathogens. Undoubtedly, some agents are more likely to damage the liver than others, due to their specific hepatotoxic effects which act as conditioning factors. Yet, it appears to depend largely upon the efficacy of the body's defenses whether any one stressor will cause a hepatic lesion and if so, whether this will be merely transitory or develop to the dangerous types of acute yellow atrophy or progressive cirrhosis.

Some preliminary observations suggest that cortisone and ACTH may be beneficial in clinical and experimental hepatic cirrhosis, due to their ability to counteract excessive fibroplasia. This would be comparable to the action of such hormones upon the fibrous tissue granulomas in rheumatoid arthritis, but pertinent observations are not sufficient to permit a definite conclusion.

Edema of the *gall-bladder* frequently accompanies the non-specific "serous inflammation" of the liver which is typical of the A-R. The possible rôle of systemic stress in the production of cholecystitis has not yet been adequately investigated.

SALIVARY GLANDS

The salivary glands exhibit particularly pronounced changes during the A-R. In rats in which an A-R was produced by colchicine, selenium compounds and other drugs, the organs containing much ribose-nucleic acid exhibited especially severe changes. "When extending this study to the salivary glands, which also contain abundant ribosenucleic acid, it was found that these glands also participated in the alarm-reaction. Microscopic examination revealed considerable degeneration and necrosis of the parenchyma of these glands and in many instances suppurative inflammation as well. These observations seem to throw light on the etiology of post-operative parotitis, which so long defied explanation. It is suggested that this post-operative complication is another part phenomenon of the alarm reaction of Selye".[1]

The frequent appearance of parotitis (sometimes associated with pancreatitis) has also been noted in patients suffering from debilitating diseases and hunger-edema,[2] intoxication with thiouracil [3] and other stress-producing

[1] Ehrich and Seifter 98683/47, B31789/48.
[2] Gros B44667/49, Mellinghoff and Hildebrandt B46539/49, Trautmann and Kanther B37154/47.
[3] Allison B44659/48.

circumstances. Painful enlargement of the sub-maxillary glands (accompanied by hard generalized enlargement of the pancreas) may occur as a complication of thiouracil therapy [4] and emotional stress situations can cause chronic recurrent sialadenitis as a consequence of the resulting alarm reaction.[5]

The "allergic parotitis" has also been regarded as a derailment of the G-A-S.[6] It is perhaps significant in this connection that mice receiving very large doses of cortisone exhibit pronounced sudden involution of the salivary glands.[7]

[4] Barclay and Leatham B45641/46.
[5] Bass and Mendlowitz B46268/49.
[6] Lucherini and Cecchi B47800/49.
[7] Antopol B47052/50.

SKIN AND APPENDAGES

Systemic Stress

The effect of systemic stress upon the skin and its appendages has not yet been studied systematically in connection with the other manifestations of the G-A-S. It is common knowledge, however, that some people flush while others blanch with anger, that fear may cover the skin with cold sweat and that telling "dark rings" appear under the eyes after great stress (no matter how pleasant it may have been). Debilitating diseases and malnutrition tend to cause loss of hair, premature graying and atrophy of the skin with a diminution of its elasticity and hydration so that cutaneous wrinkles form. All these manifestations are presumably due to systemic stress as such, but their relationship to other manifestations of the G-A-S has not yet been examined.

Significantly many systemic infectious diseases, as well as rheumatic fever and allergies, can produce skin-rashes which are often accompanied by nephritis, arthritis or cardiovascular changes similar to those that we are inclined to interpret as diseases of adaptation. Of course many of these rashes are highly specific and quite characteristic of certain pathogenic agents. However, special conditioning factors may impart great diversity to fundamentally similar non-specific responses of the skin.

Interestingly, experiments on the rat performed specifically to study the relative participation of various organs in the "catabolic response" have shown that the skin contributes a greater amount of protein-degradation products during the first twenty-four hours of an A-R than any other tissue examined, including the liver, spleen, brain, thymus, heart, kidney and the digestive tract.[1]

The extraordinary dryness of the hair and skin was specially emphasized by those who studied the effect of severe **malnutrition and mental stress** during the second World War.[2] At the same time the incidence of microbial and parasitic skin lesions was greatly increased.[3] This may perhaps partly be ascribed to decreased skin resistance against any aggression, but here probably the prevailing poor conditions of general hygiene were an even more important pathogenic factor. It remains to be shown whether the achromotrichia, which sometimes accompanies nutritional anemia, is a related phenomenon.[4]

Ionizing radiations have such an intense specific effect upon the skin and its appendages that any incidental non-specific action would be difficult to recognize. Yet in a sense, the loss of hair, erythema and perhaps even the more severe degenerative and necrotizing skin-changes elicited by x-rays or radiations from the atomic bomb,[5] could be regarded as non-specific stress effects. Marked changes of this type occur only in regions exposed to the rays, hence we must undoubtedly ascribe them to direct actions of the radiations. However, atrophy of the lymphatic tissue, leucopenia, involution of the seminal epithelium, increased capillary permeability, and many other changes characteristic of the A-R, are produced through the intermediary blood-borne principles by systemic stress during the G-A-S, yet x-rays can duplicate them by their direct action upon the target organs themselves. Perhaps ionizing radiations influence peripheral tissues directly (e.g., by destroying enzyme-systems and the selective permeability of cell-membranes) in essentially the same manner in which other alarming stimuli affect them through the intermediary of humoral substances.

[1] Leduc and Guillemin B27410/49.
[2] Brozek et al. B23241/46, Keys et al. **B46730/50.**
[3] Salzmann and Hottinger B27607/48.
[4] Roy B38638/47.
[5] Cronkite B24051/48, Ellinger **68685/35,** Liebow et al. **B41902/49.**



Trophic disturbances due to chronic starvation in man. — **A.** Legs of a 23-year-old female concentration camp inmate showing gangrene of the skin and underlying tissues developed during starvation. — **B.** Severe chilblains in a 51-year-old female concentration camp inmate with marked cachexia. — **C.** Decubitus in the sacral region of a severely undernourished 35-year-old male concentration camp inmate. Note also laxity of the skin due to cachexia. The patient also suffered from a pulmorany abscess with empyema from which he subsequently died. All these photographs illustrate decreased tissue resistance. (After Hottinger B27607/48.)

An intense **psychic shock** may also exert pronounced effects upon the skin, e.g., greying and generalized loss of hair.[6]

The so-called **allergic** rashes, which follow the administration of foreign proteins and various drugs, often closely imitate those considered to be characteristic of certain infectious diseases. Thus a rather typical morbilliform exanthema may occur after sulfonamide medication, in combination with typical renal and cardiovascular manifestations of an allergic response.[7]

[6] Trepat and Petre B42105/42.
[7] Bakken B37943/47.

The cutaneous vasodilatation produced by **incompatible blood transfusion,** has been ascribed to an endogenous histamine discharge.[7a]

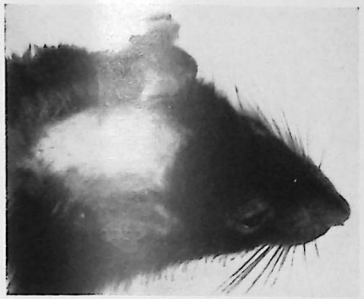
Stimuli Influencing the Response of the Skin During the G-A-S. — Several of the hormones which play an important defensive rôle during the G-A-S have long been known to affect skin structure. **Hypophysectomy** or **adrenalectomy** cause cutaneous atrophy and loss of elasticity of the skin in animals. Similar cutaneous lesions occur in men suffering from anterior-lobe or adrenocortical deficiency. It is not yet clear why, in man, **hypophyseal insufficiency** does not increase the tendency to form melanosis of the skin such as is seen in **Addison's disease,** but perhaps the residual cortical function suffices to prevent this change even in the absence of adequate corticotrophic stimulation. It is also noteworthy, though unexplained, that most animal species, unlike man, do not develop cutaneous pigmentation under the influence of hypocorticoidism. Yet it has been demonstrated that even in animals, pigment formation by the skin is largely dependent upon the adrenal cortex and can be influenced by corticoids. The melanosis of senility and that which tends to develop in chronically debilitated patients may also be related to a malfunction of the adrenal cortex.[8]

It is now common knowledge that patients receiving large doses of **ACTH** tend to develop the typical manifestations of Cushing's disease including acne, seborrhea, hirsutism of the body with loss of scalp hair and, more rarely, cutaneous striae due to atrophy of the skin. Occasionally this may be accompanied by hyperpigmentation.[8a] Facial edema may add to the development of the typical "moon face" characteristic of Cushing's disease and apparently these cutaneous manifestations are aggravated by excess sodium intake.[8b]

Chronic overdosage with **DCA** tends to cause marked loss of hair in the rat, this being frequently accompanied by "psoriasis-like" scaly skin lesions.[9] Systemic overdosage with **cortisone** may render the rat skin extremely atrophic and transparent, primarily as a result of an involution of the dermal connective tissue.[10] Some of the effects of cortisone are obviously direct, since local application of this hormone, or of an aqueous adreno-cortical extract, inhibits hair growth in the rat within the treated area only. Microscopically, there is thinning of the epidermis and failure of the hair-follicles to develop beyond the stage of epithelial bud-formation.[11]

Systemic overdosage with **folliculoids** likewise causes intense and generalized hair loss in the rat, simultaneously with an involution of the sebaceous glands. Conversely, **testoids** stimulate the development of the sebaceous glands, both in animals and in man. In human beings, they also tend to cause hirsutism and acne, similar to that of Cushing's disease. Significantly, *ACTH* may also produce such changes in man presumably due to an increased formation of adrenal testoids. The somatic hypertrichosis caused by testoids is sometimes accompanied by apical baldness in man; conversely, eunuchs are notoriously not subject to baldness unless they receive testoid therapy.[12] The possible relationship of these cutaneous changes to hormonal derangements during the G-A-S should be examined. The frequent occurrence of hirsutism after severe burns may be a related phenomenon. It is also suggestive to assume

[7a] Malméjac et al. B40969/45.
[8] Selye **94572/49.**
[8a] Dutoit and Bauer B46988/50.
[8b] Ransohoff et al. B47896/50.
[9] Selye 35935/ND.
[10] Selye 35935/ND.
[11] Baker and Whitaker B45217/48.
[12] Selye **94572/49.**



Effect of ACTH on hair growth, in the rat. Female rat (body weight 135 gm.) having received six injections of 2 mg. of ACTH per day (at 4 hourly intervals), over a period of 35 days. Note the characteristic loss of hair, resembling in its principal distribution the "apical baldness" of man. In rats loss of hair often also occurs over the shoulders and back. (Selye 35935/ND.)



Severe acne produced by ACTH. Complexion was without blemishes prior to treatment. Photograph was taken after the patient received 400 mg. of ACTH in the course of 10 days. (Courtesy of Edward F. Rosenberg, Chicago.)

some interrelation between the characteristic striae of Cushing's disease and the cutaneous atrophy which occurs in debilitated individuals and after overdosage with cortisone or ACTH.

The resistance of the skin to **local irritation** (e.g., by $Hg(CN)_2$) is greatly diminished in the aged and in patients suffering from a variety of stressors conducive to intense catabolism. This test has even been suggested as a useful indicator of the "resistance of the terrain," which may help the surgeon to assess the operability of old or debilitated individuals.[13] The so-called "intradermal salt solution test" (cf. G-A-S → Absorption, p. 743), probably depends upon similar systemic factors. Both these tests illustrate again how systemic stress may affect resistance to local stimuli.

Cutaneous Diseases of Adaptation

In the preceding pages we spoke of exanthemas, alopecia, hirsutism, seborrhea, acne, vasomotor and sudomotor reactions of the skin, cutaneous atrophy and pigmentation as conditions in whose pathogenesis systemic stress, or hormones produced during systemic stress, tend to participate. Here we shall merely add a few words concerning certain major dermatologic entities as possible diseases of adaptation.

By way of introduction let us point out that — quite independently of the G-A-S concept — certain skin diseases of unknown etiology have previously been grouped together. Thus lupus erythematosus, erythema nodosum, scleroderma and dermatomyositis have been regarded as allied among themselves and related to cardiovascular hyalinosis and the rheumatic diseases in general, since they appear to be primarily "collagen diseases". It has long been suspected that all these derangements are due to an abnormal allergic response to any one among a variety of pathogens (cf. above). Furthermore psoriasis, eczema, urticaria and the rosacea complex have been grouped with the cardiovascular and arthritic manifestations of rheumatism as psychosomatic affections because they can be elicited by emotional factors and often respond well to psychotherapy.[14] Several earlier workers found corticoid therapy efficacious in a variety of skin diseases (cf. p. 69), which appeared to have an allergic component, but the results were variable, presumably because the most effective gluco-corticoid preparations were not yet available.

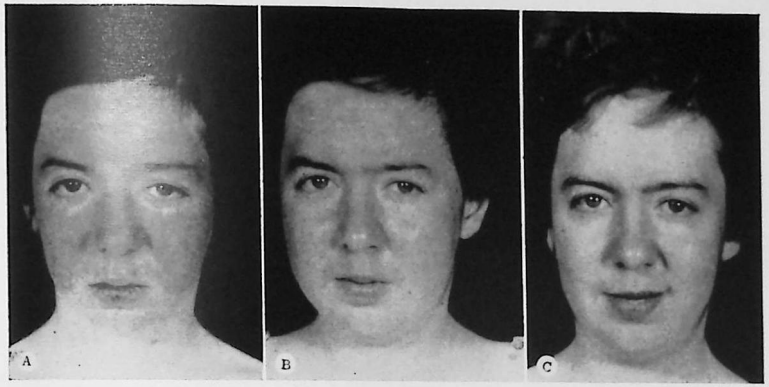
Lupus erythematosus disseminatus. — It is now generally recognized that lupus erythematosus is not merely a skin disease, but involves the blood-vessels throughout the body. The skin lesion itself is mainly characterized by dilatation of the blood- and lymph-vessels, degenerative changes in the basal layer of the skin and perivascular lymphocytic infiltration. At the same time, in the →

Effect of ACTH in lupus erythematosus disseminatus. — **A.** 15-year-old girl with diffuse erythematous rash over both upper eyelids and scattered small erythematous areas adjacent to nose over both cheeks. Photograph taken during 6th month of disease, before initiation of treatment. — **B.** Typical "rosette of L. E. cells" found in heparinized peripheral blood during acute phase before treatment. — **C.** Spongy gums exuding serum and bleeding on slightest touch. The patient could not eat, because of painful lips and gums, before treatment. — **D.** ACTH caused disappearance of gum lesions and prolonged remission. This photograph was taken approximately four months after discontinuation of ACTH. Note normal lips and gums.

(Courtesy of Dr. D. Markson, Wesley Memorial Hospital, Chicago.)

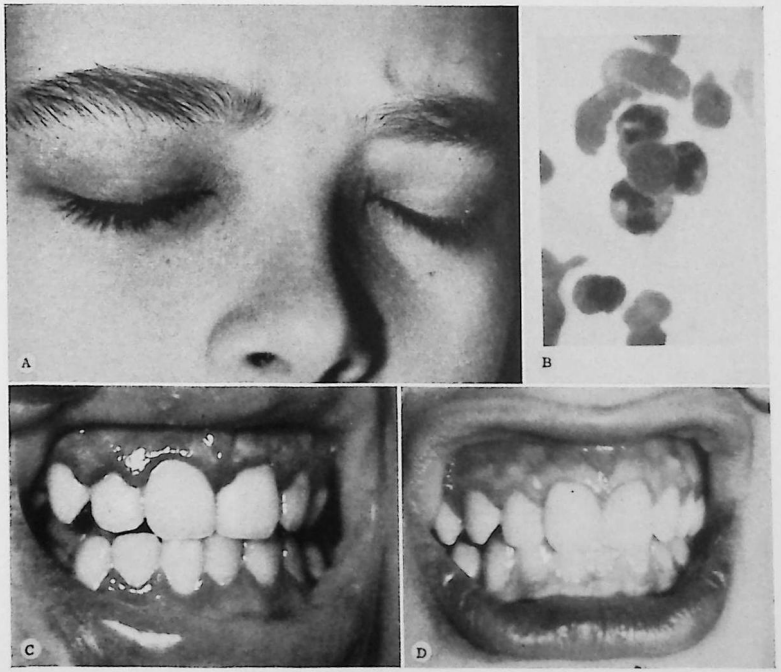
[13] Laroche and Trémolières B37795/49.

[14] Halliday B44599/43, **B46202/48.**



Effect of ACTH upon disseminated lupus erythematosus. — Changes in the facial expression, contour and skin of a 17-year-old girl, admitted moribund with disseminated lupus erythematosus and treated with ACTH (100 mg./day) for over a month. — **A.** Note the typical butterfly rash involving also the forehead. — **B.** The cushingoid facies and acne at the height of therapy associated with the characteristic hypochloremia and hypokalemic alkalosis. — **C.** The return to normal facies two weeks after discontinuing ACTH. Note the complete disappearance of the rash in this successfully treated case. Here the remission lasted for many months and no relapse occurred up to now.

(After Thorn et al. "The Effect of ACTH in Disseminated Lupus Erythematosus". To be published.)



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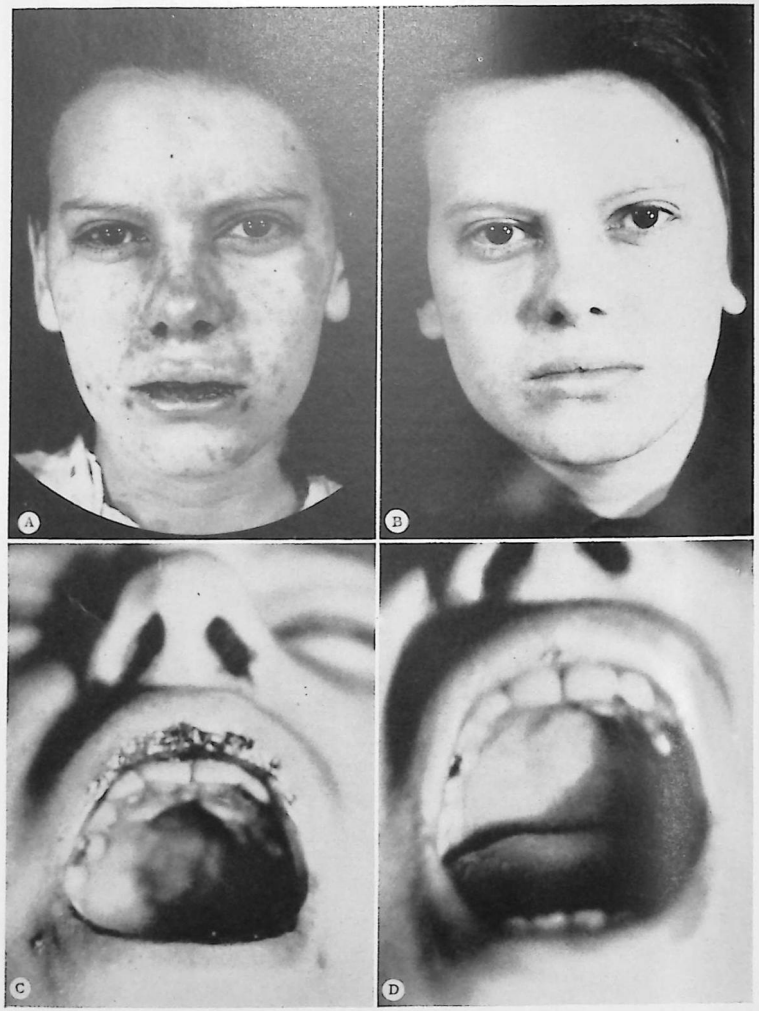
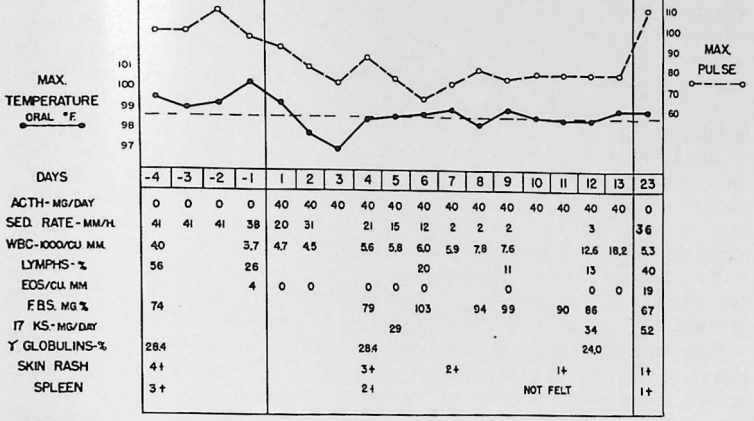


Effect of ACTH in lupus erythematosus disseminatus. 17-year-old girl with lupus erythematosus of seven months duration. Typical lupus erythematosus cells ("L.E. cells") were found in the bone marrow. — **A.** Appearance of face on admission. — **B.** Appearance of face after one month of ACTH treatment. Note that the skin lesions have disappeared. Curiously in this (as in several other cases) the lesion became fiery red after about one week of ACTH. — C. Large oblong erythematous area over the hard palate, surrounded by miliary ulcers and pronounced exulceration on upper lip, before treatment. — **D.** Note disappearance of lesions both on palate and on lip after ACTH. (Courtesy of Dr. D. Markson, Wesley Memorial Hospital, Chicago.)

EFFECT OF ACTH IN A PATIENT WITH DISSEMINATED LUPUS ERYTHEMATOSUS

D.B. # 27



DAYS	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	23
ACTH - MG/DAY	0	0	0	0	40	40	40	40	40	40	40	40	40	40	40	40	40	0
SED. RATE - MM/H.	41	41	41	38	20	31		21	15	12	2	2	2			3		36
WBC - 1000/CU MM.	40			3,7	4,7	4,5		5,6	5,8	6,0	5,9	7,8	7,6			12,6	18,2	5,3
LYMPHS - %	56			26						20			11			13		40
EOS/CU. MM.				4	0	0		0	0	0			0			0	0	19
F.B.S. MG %	74							79		103		94	99		90	86		67
17 KS - MG/DAY									29							34		52
γ GLOBULINS - %	28,4							28,4								24,0		
SKIN RASH	4+							3+			2+				1+			1+
SPLEEN	3+							2+						NOT FELT				1+

Improvement in the clinical course of a patient with disseminated lupus erythematosus during treatment with ACTH. Note also immediate return of the signs and symptoms following discontinuance of treatment. This patient subsequently received two more successful courses of ACTH. (After Thorn et al. B39546/49.)

blood-vessels of various internal organs, there are degenerative and inflammatory lesions very similar to those seen in periarteritis nodosa. In its pathogenesis, allergic and hypersensitivity reactions appear to play a major rôle.[15]

Since the systemic manifestations of lupus erythematosus greatly resemble those produced by excess mineralo-corticoid administration in animals, and since ACTH on the other hand proved to be spectacularly effective in many pertinent cases,[16] it is reasonable to classify this condition as primarily a disease of adaptation.

It is particularly interesting that the thiosemicarbazone derivative "Tb I", which proved to exert "cortisone-like" actions upon a number of rheumatic conditions, also caused pronounced remission, with a decrease in E.S.R., in a case of lupus erythematodes.[16a] Here the results were ascribed to an interference with excessive mineralo-corticoid production.

Erythema nodosum. — Erythema nodosum is likewise commonly associated with cardiovascular manifestations of rheumatism. It may be accompanied by tonsillitis or arthritis and appears to result from an allergic response to drugs, microbes, etc.[17] In view of these clinical characteristics, and especially because of the great resemblance between the lesions of erythema nodosum and those produced by mineralo-corticoid overdosage, this condition has also been interpreted as a disease of adaptation.[18]

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[15] Ayvazian and Badger **B24715/48.**
[16] Astwood et al. B47853/50, B47926/50, Boland **B47735/50,** Bordley et al. B46989/50, Elkinton et al. B45107/49, B46985/50, Grace and Combes B44786/49, Hench et al. B27892/49, Orr B47974/50, Thorn and Bayles B44425/49.
[16a] Heilmeyer B47479/50.
[17] Branwood B24253/47.
[18] Lucherini and Cecchi B35563/48.

Dermatomyositis. — This is a non-suppurative inflammation of the skin, subcutaneous tissues and muscle, with areas of dermal hyperkeratosis among which there are small foci of epithelial necrosis. The cutaneous tissue is edematous and contains lymphocytic infiltrations. The adjacent muscle tissue is also involved in the inflammatory reaction and may undergo degeneration. The disease is frequently accompanied by arthralgia and sometimes actual contracture of the joints. The spleen, liver and lymph-nodes are frequently enlarged.

The histologic characteristics of the skin and muscle lesions and the diversity of the pathogenic agents which appear to be capable of producing this malady, suggest some relationship to the diseases of adaptation. It is especially instructive in this connection, that several cases have responded well to adrenocortical extract,[19] cortisone or ACTH.[20]

Four patients with dermatomyositis exhibited marked improvement under the influence of para-aminobenzoic acid treatment.[20a] It remains to be shown whether this is in any way related to the G-A-S mechanism.

Scleroderma. — Scleroderma is characterized by an atrophy and fibrotic contraction of the skin and subcutaneous tissues. Histologically, the most striking changes are proliferation of connective tissue with lymphocytic infiltration within the derma and especially around the smaller arteries. Frequently calcium deposition occurs within the inflammatory tissue. Although originally this was believed to be a purely dermatologic condition, it is now generally recognized that scleroderma tends to affect visceral arteries as well and the malady is classified with the "diffuse collagen diseases." It is frequently accompanied by manifestations of Raynaud's disease and arthritis.[21] Allegedly, it is accompanied by some derangement in sodium metabolism since the diffusion of radio-sodium through the capillaries is frequently subnormal, as in most other collagen diseases.[22]

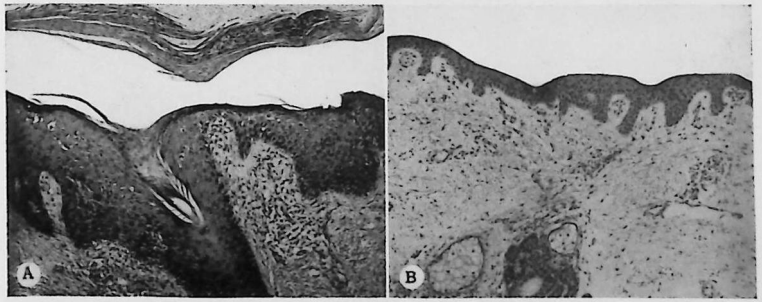
With regard to its possible relationship to the diseases of adaptation it is noteworthy that electro-shock therapy has allegedly been beneficial in some cases [23] and certain manifestations have suggested hypocorticoidism (creatinuria, myopathy, negative nitrogen balance, pigmentation, diminished 17-KS excretion and occasional low plasma Na and Cl levels). In an effort to combat this supposed hypocorticoidism, at least as far as the deficient testoid production is concerned, testosterone propionate has been given in large doses, allegedly with considerable success. ACTH has only been used in short tests up to now, and it appears to have normalized at least the biochemical manifestations of hypocorticoidism,[24] although, in this disease, ACTH does not appear to be spectacularly effective.[24a] In one case of scleroderma with dermatomyositis, para-aminobenzoic acid caused a marked remission.[24b]

In connection with the possible endocrine derangement in scleroderma, it is noteworthy that in rats, overdosage with parathyroid hormone produces a scleroderma-like skin lesion.[25] Stimulated by this observation, some surgeons performed partial parathyroidectomies and reported beneficial results.[26] Al-

[19] Joulia and Le Coulant B31462/46.
[20] Elkinton et al. B45107/49, B46985/50. Ragan B46984/50.
[20a] Zarafonetis et al. B47320/50.
[21] Bongini B43806/48.
[22] Mufson et al. B38708/48.
[23] Cordoba et al. B40719/46.
[24] Hertz and Forsham B33416/49.
[24a] Astwood et al. B47853/50, Bayles et al. B46987/50.
[24b] Zarafonetis et al. B47320/50.
[25] Selye 901/32, **43969/32.**
[26] Leriche and Jung 673/31, 53039/35.

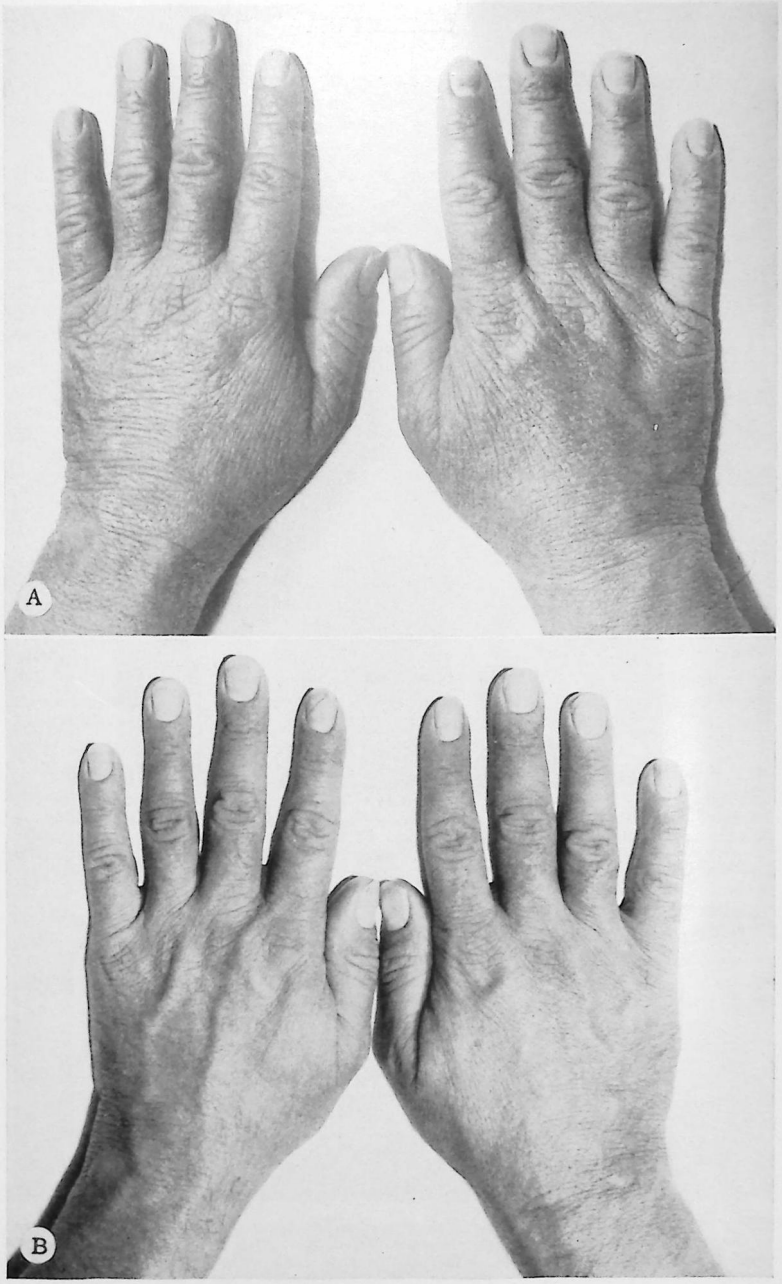


Effect of ACTH in arthropathic psoriasis. — **A.** Shows the patient before treatment, — **B.** after seven days of ACTH administration. Note the diminution in the scaling, especially obvious around the heels. The arthritic manifestations were also greatly improved. (For histologic changes see next picture.)



Effect of ACTH upon psoriasis. Histologic sections of the skin taken from the calf region of the patient shown in the previous picture; **A.** Before, **B.** — After seven days of ACTH treatment. Note great diminution of surface scaling and of the inflammatory infiltration in the derma.

(Courtesy of the staff of the Hospital for Special Surgery, New York City. Research under the direction of Drs. Freyberg and Trager.)



Legend →



Effect of ACTH in psoriatic erythrodermia. 48-year-old male in whom the skin condition was quite refractory to all usual types of therapy. — **A.** Before. **B.** after several weeks of ACTH treatment. Hands (p. 736) and feet (p. 737) of same patient.

(Courtesy of Dr. D. Markson, Wesley Memorial Hospital, Chicago.)

though signs of hyper-parathyroidism are quite inconstant and partial parathyroidectomy does not always bring relief in scleroderma, the rôle played by the parathyroids in the pathogenesis of this disease would be worthy of further study. It is quite possible that in this instance both the adrenal cortex and the parathyroids could be involved.

Psoriasis. — The frequent association of psoriasis and rheumatoid arthritis[27] suggests some relationship to the "collagen disease" group. Significantly, much before the description of the G-A-S, dermatologists had suspected that psoriasis might be an endocrine disease and particularly that some derangement in the function of the adrenal and thymus may play a rôle in its pathogenesis.[28] There are many metabolic derangements in psoriatics (diminished 17-KS excretion, flat glucose tolerance curve, ascorbic-acid depletion, high serum-potassium, low blood-pressure) which suggest hypocorticoidism and occasionally beneficial results have been obtained with impure cortical extracts.[29] High doses of cortisone or purified ACTH appear to be even more successful.[30] The benefit obtained with large doses of folliculoids[31] may well have been indirectly due to a discharge of endogenous ACTH.

Several recent investigators classify psoriasis among the diseases of adaptation.[32]

Other skin diseases. — Numerous other cutaneous manifestations of disease are presumably influenced by the G-A-S mechanism but it is not within the province of this book to discuss them in detail. Let us merely mention here the **cutaneous purpura of Waterhouse-Friderichsen syndrome,**[33] which is manifestly related to adrenal damage; and the beneficial results obtained by ACTH administration in such diverse conditions as **urticaria,**[34] **exfoliative dermatitis** due to iodine,[35] **atopic dermatitis,**[36] **neurodermatitis, eczema,**[37] and **erythema multiforme.**[38]

It is perhaps pertinent to mention that cases of **infantile eczema** with sudden collapse appear to respond very well to cortical extracts.[39] It has been claimed, futhermore, that DCA is effective in the **herpes of gestation**[40] and there is some preliminary evidence to suggest that **pemphigus** may improve upon treatment with ACTH. (Cf. also: p. 69.)

The relationship of **Raynaud's disease, Boeck's sarcoid** and allied conditions to the sympathetico-adrenal system and to psychosomatic derangements,[41] the rôle of periarteritis and allergic-rheumatic factors in the **anaphylactoid purpura of Schönlein-Henoch,**[42] as well as the many trophic disturbances of the skin which occur in **undernourished** concentration camp inmates,[43] have all been discussed elsewhere.

Capillary permeability and the responsiveness of the mesenchymal connective tissues play a particularly prominent rôle in the resistance of the

[27] Kammerer and Cecil B45752/48. Musser 88056/45, Wassmann B44683/49.
[28] Strandberg **B148/29.**
[29] Charpy B46891/45, B46929/49, B46930/50. Reiss **B41831/49.**
[30] Boland **B47735/50,** Grace and Combes B44786/49, Spies and Stone B45101/50.
[31] Frank B43263/47.
[32] Barber B44422/50, Charpy B46930/50.
[33] Hill and Kinney B45566/47.
[34] Bordley et al. B44913/49, B46989/50, Spies and Stone B45101/50.
[35] Bordley et al. B44913/49.
[36] Randolph and Rollins B46990/50, Kanee et al. B47973/50.
[37] Astwood et al. B47853/50, B47926/50.
[38] Helper et al. B46983/50.
[39] Marsden B40887/47.
[40] van Vonno B42917/47.
[41] Mufson B45910/44.
[42] Gairdner B45718/48.
[43] Lamy et al. B46507/46.

skin to local or systemic injuries, because the derma is predominantly a connective tissue and blood-vessel organ. It is to be expected, therefore, that the G-A-S — and particularly the hypophysis-adrenal system — exert a great influence upon the development of skin lesions. That is probably why so many systemic infections and intoxications are accompanied by cutaneous manifestations. Yet, we must point out emphatically that to label a condition as a "disease of adaptation" does not imply that specific factors fail to enter into its pathogenesis. Indeed there is a gradual transition between diseases predominantly due to derangements of the G-A-S and those in which these play almost no part. In most instances both specific pathogens and derailments of the G-A-S are involved. In this connection it has been emphasized that even in **leprosy** "all the agents known to be effective in the suppression of lesions shared a common factor which I referred to as debility but which Selye, perhaps more accurately, describes as stress".[44] Quite possibly, here again non-specific therapy by stress acts largely as a result of an ACTH discharge. This naturally does not imply that leprosy is merely a disease of adaptation, but it may indicate that the response to the causative organism, with cutaneous and other characteristic lesions, depends on the G-A-S mechanism.

[44] Hughes B44427/49.

THE "BROWN FAT" OR "HIBERNATING GLAND"

It will be recalled that in various animal species a special type of adipose tissue occurs which upon naked eye inspection is characterized by its brownish color. Histologically it resembles a lipid-storing endocrine gland (such as the adrenal cortex, the corpus luteum, or the Leydig cells of the testis) because its epithelioid cells contain numerous small lipid-granules and are richly supplied with capillaries. In some species (e.g., rodents and most hibernating animals), this tissue is present throughout life, in others including man, it occurs quite regularly in certain locations (e.g., the vicinity of the parathyroids, thymus and kidney) during embryonic life, but later it is more or less completely transformed into common adipose tissue.

In hibernating animals, the chief function of this organ appears to be the storage of certain lipids during the active season in order to make these available as nutrients throughout hibernation. Curiously, the "brown fat" contains an unusually large amount of cholesterol, glycogen [1] and testoids.[2]

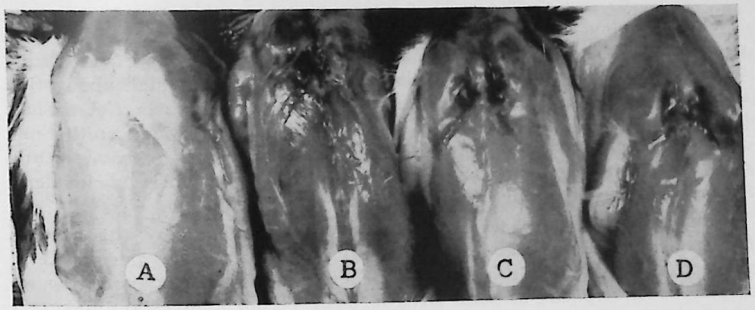
In experiments on rats the lipid and glycogen-granules of this "brown fat" are rapidly discharged during the initial phases of the A-R, irrespective of the alarming stimulus used. At the same time the gland becomes extremely hyperemic, edematous and the phagocytic power of its numerous macrophages (india-ink technique) is considerably increased. In general the discharge of lipids from the "brown fat" runs closely parallel with the elimination of sudanophilic material from the adrenal cortex. It was concluded "that discharge of lipids from the brown fat represents a characteristic response during exposure to various types of systemic stress; it appears to be a sensitive, early indicator of catabolism during the alarm-reaction".[3] **Adrenalectomy** does not prevent the discharge of lipid granules from the brown fat of the rat during the A-R.[4] It is interesting, however, that either adrenalectomy or **hypophysectomy** depletes the hibernating gland of its stored lipids in the mouse and rat. In hypophysectomized mice *ACTH* prevents this change "it is concluded therefore that the maintenance of the normal complement of lipid, in brown adipose tissue, depends upon the functional integrity of the adrenal cortex. The pituitary apparently exercises its effect upon this tissue through its regulation of adrenal cortical activity".[5]

In another series of experiments on rats it was noted that **ACTH** increases the glyceride content of the brown adipose tissue, but even very large doses of ACTH failed to maintain the fat content of the hibernating gland in hypophysectomized rats.[6] Heavy overdosage with **cortisone** reduces the size of the hibernating gland in the mouse and produces A-R changes.[7] While it is evident that the A-R, and particularly the hypophysis-adrenal axis, play an

[1] Cramer 12008/20.
[2] Sweet and Hoskins A35449/40.
[3] Selye and Timiras B36272/49.
[4] Timiras B38908/49.
[5] Fawcett and Jones B46248/49.
[6] Baker et al. B47621/50.
[7] Antopol B47052/50.

important rôle in the maintenance of this peculiar lipid- and steroid-rich tissue, the exact mechanism by which the hibernating gland responds to stress is not yet clear; indeed some relevant data appear to be contradictory.

Apparently **nervous** stimuli also participates in the involution of "brown fat", since in fasting rats this was considerably retarded by denervation.



Hibernating gland during the A-R in the rat. — **A.** Control for B, C and D. After removal of the skin between the shoulder blades, a yellowish or light-brown tissue, the "hibernating gland" is visible (butterfly shaped). In the other animals an A-R was produced by exposure during 48 hours to the stressor effect of: — **B.** Spinal cord transection at the height of the 7th cervical vertebra, — **C.** Exposure to cold (+2°C), — **D.** Repeated forced muscular exercise, while food was withdrawn. Irrespective of the nature of the stressor agent, the hibernating gland became dark-red due partly to discharge of stored lipid granules and partly to intense hyperemia. (After Selye 35935/ND.)

Summary. — The lipid and glycogen-granules of the hibernating gland, or "brown fat" are discharged during the A-R and reappear as the resistant stage develops. The adrenal gland is not essential for the discharge of these granules.

[8] Clément B38524/47.

ABSORPTION

The absorption of diverse substances from the alimentary canal or from parenteral sites is dependent upon many factors. Especially important among these are: the blood and lymph-circulation of the area from which absorption is to take place, the distribution or "spreading" of substances in the tissues, the permeability of the membranes (e.g., peritoneum, intestinal epithelium, capillary endothelium) through which these compounds have to traverse and the ability of the body to attack these substances (by phagocytosis or chemically) to render them optimally absorbable, etc.

Many of these factors have been discussed in other sections of this volume (cf. metabolism, hyaluronidase, gastrointestinal tract, capillary permeability, phagocytosis, R.E.S., etc.). Nevertheless it seemed advisable to devote a small chapter to "absorption" as such, since in many pertinent investigations this complex process has not been broken down into its constituent elements.

During the A-R, the decreased vitality of the gastrointestinal epithelium and the wound surfaces which result from erosions in its lining, render the gut passively permeable for substances which normally do not traverse it unchanged. Thus in the guinea-pig and rat, orally administered adrenaline and histamine proved to be highly toxic during an A-R produced by cold or excessive muscular exercise. Hence if we consider the possibility that toxic materials liberated from tissues may be responsible for some manifestations of the A-R, we must also keep in mind that the increased permeability of the alimentary tract opens the way for the invasion into the blood of poisonous substances (and perhaps also of living micro-organisms), which normally are retained in the intestine by a resistant surface-epithelium. Some types of food-allergy may also find their explanation in this phenomenon (cf. serologic reactions, p. 752). Yet, the absorption of toxic materials from the gastrointestinal tract cannot solely be responsible for the systemic "intoxication" during acute stress, since an A-R can be produced even in a completely eviscerated rat.[1]

Perusal of the pertinent literature suggests that, during the A-R, the intestinal epithelium first loses its selective power to absorb preferentially certain substances, while rejecting others. Thus in rats in which shock was produced by muscle **trauma**, the selective oral absorption of glucose was delayed and very irregular.[2] In guinea-pigs the intestinal absorption of phosphates is diminished during traumatic shock.[3]

After a severe **hemorrhage** the intestinal absorption of an isotonic NaCl-solution is accelerated in the dog,[4] yet the absorption of magnesium sulfate is not significantly influenced.[5]

After total body exposure to the **ionizing radiations** of an atomic bomb explosion, the gastrointestinal exulcerations tend to be particularly severe. Here, "absorption of toxic substances through the injured intestinal mucosa

[1] Selye A8052/38.
[2] Cordier and Touze B37155/48.
[3] Moyson and Toussaint B45998/49.
[4] van Liere et al. B26762/47, B37655/38.
[5] van Liere et al. B26761/47.

and accumulation of tissue break-down products in the blood-stream, are phenomena which logically might follow the wide-spread necrosis that occurs after total body irradiation".[6] Although the lack of evidence in support of such an assumption has been deplored, some of the previously mentioned observations indicate that there is much in favour of this suggestion and indeed that it may also apply to other types of alarming stimuli.

The so-called *"intradermal salt solution test"*[7] has often been utilized in clinical medicine to examine the effect of systemic factors which influence the rate of absorption from the skin. It is based upon a determination of the rate at which intradermally injected physiologic saline disappears. Usually this is judged by the vanishing of a palpable wheel. A large number of apparently unrelated **diseases** accelerate the disappearance of the fluid so injected. Among these are nephritis,[8] scarlet fever and diphtheria,[9] tuberculosis,[10] pregnancy toxicoses,[11] icterus,[12] serum sickness,[13] lobar pneumonia,[14] thyrotoxicosis,[15] various types of circulatory failure[16] and heart disease.[17] Allegedly, in diabetic subjects, the acceleration of the "disappearance time" in this test closely parallels the severity of the condition,[18] but this has not been confirmed.[19] This may well depend upon increased gluco-corticoid secretion, since the latter exert similar actions upon the dermal edema of the experimental "topical iritation arthritis".

The "disappearance time" is lengthened only by very few conditions, for instance myxedema,[20] but here, the delay in absorption is probably due to the generalized edema tendency.

It has been found convenient to add dyes, for instance "Evans blue" to the injected fluid, since this greatly increases the accuracy of readings. With this improved technique it was found that in young persons the initial wheel is smaller, while in older subjects, the dye tends to disappear faster from the skin. "In the older subjects the ready spread of the dye opens a larger absorbing area; initial absorption may be poor due to fewer lymphatic vessels, lesser pressure, possibly less tissue damage, less motility of the skin and consequently, less lymphatic suction, but the secondary stage of absorption (24 and 48 hours) may be faster due to the greater area occupied by the dye." However, the outcome of the test depends on a multitude of factors whose relative participation in any one case would be difficult to analyze. Important among these factors are: hyaluronic-acid salts, hyaluronidase, histamine-liberation, the water and salt content of the skin, binding of the dye by proteins in macrophages, and perhaps to some extent also blood- and lymph-flow. We feel that from the point of view of the G-A-S, the "disappearance time" can only be interpreted somewhat like a blood-sedimentation test; the latter also depends upon a multitude of largely unknown factors, nevertheless it is a good empirical indication of many systemic stress conditions. Hence both these

[6] Tullis B27010/48.
[7] Aldrich and McClure B37663/24. McClure and Aldrich B37662/23.
[8] Aldrich and McClure B37663/24. Feldman and Reifsneider B37677/28. McClure and Aldrich B37662/23.
[9] Baker B37665/24, Lovett B37664/27.
[10] Feldman B37668/28.
[11] Lash B37670/26.
[12] Mora and Jirka B37667/35.
[13] Bradford B37669/27.
[14] Harrison B37666/25.
[15] Mora B37675/29.
[16] Cohen B37671/25, Cohen and Stern B37673/26, Cohen et al. B37672/26, Stern B37674/27.
[17] Olmstead B37679/26.
[18] Berg A37797/42.
[19] Leivy and Rynes B37678/35.
[20] Thompson B37676/26.

clinical laboratory tests may well deserve to be used more extensively by those interested in the pathology of systemic stress.[21]

Summary. — During the A-R, there is a great diminution in ability of the intestinal epithelium to absorb selectively certain substances while rejecting others. If extensive gastrointestinal ulcers occur, even substances normally not absorbed from the alimentary tract can readily traverse the gut through the wounds and thus cause systemic intoxication. This derangement vanishes during the resistant stage but no systematic studies have yet been carried out in the stage of exhaustion.

A number of damaging agents, especially a variety of spontaneous diseases, accelerate the disappearance of intradermally injected physiologic saline in man.

Although the corticoids presumably participate in these changes in absorption rate their precise rôle remains to be determined.

[21] Strauss and Necheles B27843/48.

SEROUS CAVITIES

Serous transudates are frequently found in the pleural, pericardial and peritoneal cavities of animals during the A-R, irrespective of the alarming agent used.[1] The formation of such transudates appears to depend upon many conditioning factors, such as the total salt and fluid intake, the excretory ability of the kidney for water and electrolytes, and the blood-protein-osmotic pressure. Not all of these factors are equally affected during an A-R produced by different agents, hence the degree of serous transudation is rather variable.

In men exposed to **heat-stroke,** transudates occur in the pericardium, pleura and peritoneal cavity, in decreasing order of frequency. Sometimes the fluid thus formed is tinged with blood.[2] Comparatively little is known about the effect of the G-A-S upon the accumulation of fluid in joint cavities and the formation of cerebrospinal fluid. Incidental observations on animals suggest however, that fluid accumulation in the synovial and meningeal spaces is also enhanced by the A-R.

Experiments on rabbits showed that an A-R, produced for instance by **colchicine,** greatly diminishes the permeability of some membranes as measured by dye methods. The urinary bladder [2a] and the synovial membranes [2b] both showed this diminution.

ACTH was found to be "almost as effective in decreasing permeability of the synovial membrane as the alarm-reaction".[2c]

Overdosage with **mineralo-corticoids** (e.g., DCA, desoxocortisone) tends to cause fluid accumulation in the large serous cavities of the body, especially in the pericardium and the peritoneum, but occasionally also in the meningeal and pleural spaces. This may be accompanied by fibrinous inflammatory lesions.[3]

Hyaluronidase enhances osmosis through the bladder membrane in vitro and this is further increased by DCA. **Adreno-cortical extracts** abolish this enhancing effect. Yet, this action is not specific since testosterone and cholesterol were similarly active, and various folliculoids actually reverse the direction of the flow through hyaluronidase-treated membranes. It was noted furthermore, that "hyaluronidase did not alter the complete inhibition of osmosis through the bladder membrane of rabbits which had been exposed to an alarming stimulus" [4] (cf. Hyaluronidase on p. 248).

Similar experiments on the joints of rabbits showed that adreno-cortical extract and **cortisone** diminish (while DCA increases) the permeability of the tissues lining the joint cavity. "It is suggested that the normal permeability of the synovial membrane is in part controlled by the balance between adrenal steroids of the DOCA (DCA) type and of the compound-E (Cortisone) type.[4a]

[1] Selye 36031/36, 38798/37, B1204/46.
[2] Malamud et al. B18019/46.
[2a] Seifter et al. B39251/49.
[2b] Seifter et al. B43460/49.
[2c] Seifter et al. B43460/49.
[3] Selye B1204/46. B43385/50.
[4] Seifter et al. B39251/49.
[4a] Seifter et al. B43460/49.

The effects of mineralo-corticoid overdosage are reminiscent of the clinical syndrome of **polyserositis.** This in turn, appears to be related to the rheumatic-allergic diseases and may co-exist with periarteritis nodosa and the Libman-Sacks' syndrome.[5]

Summary. — During the A-R, the formation of transudates in the pleural, pericardial and peritoneal cavities is enhanced. Intoxication with high doses of mineralo-corticoids exerts similar effects. The syndrome so produced resembles polyserositis, a clinical condition which appears to be related to the rheumatic-allergic derangements and the diseases of adaptation.

[5] Palacio B43773/47.

INFLAMMATION, PHAGOCYTOSIS AND CAPILLARY PERMEABILITY

The phenomena of inflammation, phagocytosis, capillary permeability and the spreading of chemicals and microbes through the connective tissue spaces are so intimately interdependent that it is most expedient to discuss them conjointly. It must be kept in mind, however, that some of these factors have already been touched upon in other connections, for instance, phagocytosis (cf. R.E.S. hemopoietic system, p. 458 ff.), capillary permeability (cf. cardio-vascular system, p. 489 ff.) and "spreading" (cf. hyaluronidase under metabolism, p. 248 and absorption, p. 742 ff.).

The G-A-S exerts a very pronounced effect upon **inflammatory reactions.** It has been emphasized that while bacterial exotoxines have very specific effects (e.g., tetanus-toxin causes muscle-contractions, diphtheria-toxin vascular disturbances), the endotoxins produce a rather non-specific syndrome reminiscent of the A-R. There is prostration, variations in blood-sugar, hyperlactacidemia, diarrhea, congestion of the viscera with massive intestinal and occasionally widespread capillary hemorrhages, disintegration of the lymphatic organs, discharge of the chromaffin granules from the adrenal medulla, etc. It is interesting that in guinea-pigs the subcutaneous injection of various living or killed microbes (staphylococcus, Koch bacilli), or microbial extracts (polysaccharides, nucleo-proteins, etc.) regularly produces an intense inflammatory reaction at the site of injection. There is edema and diapedesis of polymorphonuclear leucocytes. This diapedesis (but not the edema) can be inhibited by *systemic intoxication* with bacterial endotoxins. In response to a systemic intoxication with endotoxins the adrenals discharge adrenaline, hence it appeared of interest to examine whether this hormone is responsible for the inhibition of diapedesis. When *adrenaline* was injected subcutaneously together with an irritant (e.g., staphylococci) it did indeed prevent diapedesis, but no such inhibition could be produced even with very high doses of this hormone if it was injected at a distance from the irritant. Furthermore, ergotamine (which blocks most of the adrenaline actions) can not prevent the inhibition of diapedesis produced by systemic intoxication with bacterial endotoxins. This is all the more significant since the direct effect of adrenaline (topically applied to the area of injury) is prevented by ergotamine. In view of these observations it has been concluded that "in animals treated with endotoxins it is not adrenaline — or some allied substance — that is primarily responsible for the inhibition of diapedesis".[1]

It has been found, furthermore, that systemic stress does not only inhibit diapedesis in inflammatory reactions to microbial products, but even the "Arthus phenomenon", elicited in the skin of the guinea-pig, is no longer accompanied by polymorphonuclear leucocytic infiltrations if the animals have previously received toxic amounts of bacterial endotoxins.[2]

[1] Delaunay and Pages 94811/45.

[2] Delaunay and Pages 94811/45.

Further investigations showed that anaphylactoid [3] as well as traumatic and toxic "shock" [4] also inhibit diapedesis. This inhibition is demonstrable both after subcutaneous and after intraperitoneal injection of the irritant.

Although, as we have seen above, adrenaline is not the responsible agent, the adrenals do appear to participate in this inhibition of diapedesis. If intact rats receive a small amount of sterile broth (such as is used by bacteriologists) intraperitoneally, fluid recovered from their peritoneal cavity a few hours later is found to be invaded by many mono- and polymorphonuclear leucocytes. On the other hand, if these same animals are simultaneously given a fatal subcutaneous injection of typhoid-endotoxin, the diapedesis of leucocytes into the peritoneum is almost completely inhibited. *Adrenalectomized* rats — though much more sensitive to the lethal effect of the typhoid-toxin — show a normal diapedesis of leucocytes into the peritoneum after the injection of sterile broth. "These results appear to show that principles liberated from the adrenal cortex play a rôle in the inhibition of diapedesis. Most probably, these principles are hormones".[5] Such observations led to the assumption that the inhibition of diapedesis is a *result of the A-R*, which, through the increased production of adrenal hormones, renders the capillaries impermeable to leucocytes. This might explain why adrenalectomy prevents the inhibition of diapedesis, although, at the same time, the animal's resistance to stress diminishes because it can not form defensive adrenal hormones.[6] The decreased resistance to infections, which is often apparent during traumatic shock, has been ascribed to this same inhibition of diapedesis. During systemic stress "the microbes, which infect the wounds, can proliferate without inhibition when they are protected from the aggression of the blood phagocytes".[7]

Since corticoids share many pharmacologic actions of *antihistaminics* and *salicylates* it is interesting to compare the above hormone actions with the antiphlogistic effects of the latter drugs.[8]

Recently, much attention has been given to the antiphlogistic effect of the *thiosemicarbazone* derivative "Tb I", since the latter appears to exert cortisone-like actions in a variety of rheumatic, allergic and other inflammatory conditions. It has been claimed that "Tb I" decreases the "inflammatory potential" of tissues, somewhat like gluco-corticoids do, perhaps because it blocks the action of the antagonistic mineralo-corticoids.[8a]

On the basis of experiments on dogs, it appears that the **phagocytic power** of the blood-leucocytes falls rapidly to very low levels during the first few hours of traumatic shock, but returns to normal after 24 hours. Here, blood-samples were taken before, during and after shock, and the phagocytic power was estimated by the number of added bacteria ingested by the blood-leucocytes in vitro.[9] Since these observations have not been followed into the resistant stage of the G-A-S we cannot say whether at that time, phagocytosis would have risen above normal. However, so many manifestations of the A-R have been shown to be actually reversed during the resistant stage that this possibility should be considered. In any case, one cannot merely speak of an effect upon phagocytosis in general, since certain reticulo-endothelial cells

[3] Delaunay et al. 94910/46.
[4] Delaunay et al. B3114/46.
[5] Delaunay et al. 93023/46.
[6] Delaunay and Lebrun B3182/47.
[7] Delaunay et al. B3114/46.
[8] Fabinyi et al. B37516/48, Gross and Meier B37521/48.
[8a] Heilmeyer B47479/50.
[9] Colombo and Zanetti A8284/37. Gerlach B37660/23, B37661/25.

have been shown to become extremely phagocytic during the A-R, while others remain uninfluenced or actually exhibit an inverse type of response (cf. R.E.S., p. 458 ff.).

It has also been claimed that macrophages can be formed locally from connective tissue elements, under the influence of systemic stress. In animals, whose polymorphonuclear leucocytes had previously been destroyed by benzol, a subsequently produced Arthus phenomenon nevertheless evolves in a normal manner. Furthermore, in an isolated rabbit-ear, perfused with physiologic saline, local allergic reactions can still occur and these cause the appearance of numerous macrophages (though not of polymorphonuclears) around the blood vessels. Apparently, at least the macrophages can be formed locally from connective-tissue cells and do not have to be brought into the inflammed area by the blood. The fact that an allergic tissue-reaction can be elicited in the absence of any blood-borne antibody, likewise suggests that local anaphylaxis is not merely a humoral phenomenon, but also a tissue-reaction.[10] Of course, it is undoubtedly true that blood-borne antibodies nevertheless play an important part in such responses, since the intensity of the Arthus phenomenon runs parallel with the blood-antibody titer.[11]

Experiments on frogs showed that a perfusate of the heart, obtained after vagus-stimulation, impairs the phagocytic power of the leucocytes (against Friedmann bacilli). This effect has been ascribed to acetylcholine, which exerts the same effect in vitro. Subcutaneous injections of adrenaline increases phagocytosis, while pilocarpin exerts an opposite effect.[12]

Considerable attention has been given recently to the effect of *corticoids* upon phagocytosis. This problem has been discussed in connection with the activities of the RES particularly the sections on the hemopoietic system (cf. page 452) and the blood-count (cf. pp. 420 ff.). There we mentioned that the phagocytic power of the RES cells is increased by corticoids and that this may lead to destruction of erythrocytes with a corresponding hemochromatosis of sessile phagocytes, e.g., in the spleen and liver. Such damage to red cells, with their consequent ingestion by phagocytes, may play an important rôle in the "anemia of infection" and other non-specific anemias and hypoferremias.

Let us merely add here that a variety of agents (histamine, adrenaline, bone fractures, anaphylactoid shock), in addition to bacterial or sterile abscesses, are capable of producing hypoferremia and anemia in the dog. *Adrenalectomy* prevents the drop in plasma-iron caused by mild stress or ACTH. Intravenously administered iron is removed rapidly from the plasma in intact dogs given *ACTH* and more slowly in adrenalectomized dogs. "It is postulated that the level of plasma-iron is regulated by the reticulo-endothelial system, and that the functional activity of its cells is influenced by the adrenal cortex".[12a] There is no doubt that gluco-corticoids such as cortisone can stimulate the phagocytic ability of the RES [12b] and there is some evidence that desoxycorticosterone (given as the glucoside) shares this potency to some extent.[12c]

An increase in **capillary permeability** is characteristic of the A-R (cf. cardiovascular system). It manifests itself by increased transudation of plasma from

[10] Betz B26164/48, Gerlach B37660/23, B37661/25.
[11] Cannon and Marshall 79817/41.
[12] Golodets and Putshkov B37610/48.
[12a] Cartwright et al. B47860/50.
[12b] Selye B39702/49.
[12c] Köhler et al. B47098/49.

the capillaries into the surrounding intercellular spaces of various tissues, especially those of the connective tissue and Disse's spaces around the hepatic sinusoids. This leads to an increased lymph-flow (cf. lymph, p. 487) and, in the case of very intense reactions it may be conducive to capillary hemorrhages with the formation of hemolymph nodes (cf. lymph nodes, p. 456). Even mild degrees of increased capillary-permeability are readily demonstrable by the intravenous injection of dyes (e.g., trypan blue) which do not pass through normal capillary walls, these stain the tissues intensely only when the capillaries become permeable to such substances (e.g., during the A-R).[13] In certain experiments on guinea-pigs the rate of disappearance of intravenously injected Evans blue was not accelerated by anoxia,[14] but here the exposure was perhaps too short to produce marked systemic stress.

In areas directly exposed to damage (cold, x-rays, carbon-arc-irradiation, ultraviolet-rays, mechanical trauma, burns, etc.) the increase in capillary permeability is particularly pronounced; however, if such local damage causes grave systemic stress and a severe A-R, the capillary permeability is increased even in distant regions. The enhanced permeability of capillaries undoubtedlv plays an important rôle in various inflammatory reactions, the formation of edema, and especially the diapedesis of formed blood-elements. The capillaries may allegedly also become selectively permeable to cells or to fluids of certain protein-concentration. This may partly account for the formation of edema, transudates and exudates of different cellular and chemical composition.[15] We do not know what factors are responsible for such specific changes in permeability, nor can we assess the possible interrelations between the intense, local increase in capillary permeability at the site of a direct trauma and the much less pronounced, but qualitatively similar, response of distant capillary territories. Yet the essential similarity between these local and systemic reactions gives further support to the view that most of the principal manifestations of the A-R merely represent systemic counterparts of such simple, local non-specific reactions as capillary leakage, edema, inflammation and necrobiosis.[16]

As previously mentioned in other connections the increase in capillary permeability caused by stress is largely prevented by **adreno-cortical extracts** or **ACTH.**[17] The spreading of intradermally injected dyes is accelerated by **adrenalectomy** and inhibited by **cortisone** [17a] or procedures which cause an ACTH discharge, e.g., **adrenaline injection** [17b] (c.f. also: Hyaluronidase, p. 248 ff.).

Inflammation as a disease of adaptation. — In the preceding pages, we emphasized certain fundamental similarities between inflammation and the A-R. In many respects, the A-R may be looked upon as an inflammation of the organism as a whole. In both instances the reaction is non-specific involving defense, characterized by a decrease in the selective permeability of membranes (particularly capillaries) with leakage of chemical (and later even cellular) blood-constituents into the intercellular spaces. While in circumscribed inflammatory foci, phagocytic elements tend to accumulate locally, in the A-R there is a corresponding activation of the R.E.S. throughout the body. In both

[13] Herlant et al. B46421/ND.
[14] Hopps and Lewis B37875/47.
[15] Eppinger **B37085/49.**
[16] Selye 36031/36, 38798/37.
[17] Grenell and McCawley B33889/47, Prados et al. B39657/45.
[17a] Winter and Flataker B47198/50.
[17b] Shuman and Finestone B47062/50.

instances, the resulting increase in phagocytic power may help to free the organism of particulate substances such as micro-organisms.

Many instances have been cited to illustrate that the hypophysis-adrenocortical system can affect not only systemic resistance to non-specific insults, but also local resistance to topically applied stressors which cause inflammation. The effect of mineralo and gluco-corticoids respectively upon the course of "topical irritation arthritis" [18] is a clear-cut case in point. Here it depends largely upon the efficacy of defensive corticoid production whether the local irritant will cause disease or will be removed with impunity. If under the influence of gluco-corticoids, the connective tissue cells around joints can become "indifferent" to such agents as formalin or mustard, it is highly probable that their response to other inflammation-producing agents (e.g., microbes) would be similarly influenced by such hormones. Thus, in many instances, the appropriate production of cortical hormones can determine whether the introduction of irritants into the body will cause disease.

On this general rationale ACTH has been given to a patient with beryllium granulomatosis; striking improvement was noted in this disease, which does not regress spontaneously and does not respond to any other type of treatment.[19]

Two cases of acute peritonitis, one associated with perforated duodenal ulcer, have been reported to have occurred during ACTH treatment. Some of the characteristic signs and symptoms of peritonitis (fever, abdominal rigidity) were absent, thus rendering diagnosis difficult.[20]

The integration of systemic defense-reactions and local responses to injury is perhaps one of the most promising and hitherto least carefully investigated aspects of the G-A-S concept.

Summary. — Inflammation, with the accompanying changes in phagocytic power and capillary permeability, are largely dependent upon the systemic defense phenomena of the G-A-S. Gluco-corticoids prove highly effective in combatting an excessive fibroplasia in inflammatory foci as well as the spreading of extraneous materials introduced into the organism. The loss of selective permeability in capillary regions affected by direct (locally applied) or systemic stress is likewise inhibited by gluco-corticoids.

It largely depends upon systemic defense reactions, and particularly upon the production of corticoids, whether the introduction of foreign irritating materials into the body will lead to excessive inflammatory reactions and hence to disease.

[18] Selye B39702/49.
[19] Kennedy et al. B47972/50.
[20] Beck et al. B47971/50.

SEROLOGIC REACTIONS

Numerous observations suggest that systemic stress can influence serologic defense reactions. Some pertinent data have already been discussed in connection with the changes in blood-γ-globulins (p. 165 ff.) and in the hemopoietic system (cf. spleen, R.E.S., lymph, p. 452). Serologic antibodies are presumably manufactured from blood-proteins or amino-acids by certain lymphatic and reticulo-endothelial elements, perhaps mainly the plasma cells;[1] hence some overlapping with previously discussed data is unavoidable. However, here, we shall deal mainly with observations concerning the serologic aspects of the problem.

Experiments on rabbits and man suggest that the formation of certain **immune-bodies,** especially agglutinins and hemolysines, is accelerated by an *ultraviolet-irradiation* of sufficient intensity to produce an A-R.[2] Observations on dogs led to the conclusion that the opsonin-titer of the blood rises after *peptone, histamine* and *spinal shock,* but is not changed during *traumatic* or *anaphylactic* shock.[3] This would suggest a certain specificity of this response, but the duration and intensity of treatment may not have been quite comparable in the animals exposed to diverse damaging agents. Other investigations, on dogs submitted to severe *trauma,* revealed "a constant diminution of the complement fixation, phagocytic and bactericidal properties" of the blood, which was not manifest if the animals were partially protected against the stress-effect of the trauma by general anesthesia.[4] A systematic review of the pertinent literature and some personal observations led to the conclusion that mild surgical trauma, treatment with *foreign proteins* and *x-irradiation,* usually increase the bactericidal power of the blood, but the response is often biphasic and very severe injury may actually reverse it.[5] Significantly, recent observations have shown that "the destruction of lymphocytes, which accompanies the A-R caused by x-irradiation of the posterior limbs, is not conducive to any simultaneous increase in circulating antibodies".[5a] Additional experiments will be required to determine to what extent such immune reactions are dependent upon conditioning factors.

In connection with the development of cardiovascular hyalinosis (cf. cardiovascular system, p. 543) we mentioned data which suggest that *auto-antibodies* against certain tissues (e.g., kidney, heart) may lead to the development of the rheumatic-allergic type of lesions. Thus, anti-kidney sera can cause nephrosclerosis and their ability to do so appears to be increased by mixing them in vitro with dead hemolytic streptococci. On the basis of such experiments, the pathogenesis of acute rheumatic fever was tentatively ascribed to an influence of streptococci (or their toxins) upon certain tissues which are thus transformed into antigens.[6] Although these observations have not been

[1] Ehrich et al. **B40164/49,** Teilum B38105/48.
[2] Wada 1245/29.
[3] Sonobe A8283/37.
[4] Colombo and Zanetti A8284/37.
[5] König A32639/32.
[5a] Lecompte and Fischer B46838/49.
[6] Cavelti B38103/48, B4336/47, Werkö B45656/46.

uniformly confirmed, they would deserve further study since they suggest interesting new possibilities.

The renal lesions produced by various drugs such as the *sulfonamides* are likewise often accompanied by cardiovascular manifestations of hyalinosis; they have been interpreted as a special type of "renal allergy".[7] It remains to be seen to what extent this hyalinosis is elicited through the hypophysis-adrenal system or through a direct effect upon a lower link of the G-A-S mechanism, e.g., the kidney.

In view of the marked lympholytic effect of alarming stimuli, it is interesting that most investigators consider lymphoid elements to be the main **site of antibody formation.** It was found, for instance, that after destruction of all lymphoid tissues by intense x-irradiation[8] or nitrogen mustards,[9] antibody-formation is greatly diminished. Damage to the bone-marrow probably does not play a very important rôle in this inhibition. If the lymphoid tissue is destroyed by repeated small doses of soft x-rays which produce no detectable change in the bone-marrow, antibody-production is nevertheless diminished. Furthermore, in rabbits whose lymphoid system had been stimulated by dry heat, the production of immune-substances is augmented.[10]

If, following a first sensitizing injection of horse serum, the lymphoid system of guinea-pigs is kept in an atrophic condition (G-A-S ?) by x-irradiation, they develop no anaphylactic manifestations upon receiving a second injection of this same serum. In these animals, the antigen remains free in the circulation as long as the x-ray treatment is continued.[11] These and many other observations suggest that the lymphocyte is responsible for the antibody formation.[12]

On the other hand recent observations on the regional lymph-nodes of rabbits injected with typhoid vaccine suggest that antibody formation parallels the development of plasma cells and hence was ascribed to an activity of the latter.[13]. Certain anatomo-pathologic observations give support to this view.[14]

In guinea-pigs sensitized to egg-white, an A-R elicited by formaldehyde, cold or muscular exercise 18 to 24 hours before re-injection with the antigen, also diminishes or abolishes the manifestations of **anaphylaxis.** However, if the A-R is very intense, and given without permitting a period of recovery before the re-injection, it actually aggravates the anaphylactic shock.[15] The prevention of anaphylactic shock in the guinea-pig by such stressor agents as papain,[15a] formalin,[15b] atropin[15c] or x-rays[15d] may likewise be due to the production of an A-R.

Perhaps certain types of **food allergy** could also be explained on the basis of the G-A-S mechanism. In the guinea-pig oral administration of horse serum (which normally causes no sensitization) proved to be allergenic during an A-R produced by various stressors. Presumably, the damaged gastro-intestinal mucosa of the stressed animal permits the absorption of undigested foreign protein, which leads to sensitization, so that a subsequent parenteral

[7] Wernitz B37758/49.
[8] Hektoen B37680/15, B37681/18, B37682/20.
[9] Philips et al. B37687/47.
[10] Murphy and Sturm B37683/25.
[11] Hussey B37684/21.
[12] Boivin and Delaunay **B2509/46.** Murphy and Sturm **B4336/47,** White and Dougherty B34049/46.
[13] Ehrich et al. B40164/49.
[14] Teilum B38105/48.
[15] Karady et al. A9072/38.
[15a] Zacco and Biozzi B39573/47, B37976/47.
[15b] Rosalia B37876/47.
[15c] Danielopolu B38202/48.
[15d] Hussey B37684/21.

injection of the same serum may precipitate a severe anaphylactic shock. It was concluded that "the alarm-reaction permits the sensitization of healthy animals by the oral administration of normal horse serum".[16]

Serum sickness has long been regarded as due to abnormal adaptive reactions.[17] Experimental investigations revealed that the destruction of antibody-forming lymphoid cells during the A-R (e.g., produced by colchicine) tends to prevent the development of this and other allergic conditions. Indeed, allegedly, even the familiar antirheumatic effect of salicylates is largely mediated through this mechanism.[18] Perhaps the inhibition of serum shock, in the dog, by yohimbine is also a related phenomenon.[18a]

Pirquet's reaction is based upon the fact that in tuberculous subjects the local inflammatory response to a cutaneous tuberculin inoculation is more pronounced than in normals. This response is diminished by such "non-specific therapeutic agents" as parenteral administration of milk or foreign sera, as well as by intercurrent systemic infections (e.g., scarlet fever or measles). Although systemic stress in itself has an inhibitory effect, the inhibition is particularly pronounced whenever there are exanthemas. Even ultraviolet irradiation of the skin, or previous local intracutaneous administration of irritative substances diminish this response. "It is assumed that in the tissues and in the blood there is an active substance which directs inflammatory processes and is essential for their development. A diminution or utilization of this substance by preceding inflammation explains the decrease or abolition of an inflammatory response to a subsequent irritant of equal intensity. The absence of a positive tuberculin reaction after exanthemas and other diseases causing extensive inflammatory responses in organs other than the skin appears to be thus explained".[19] This rather original interpretation certainly deserves further study. In our experiments with the "topical irritation arthritis" we often noted that a second injection into a joint previously treated with an irritant causes a less pronounced response, but it is difficult to prove whether this is due to the utilization of some hypothetical "inflammation substance". If the above theory is correct, the systemic antiphlogistic action of cortisone may well be due to the utilization or discharge (consequent tissue to catabolism ?) of the substance(s) necessary for the normal development of an inflammation.

The extensive **"anaphylactoid"** edema of the nose, tongue, and paws which is elicited in rats by parenteral administration of egg-white can be completely inhibited by a variety of alarming stimuli (e.g., formaldehyde, muscular exercise, exposure to cold) [20] as well as by antihistaminics.[21] In all these experiments, it has been assumed that the A-R exerts a protective influence in the sense of a so-called "crossed resistance". The exact mechanism through which this defensive effect is mediated has not yet been elucidated, as we shall see, it appears to depend largely upon a defensive production of adrenal hormones.

In a study concerning the mechanism of the **Shwartzman phenomenon** (cf. Glossary p. 45), advantage was taken of the fact that x-irradiation, benzol and nitrogen-mustards are notoriously active in destroying the hemo-

[16] Karady B44929/41.
[17] Meessen A33183/39.
[18] Ehrich et al. B17866/48, Forman et al. B37491/48.
[18a] Quinquaud B38201/48.
[19] Thalhammer B45955/49.
[20] Léger and Masson B4327/48, Selye 38798/37.
[21] Clark and McKay B36925/49, Léger and Masson B4327/48.

poietic organs [22] and place the R.E.S. under strain.[23] Interestingly in rabbits, a Shwartzman phenomenon, produced by meningococcus-endotoxin, can be completely suppressed by pretreatment with nitrogen-mustards or benzol and sometimes also by x-irradiation. "It is suggested that this study provides an experimental basis for a new therapeutic concept in the treatment of diseases involving tissue and vascular reactivity" ... "This concept would be directed toward suppressing the ability of the vascular endothelium to react adversely to whatever circulating toxin might be the inciting agent. A group of these diseases would include acute rheumatic fever, acute, sub-acute and chronic disseminated lupus erythematosus, periarteritis nodosa, generalized vascular diseases due to hypersensitivity-reactions to drugs, sera or vaccines and probably dermatomyositis, rheumatoid arthritis and acute and sub-acute glomerulonephritis".[24]

For further pertinent data concerning the influence of the G-A-S upon the resistance to allergic and other hyperergic responses, see also the section on "Resistance", p. 53 ff.

Stimuli Influencing Serologic Responses During the G-A-S

Hypophysis. — There is much to suggest that the hypophysis, through the adrenal cortex, exerts an important regulating influence upon serological responses. Much of the relevant evidence was derived from a study of the "anamnestic response". This, it will be recalled, is the enhancement of antibody-titer which occurs following the injection of a variety of substances other than the original antigen. It has been shown that those same alarming stimuli, which are effective in causing lympholysis, raise the antibody-titer of the blood of previously immunized animals while the disintegrating lymphocytes are absorbed.[25] ACTH, which induces a similar lympholysis, also elicits an intense anamnestic response in previously immunized rabbits and mice, but only in the presence of the adrenals; hence, both these reactions (lympholysis and the anamnestic response) were assumed to be caused by corticoids.[26] In more recent pertinent observations on man, staphylococcal toxoid was chosen as an immunizing agent, because the estimation of antihemolysin is not time-taking and can be carried to a finer end-point than titrations involving agglutination. However here, as large a dose as 400 mg. of ACTH failed to raise the circulating antibody-level.[27] Similarly, in rabbits previously immunized with crystalline ovalbumin, a fall in circulating lymphocytes produced by ACTH or x-rays resulted in no change of blood-antibody content following treatment with this antigen.[28]

Among men vaccinated with pneumococcal polysaccharides "antibody was produced as promptly and in as high titer in patients receiving ACTH or cortisone, as in controls. However, the degree of induced sensitivity of pneumococcus polysaccharide (Francis test) was depressed in some patients during treatment. The γ-globulin fraction decreased in the ACTH and cor-

[22] Kindred 99940/47, Krumbhaar and Krumbhaar B19937/19, Pappenheimer and Vance B19939/20, Seeling and Osgood B37688/38.
[23] Hektoen B37680/15, B37689/16, Hektoen and Corper B19940/21, Jaffe B37693/31, Philips et al. B37687/47, Simonds and Jones B37690/15, Spurr B37691/47, Taliaferro and Taliaferro B37692/48.
[24] Becker B28260/48.
[25] Cannon 83773/42.
[26] Dougherty et al. B142/45.
[27] Herbert and de Vries B33146/49.
[28] Fischel et al. B43682/49.

tisone treated individuals even though specific antibody against the pneumococcus was increasing at the same time".[28a] The diminished skin-sensitivity of these patients is probably just another manifestation of the "indifference of the cells" to injurious agents after ACTH or gluco-corticoid treatment; it is reminiscent of that exhibited in the "topical irritation arthritis" test.[28b] This is one more observation showing that the gluco-corticoids do not act upon the pathogens of diseases but merely render them non-pathogenic.

In patients with rheumatoid arthritis or scleroderma ACTH reduced the complement titer as well as the blood γ-globulin and fibrinogen concentration. Curiously in lupus erythematosus, where the complement titer tends to be subnormal, it is elevated during effective ACTH treatment. Pertinent investigations led to the suggestion "that the effect of ACTH upon γ-globulins is probably mediated through the depressant effect of these drugs upon the lymphoid tissues of the body. The changes in the fibrinogen are to be directly related only to the degree of disease activity. The mild depressant effect of ACTH upon serum complement is modified in lupus erythematosus by the fact that this is a disease apparently associated with some other specific mechanism for reducing complement activity. It would appear that ACTH also depresses this mechanism".[28c]

The clinical manifestations of the "anaphylactoid edema" of rats treated with egg-white can be completely inhibited by ACTH.[29]

Somewhat unexpectedly, it has been found that pretreatment with ACTH does not influence the course of anaphylactic shock in the guinea-pig.[29a] However, this conclusion was based upon experiments in which the hormone was administered six to eight hours prior to the shocking dose of the antigen; by this time the peak of the ACTH response had passed. Preliminary experiments suggest that if the hormone is administered one hour prior to the shocking dose, the anaphylactic shock is greatly diminished or inhibited.[29b]

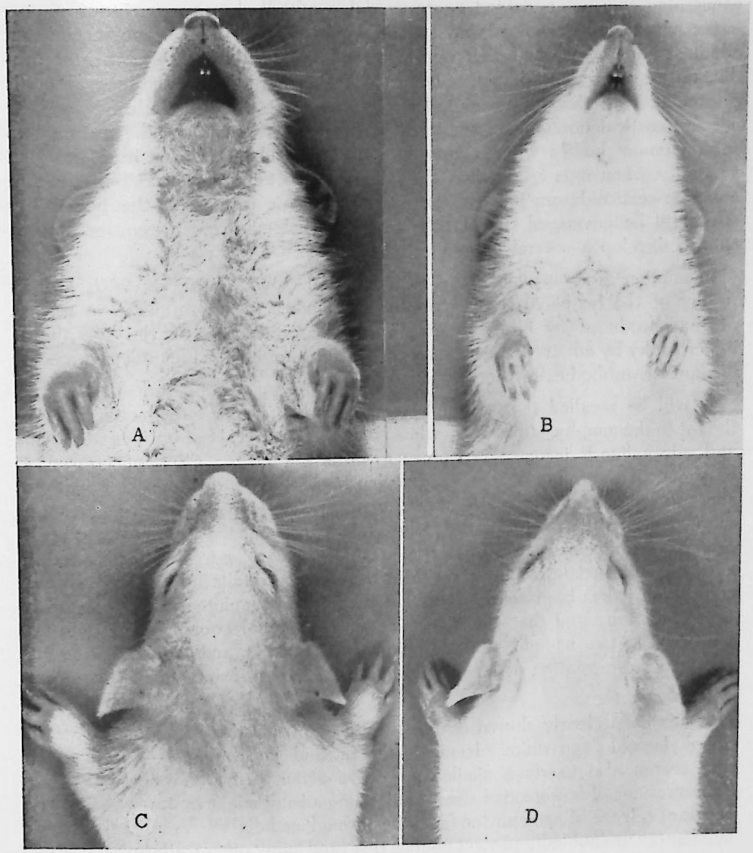
ACTH administration to patients who previously showed a positive tuberculin reaction makes them non-responsive in this respect.[29c] Using hypersensitivity to tuberculin in guinea-pigs, as an example of "bacterial allergy", it was found that ACTH, or cortisone, exert a pronounced immediate anti-allergic effect, but after discontinuation of the treatment these animals became actually more sensitive than the controls (thyroxine exerted opposite effects).[29d]

ACTH given just before the provocative injection also suppresses the Shwartzman phenomenon in the rabbit.[29e]

The above-mentioned observations show that the formation and release of antibodies is not consistently influenced by ACTH; this is perhaps due to differences in the techniques employed by different investigators. There appears to be no doubt, however, that ACTH can inhibit the manifestations of allergic-anaphylactic responses at the level of the peripheral "shock organs". Perhaps here — as in the case of the "topical irritation arthritis" — the peripheral cells become indifferent to the antigen-antibody reaction.

Adrenals. — The pronounced adrenal changes which occur in the course of most infectious diseases, inspired many investigations concerning the pos-

[28a] Mirick B47891/50.
[28b] Selye B39702/49.
[28c] Vaughan et al. B47904/50.
[29] Selye B39703/49.
[29a] Leger et al. B39369/48.
[29b] Selye 35935/ND.
[29c] Tompsett et al. B47903/50.
[29d] Long and Miles B47313/50.
[29e] Soffer et al. B47030/50.



Effect of ACTH upon anaphylactoid edema in the rat. — **A** and **C**. Head and paws of an unpretreated rat injected with egg-white. Note marked edema and hyperemia of the paws, lips and nose. — **B.** and **D.** Received ACTH just prior to treatment with egg-white. Note the complete absence of the anaphylactoid response. (After Selye B39703/49.)

sible participation of these glands in serologic defense reactions (cf. p. 309 ff.). The influence of the pituitary and adrenals upon antibody proteins has been discussed in conjunction with the blood-globulins (cf. p. 173 ff.) and many pertinent serologic data have been mentioned in the just preceding paragraphs, to which the reader is referred to avoid unnecessary repetition.

Several reports in the early literature suggested that **adrenalectomy** inhibits, while cortical extracts enhance antibody-formation.[30] Recent investigations

[30] Herbert and de Vries **B33146/49.** and Marmorston-Gottesman **32161/35.** Perla Trowell **B31917/47.**

concerning this point yielded controversial results.[31] In one pertinent experiment on adrenalectomized cats maintained on DCA, it was noted that administration of washed sheep erythrocytes still resulted in the normal production of circulating immune bodies and upon reinjection, these animals responded with the usual anaphylactic reaction. It was concluded "that the adrenal cortical hormones do not either affect the capacity of the animals to form immune bodies when exposed to antigens nor alter the titer of such immunity when it is established".[32] Although most investigators believe that mineralo-corticoids are inactive as regards serologic responses, the possibility must still be envisaged that DCA may have helped these adrenalectomized cats to develop a normal anaphylactic response.

In another study it was found that "adrenalectomized rabbits with hypertrophy of the lymphoid tissues, produce antibodies in amounts far in excess of that produced by intact animals." ... "the prevention of the lymphoid-hypertrophy by administration of adrenal cortical hormones does not reduce the amount of antibodies in the sera".[33]

It will be recalled that adrenalectomy greatly increases the sensitivity of the rat to the anaphylactoid "egg-white edema", however, here both corticoids,[34] and adrenaline[35] increase resistance towards normalcy. This, of course, is only one of the many actions of gluco-corticoids which adrenergic hormones share to some extent. (Cf. also effects upon glycemia, blood-pressure, muscular work, etc.) Adrenalectomy allegedly tends to prevent the "anamnestic reaction", yet unlike most of the alarming stimuli, heavy x-irradiation causes a marked "anamnestic response" even in the absence of the adrenals.[36] In this connection it has been emphasized that the adrenal regulates only the rate of these reactions and that the adrenalectomized animal continues to produce antibody.[37] Let us add that adrenalectomy inhibits and cortical extracts increase the formation of hemolysin against sheep erythrocytes in the mouse and rat.[37a]

It has been clearly shown that **adrenaline** prevents the development of an anaphylactoid "egg-white edema" in the rat and since an A-R produced by any means also exerts a similar protective action[38] it was concluded that "observations of a protective effect of alarming stimuli might be interpreted as a result of release of epinephrine from the adrenal medulla".[39] While adrenergic substances undoubtedly protect against this (and many other) allergic phenomena, pure corticoids share this effect; hence there is no reason to doubt that both types of hormones can participate in the anti-allergic effect of the A-R.

As regards the effect of **corticoids** upon the concentration of circulating antibodies, the published data are very contradictory. It has been claimed that *adrenal-cortical extract* stimulates the production, or at least the release into the blood, of antibodies in animals which had previously received an antigen.[40] Furthermore, allegedly, ACTH or exposure to various alarming

[31] Valentine et al. B33082/48.
[32] Houghton et al. B40870/47.
[33] Murphy and Sturm B4336/47.
[34] Léger B25569/48, Selye 38798/37.
[35] Clark and McKay B43446/49.
[36] Dougherty and White 95612/46.
[37] White B38901/48.
[37a] Chase B42666/47.
Roberts and White B47235/50.
[38] Selye 38798/37.
[39] Clark and McKay B36925/49.
[40] Chase et al. B4950/46,
Dougherty and White 95612/46.
Dougherty et al. A91821/44.
Fox and Whitehead 34956/36.

stimuli releases antibodies into the blood only in intact, not in adrenalectomized animals.[41]

In cold-blooded species the release of antibodies into the circulation is inhibited during exposure to low temperatures. Allegedly, cortical extract can cause a release of serum agglutinins in the frog and fish even while they are kept in the cold, although the extracts have no effect upon the process of immunization itself.[42]

Other investigators were unable to raise the blood-antibody titer by cortical extracts (or to diminish it by adrenalectomy) in mammals.[43] Yet, in one experimental series, there was a slight elevation of serum-antibody-nitrogen shortly after cortical extract injection in rabbits previously immunized with pneumococcus Type I. It was concluded "that increased adrenal cortical activity may exert a transitory influence upon the distribution of pre-existing antibodies", although it is not indispensable for such release (since this still occurs after adrenalectomy) and, in any case, the effect is small and transitory.[44]

Mice receiving large doses of *cortisone* appear to have lost their resistance to infection (with corynebacterium pseudotuberculosis murium); this was attributed to the disappearance of lymphocytes and their contained antibodies.[44a] It will be remembered, however, that even latent infections in rats tend to be aggravated as a result of cortisone overdosage, so that septicemias with pulmonary, renal and hepatic abscesses may ensue. A diminution of circulating antibody may be involved in this loss of resistance when cortisone overdosage is severe, but the possibility must also be considered that normally latent foci of micro-organisms develop excessively when fibroblastic encapsulation is inhibited through the gluco-corticoid effect.

Certain observations with *DCA* suggested that guinea-pigs can be protected against anaphylactic shock (and somewhat less evidently against histamine) by this mineralo-corticoid.[45] In rabbits, allegedly small doses of DCA increase, while large doses diminish, the production of agglutinines against typhoid bacilli.[46] On the other hand, DCA proved ineffective in preventing the anaphylactoid response of the rat to parenteral egg-white administration (and indeed tended to aggravate it) while *cortisone* exhibited a pronounced protective effect.[47]

In **summary,** the pertinent literature and particularly the above-mentioned observations, lead us to assume that perhaps certain stimuli (e.g., the specific antigens themselves and x-rays) can liberate antigen from the lymphoid tissues, even in the absence of the adrenal, but that under suitable conditions, corticoids can do this even in non-toxic concentrations. Perhaps the A-R helps to discharge the stored antibodies from lymphoid tissues through the hypophysis-adrenal mechanism, while direct lympholytic agents (e.g., x-rays) do so even in the absence of the adrenals. The organism undoubtedly also possesses specific means to produce and discharge certain immune bodies in response to their particular antigens. In other words, those agents which possess a direct lympholytic effect, such as ionizing radiations and corticoids, would act non-specifically by merely destroying the antibody stores (the

[41] Dougherty and White 95612/46.
Dougherty et al. B142/45.
[42] Bissett B36695/49.
[43] Eisen et al. 98924/47.
Stoerk et al. B25605/47.
Thatcher et al. B29438/48.
Vollmer and Samsell B39046/49.
[44] Eisen et al. 98924/47.
[44a] Antopol B47052/50.
[45] Velasco B44443/49.
[46] Caniggia and Bolognini B45064/49.
[47] Selye B39703/49.

lymphoid tissue), while specific serologic stimuli could cause discharge of the corresponding antibodies through a more selective action.

Gluco-corticoids probably play an even more important part in allergy by diminishing the sensitivity of the shock-organ to the local stress-effect of the antigen-antibody reaction.

For further pertinent data, the reader is referred to the sections concerning the rôle of the adrenals in the resistance of animals (against bacterial toxins, sera and infections) and formation of blood-globulins (the fraction which presumably contains the antibodies).

Other Endocrines. — In connection with the influence of hormonal stimuli upon serologic responses during the G-A-S, the phenomenon of "**endocrine allergy**" should also be mentioned. This term was used to designate "manifestations of the condition of hypersensitivity to the endogenous products of the endocrine glands." Usually, allergy is elicited by substances foreign to the body; it is noteworthy, therefore, that allegedly typical allergic reactions can arise from endogenous hormones and hormone-metabolites. In man, such hormonal allergy can be detected by skin-tests in which hormones are injected in oil solution into the epidermis. Desensitization with the "allergenic hormone" or elimination of the latter from the body, by inhibition of its formation (e.g., inhibition of gonadotrophin-production with folliculoids), is claimed to exert a curative effect.[48] This phenomenon has not yet been extensively studied. It is obvious, however, that should allergy occur to the hormones produced for defense, this would greatly alter the course of the G-A-S.

In rabbits immunized to typhoid antigen, allegedly, small doses of *testosterone, progesterone,* or *folliculoids* increase, while large doses of these same hormones diminish the production of agglutinines. Under the same conditions *thyroxine* invariably inhibited agglutinine formation.[49]

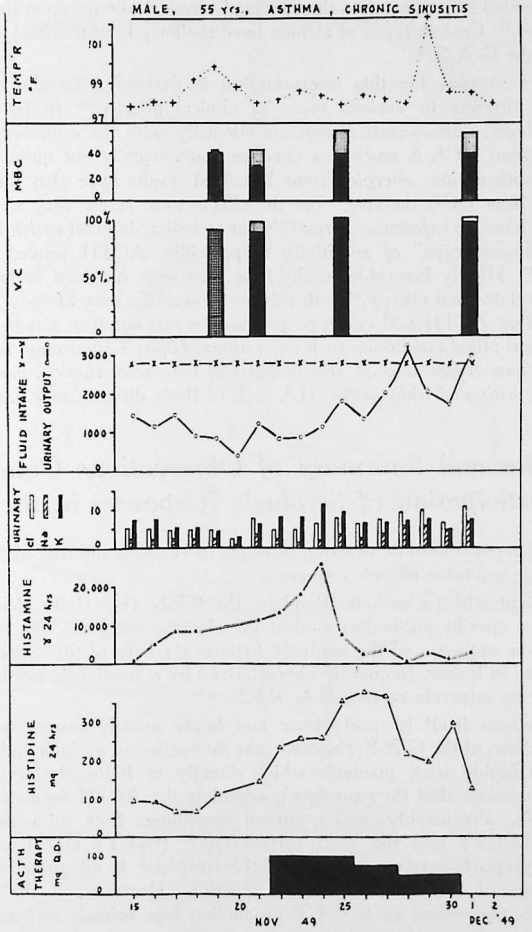
Serologic Diseases of Adaptation

The **experimental** observations discussed in the preceding pages indicate that adrenal hormones (both corticoid and adrenergic) play an important rôle in the development of allergic-anaphylactic manifestations. Indeed it appears to depend largely upon the efficacy of defensive adrenal hormone production whether a potential allergen will cause disease or whether the cells will tolerate its presence with impunity.

Many **clinical** observations could be cited in support of the view that the allergic-anaphylactic manifestations are closely related to the so-called rheumatic diseases and to that group of the hyalinoses which we regard as diseases of adaptation.[50] In particular, much evidence has been brought forth to show that such a typical hyalin disease as lupus erythematosus is a member of the "collagen disease"' family [51] and depends upon an allergic reaction; that an allergic factor is also manifest in the pathogenesis of certain hypertensive diseases; [52] that "allergic hyperglobulinosis" is the basis of Boeck's sarcoid, Letterer-Siwe's disease, lupus erythematosus and amyloidosis [53] and that such

[48] Zondek and Bromberg 99158/47, 99159/47.
[49] Caniggia and Bolognini B45064/49.
[50] Arthus **99345/21.** Urbach and Gottlieb **B2133/46.** Selye **B1204/46.**
[51] Klemperer B37973/48.
[52] Alpern B40701/46.
[53] Teilum B38105/48.

a typical alarming agent as emotional stress can precipitate allergic responses in predisposed individuals.[54] It has been emphasized that hyalin necrosis and granuloma formation is one of the most characteristic morphologic features of allergic diseases and that the structural changes which we observed in the



Case af asthma with mild emphysema treated with ACTH. Note the marked rise in histamine and in histidine excretion, which occurred during the period of administration of the drug. V.C. = Vital Capacity, M.B.C. = Maximum Breathing capacity. The dark hatched areas in the blocks represent the change which occurred following the injection of mecholyl.
(Courtesy of Dr. B. Rose.)

[54] Wolf B26123/48, Zivitz B45510/49.

various types of experimental hyalinosis closely resemble those of clinical allergic syndromes.[55]

On the basis of clinical studies the hypothesis has been presented furthermore that "physical or intrinsic allergy seems to be a perversion of a normal physiologic reaction, the 'alarm reaction' of Selye".[56] This interpretation has been extended in particular to the effects of physical allergy upon the ear, nose and throat.[57] Certain types of asthma have similarly been ascribed to a derailment of the G-A-S.[58]

Further support for this interpretation is derived from the efficacy of corticoid **therapy** in various types of clinical allergy.[59] In patients with typhoid fever, adreno-cortical extracts allegedly raise the *agglutinine* content of the serum; DCA is much less effective, but allegedly not quite inert.[60] In patients with *various allergies,* some beneficial results have also been claimed to result from DCA therapy,[61] but the effects were rarely very striking. On the other hand, in *exfoliative dermatitis* due to iodine, in giant *urticaria* and in a *"serum disease type" of sensitivity* to penicillin, ACTH proved extremely effective.[62] Highly favorable results have also been obtained in *hay fever* [63] and gastrointestinal allergy,[64] with this hormone. We have already mentioned the fact that ACTH and cortisone produces remissions in a number of other allergic and allied conditions such as: *asthma, Löffler's syndrome, periarteritis nodosa, lupus erythematosus, certain types of vasomotor rhinitis, nasal polyps, rheumatic iritis and iridocyclitis.* (Cf. each of these diseases and p. 69.)

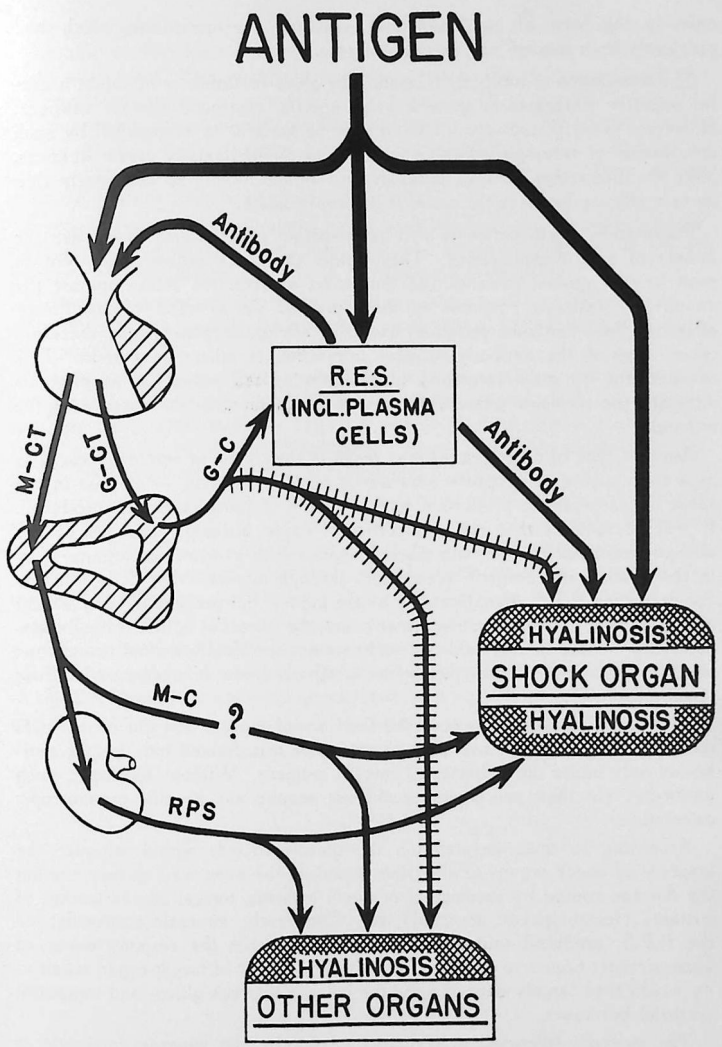
Theories and Summary of Observations Concerning the Participation of Serologic Responses in the G-A-S

The adjacent schematic drawing attempts to visualize the rôle of the G-A-S in serologic and other allergic responses.

Treatment with an **antigen** stimulates the R.E.S. (especially plasma cells) to produce specific **antibodies** against the eliciting antigen. The interaction between the antigen and the antibody irritates the cells of the "shock organ" and results in lesions frequently characterized by a hyalinosis similar to that produced by mineralo-corticoids or R.P.S.

The antigen itself is rarely toxic and hence usually causes no marked manifestations of the G-A-S. However, the interaction of antigen and antibody results in highly toxic products which directly or indirectly (through the systemic damage that they produce), stimulate the ACTH formation of the **hypophysis.** Presumably, under normal conditions, both mineralo-corticotrophic (M-CT) and the *gluco-corticotrophic* (G-CT) stimuli affect the **adrenals** proportionately and the adaptive response is adequate to combat the damage of the antigen-antibody reaction. However, if the serologic response is too violent or if G-CT production lags behind, serious allergic-

[55] Bohrod **B38447/47**, Kline B37972/48.
[56] Williams B1187/45.
[57] Williams 89006/44, B1184/45, B15854/46.
[58] Rackemann 94305/44, 94118/45, 94117/45, 94119/46. **B27677/48.**
[59] Astwood et al. B47926/50, Ruskin B40907/47.
[60] Patrono and Romeo B38403/48.
[61] Velasco B44443/49.
[62] Bordley et al. B44913/49.
[63] Spies and Stone B45101/50.
[64] Randolph and Rollins B46521/50.



anaphylactic reactions may result. It will be recalled that the *gluco-corticoids,* produced under the influence of gluco-corticotrophic stimuli, facilitate the formation of antibodies by the R.E.S. However, this effect is non-specific: it is presumably a mere discharge of globulins from which specific antibodies are formed only under the influence of specific antigens. Release from the R.E.S. of specific antibodies occurs as a result of gluco-corticoid stimulation

only, in the form of an "anamnestic reaction", in individuals which had previously been treated with certain antigens.

The stimulation of antibody formation by gluco-corticoids is no doubt a useful adaptive phenomenon since it helps specific resistance against antigens. However, under certain conditions, it may be harmful as exemplified by such derailments of serologic adaptive reactions as anaphylaxis or serum sickness. Here the interaction between antibody and antigen occurs so explosively that its very efficacy becomes the cause of disease or death.

Fortunately gluco-corticoids also have another effect, which diminishes the danger of such complications. They render the shock organs indifferent to most locally applied irritants and thus exert a protective action against the anaphylactic-allergic response of these organs. As a result of insufficient adaptive gluco-corticoid secretion, excessive allergic responses may therefore occur, even if the antibody-antigens interaction is otherwise normal. This accounts for the great sensitivity of adrenalectomized animals to anaphylaxis although the serologic phenomena are not exaggerated in the absence of the adrenals.

Another type of derangement may result in the course of serologic reactions as a consequence of excessive *mineralo-corticoid* production — at least in the sense of an excess in proportion to the amount of gluco-corticoids produced. It will be recalled that mineralo-corticoids cause histologic changes of the allergic-anaphylactic type with marked hyalinosis in a variety of organs, even in the absence of allergens, presumably through increased R.P.S. production (or decreased R.P.S. detoxification) by the kidney, but perhaps to some extent also as a result of a direct action. In any case, the (direct or indirect) hyalinosis-producing actions of mineralo-corticoids are not specifically limited to any one shock organ; they manifest themselves in the syndrome of widespread diffuse "hyalin disease".

This interpretation of the observed facts would suggest that gluco-corticoids merely make γ-globulins available; these can be transformed into specific antibodies only under the influence of specific antigens. Without the latter, such antibodies (or their precursors) could not acquire any specific organotropic orientation.

According to this interpretation the gluco-corticoids would mitigate the response of shock organs to allergenic stimuli in the same way as they combat the damage caused by rheumatoid or gouty arthritis, topical administration of irritants (formaldehyde, mustard), etc. Conversely, mineralo-corticoids (or the R.P.S. produced under their influence) increase the responsiveness of various target organs to allergenic stimuli. The degree of target-organ sensitivity would then largely depend upon the balance between gluco- and mineralo-corticoid hormones.

The systemic allergy-like hyalinosis caused by the mineralo-corticoids is likewise diminished by gluco-corticoids. Thus the responsiveness of the organism as a whole to a great variety of stimuli is also largely dependent upon the balance between gluco- and mineralo-corticoids. In the light of these considerations, it is understandable that even the actions of agents which do not produce demonstrable antibodies, for instance drugs (drug allergy), physical insults (physical allergy) and emotional stressors (psychosomatic allergy) are largely dependent upon the G-A-S mechanism. Apparently in predisposed

patients the response to various stressors is channeled into a set reaction pattern and tends to affect certain shock organs which, in a particular patient, represent a weak point. Even in the absence of any true antibody formation, allergy-like responses can thus occur in this "shock organ" if gluco-corticoid production is subnormal or mineralo-corticoid formation excessive. In other words, in the case of serologic reactions the antigen itself is organotropic, while with allergy-like selective responses to systemic stressors, the organ specificity of the response depends upon conditioning of the target.

These theoretical considerations agree with the fact that hypophysectomy, adrenalectomy or mineralo-corticoid overdosage increase sensitivity to allergic reactions and hyalinoses, while gluco-corticoids act inversely.

Adrenergic hormones also exert many anti-allergic actions. These are not represented in our drawing, because their mechanism of action is not sufficiently understood.

Non-specific therapy by systemic stressors (e.g., parenteral milk or foreign serum therapy) is largely due to increased gluco-corticoid production, with a resulting desensitization of the target organs to the allergenic stimulus. This would also be the basis of many so-called *"crossed resistance phenomena"* (cf. pp. 55, 106) which are not strictly speaking allergic in nature.

The mechanism through which gluco-corticoids diminish the sensitivity of cells is not yet known. It is possible, however, that concurrently with their catabolic effect, they deprive the cells of certain *specific substances* (e.g., the "inflammation substance" described above) which may be necessary for maximal local reactions to stress.

Derangements of this interaction between the antigen-antibody response on the one hand and the G-A-S mechanism on the other, may be responsible for certain **serologic diseases of adaptation.** Among these, we have given particular attention to *food allergy, anaphylaxis, serum sickness, Pirquet's reaction,* and the *Schwartzmann-Sanarelli phenomenon.*

WOUND-HEALING AND REGENERATION

Wound-healing and regeneration are delayed by many agents causing **systemic stress**, such as infections, intoxications and malnutrition.[1] In this delay, humoral factors undoubtedly play an important part. Among these, special attention has been given to hormones, nitrogenous substances derived from protein during the catabolic phase, the hydrogen-ion concentration of the blood and tissues, specific enzymes, vitamins and other essential food factors, the so-called "proliferation-promoting factors" and substances derived from embryos.[2]

Traumatic shock decreases mitotic proliferation throughout the body.[3] This undoubtedly adds to the difficulty of repair and wound healing, but the effect of trauma largely depends on the intensity of the resulting stress. After mild interventions, such as a skin incision made on one side of a body of a rabbit, a second similar wound made on the other side heals more rapidly than the first. The acceleration of healing appears about five days after the initial injury and lasts approximately 6 to 7 weeks. Allegedly, "this course resembles the curve of the post-traumatic catabolic phase of protein metabolism." The response appears to be related to changes in the quality of the wound coagulum and fibroplasia, similar to those which occur in the G-A-S.[4]

Urethane inhibits fibroplasia and capillary formation in wounds only when it is administered in doses causing severe systemic intoxication. Previous protein depletion of the body enables small, otherwise inactive, doses of urethane to inhibit fibroplasia and endothelial proliferation in the rat. From this it was concluded that the inability of capillaries to proliferate, in the presence of "mitosis arresting" doses of urethane, may also be the principal mechanism through which this drug retards neoplasia.[5]

Animal experiments concerning the tensile strength of wounds showed that *hemorrhage, dehydration* and *acidosis* (induced by administration of NH_4Cl) delay wound healing. On the other hand, contrary to expectations, *anticoagulants* (e.g., dicumarol) do not influence it, although they delay fibrin-formation.[6]

It has been stated that slight *topical irritation* by turpentine, or chick-embryo-extract, is beneficial in that it shortens the latent period of wound-healing in dogs.[7]

Allegedly some *"accelerating factor"* operates in the healing of secondary wounds which is lacking in primary wounds. The nature of this factor has not been determined, but it was considered to be a systemic, rather than a local factor.[8]

The humoral changes elicited by the G-A-S undoubtedly affect wound-healing and regeneration, yet the hypophysis-adrenal system is not entirely

[1] Medawar and Green **B26845/44.**
[2] Davidson **89883/45.**
[3] Bullogh and Green B44598/49.
[4] Sandblom B37838/49.
[5] Lushbaugh et al. B43969/48.
[6] Sandblom B26479/44.
[7] Carrel 12769/21.
[8] Young et al. B37685/41.

indispensable. **Hypophysectomy** does not seriously interfere with the proliferation of fibroblasts and epithelial cells in healing skin-wounds, nor does it completely prevent the regeneration of kidney or liver tissue after partial ablation of these organs.[9] From this it has been concluded that although the growth hormone of the anterior-lobe is responsible for the proportionate development of the organism as a whole, it is not indispensable for local regenerative phenomena in various individual organs.[10] Accordingly, it was found that growth-hormone-containing **anterior-lobe extracts** do not significantly affect the time required for the healing of superficial wounds, although they diminish the loss of body weight and nitrogen following traumatic injuries.[11] **ACTH** inhibits wound healing and fibroplasia after traumatic [11a] or chemical [11b] injuries.

Adrenalectomy retards wound-healing. *Cortical extracts* restore the regenerative powers of the suprarenal-deficient animal towards normal, although they do not readily improve the rate of wound-healing beyond the normal level.[12] (Cf. liver-regeneration, pp. 716-721.) As judged by the formation of granulation-tissue in the walls of turpentine abscesses in rats, adrenalectomy (or castration) results in an only slightly inferior fibroblastic response, but **DCA** "stimulates fibroblasts and encourages the deposition of a homogeneous, diffuse ground-substance of collagen".[13] Conversely, **cortisone** inhibits the production of granulation tissue in experimental wounds of rabbits.[14] This agrees with the mutually antagonistic actions of DCA and cortisone upon the formation of a granuloma in rats with a "topical irritation arthritis".[15]

Testosterone and **estradiol** inhibited the formation of normal granulation-tissue in the walls of turpentine-abscesses in rats; [16] yet under certain conditions testosterone allegedly promotes wound-healing and regeneration, at least to some extent, thanks to its protein-anabolic effect [17] and perhaps also because of an influence upon hyaluronidase activity.[18]

Preliminary experiments suggest that an insulin-free **pancreatic extract** accelerates the healing of standard areas of denuded skin in the rat,[18a] it has not yet been proven that this is due to a specific principle present in this extract.

The **diet** also exerts a very important effect upon cicatrization. Thus in rats rendered hypoproteinemic by dietary means, the tensile strength of wounds is significantly subnormal. The mere addition of one amino-acid, dl-methionine, allegedly helps to accelerate the healing of the wounds in these animals, but does not speed healing in normally fed rats. Nevertheless, clinical tests suggested that "dl-methionine" may be worthy of trial in stubborn unhealed surface wounds in protein-depleted humans.[19] The inhibition of wound-healing due to **advanced age** used to be a serious contra-indication for surgical interventions in older patients, but modern surgery has largely overcome this obstacle.[20]

[9] Canzanelli et al. B37729/49, Selye et al. 30634/34.
[10] Selye **94572/49.**
[11] Cuthbertson et al. 82868/40-41, 82869/40-41.
[11a] Ragan B46310/50.
[11b] Selye B39702/49.
[12] Selye **94572/49.**
[13] Taubenhaus and Auromin B27881/49.
[14] Ragan et al. B44795/49, B46310/50.
[15] Selye B39702/49.
[16] Taubenhaus and Auromin B27881/49.
[17] Selye **94572/49.**
[18] Ubatuba and de Moraes B41753/47.
[18a] Gley et al. B45981/48.
[19] Localio et al. B38655/48, B39166/49.
[20] Welch **B26323/48.**

Summary. — The G-A-S exerts a marked effect upon the repair of tissue after trauma. It is apparent from the data now available that severe systemic stress, ACTH and gluco-corticoids inhibit fibroplasia and wound-healing, while mineralo-corticoids act inversely. The latter effect is not very pronounced and we know deplorably little about other humoral factors which may improve the regenerative powers of the organism.

During the G-A-S, regenerative phenomena play an important rôle in compensating for tissue loss (systemic "catabolic reaction", topical tissue-destruction by injury); hence, in the interest of homeostasis, it would be important to enhance the regenerative powers at times of stress. Available data suggest that (at least under certain conditions) mild alarming stimuli and mineralo-corticoids have such a beneficial effect; but we do not yet know through what mechanism this is effected. The high regenerative powers of the young as compared with the old individual appear to be correlated with the phenomenon of "exhaustion of adaptability" or "loss of adaptation-energy", but the nature of this relationship is likewise still mysterious.

NEOPLASIA

The relationship between the G-A-S, or the hormones produced during stress, to neoplasia has been discussed elsewhere [1a] and in other chapters of this book (with certain types of tumors). Thus the fact that adrenalectomy favors, while gluco-corticoids inhibit the development of lymphoid tissues led to the use of ACTH and cortisone in various leukemias and lymphomas (cf. hemopoietic organs). Similarly, the inhibitory action of gluco-corticoids upon connective-tissue proliferation suggests that these hormones may be valuable in the treatment of certain fibroblast tumors. Non-neoplastic granulomatous proliferations, around arthritic joints or in nasal polyps, have already been shown to respond to this therapy. However, at present, little is known as yet concerning the long-term efficacy of ACTH or gluco-corticoid treatment, even in the tumors of tissues (lymphoid organs, connective tissue) which are particularly sensitive to the catabolic action of these hormones; even less information is available as regards their use in tumors of other tissues.

In relation with the G-A-S concept, it is of special import that systemic **x-irradiation** of rats, prior to transplantation of lymphosarcoma cells, actually increased the number of takes as compared with similar implants in non-irradiated controls.[1] This somewhat unexpected finding requires confirmation on a larger series, but in mice the incidence of lymphomas was also raised after exposure to ionizing radiations.[1b]

Occasionally, systemic **infections** may cause regression of malignant tumors. Thus in one case, an inoperable ovarian psammocarcinoma (confirmed by biopsy) disappeared completely following intercurrent infection with scarlet fever.[2] While here the regression may have been coincidental, there is no doubt that numerous pseudomucinous ovarian cystomas and carcinomas, which were

[1] Roussy and Guérin B38518/47.
[1a] Mosinger B44600/47-48.
[1b] Brues B38697/48.
[2] Kastranek B37948/47.

considered to be inoperable when the abdominal cavity was opened, quite unexpectedly regressed following this surgical intervention.[3] Would ACTH and cortisone be similarly effective ?

Vesicants cause particularly pronounced catabolic responses similar to those obtained with gluco-corticoids, hence it is pertinent that nitrogen mustards inhibit the growth of transplantable mouse "sarcoma 180". However, this inhibition can be duplicated by food restriction causing a comparable catabolic response.[4]

Other toxic drugs, for instance **emetin hydrochloride,** which cause a shock-like condition when given parenterally, are allegedly effective in retarding the growth of carcinomas in man. It was concluded that "the shock treatment as administered so frequently in our psychopathic hospitals, might prove useful for malignancy".[5] Shock-therapy has not given such favorable results in the hands of most other investigators; nevertheless, these and the other above-mentioned observations suggest that the G-A-S mechanism may play a rôle in combatting neoplasia. The treatment of tumors with **bacterial toxins** [5a] might also be explained on this basis.

Since the growth of many types of tumors is delayed or inhibited by caloric restriction, the manifestations of the G-A-S have been explored in mice receiving a **diet** known to inhibit neoplastic growth. It was found that such characteristic G-A-S changes as thymus atrophy, adrenal enlargement, leucopenia and lymphopenia occur under these conditions and the possible relation of these lesions to carcinogenesis has been debated.[6]

Hypophysectomy or **adrenalectomy** do not prevent the growth of experimental tumors in animals, but may delay it or diminish the number of takes. This has been ascribed to the general decrease in tissue anabolism and cell proliferation that occurs in hypophyseal or adrenal insufficiency.[7]

It is especially interesting, however, that a patient with squamous cell carcinoma of the lip had prompt relief of sensitiveness, with a marked diminution in the size of the tumor, following **ACTH** treatment. Biopsy showed that the carcinomatous cells were still present.[8] Presumably here the apparent involution was due to the decreased responsiveness of the connective tissue cells surrounding the tumor, rather than to an actual antitumorigenic effect.

In another series of patients with carcinoma of the breast, carcinoma of the trachea, Ewing's tumour and mycosis fungoides, beneficial effects were noted only in the latter condition.[8a]

The metabolic and hematologic actions of ACTH likewise do not show any significant deviation from the normal in cancerous patients.[8b] Yet there is some evidence suggesting that patients with gastric cancer have a deranged adrenocortical function, in that the usual increase in the urinary uric acid: creatinine ratio and in the urinary inorganic phosphorus:creatinine ratio is diminished or absent.[8c] It must be kept in mind, however, that cachexia also diminishes responsiveness to ACTH. Data concerning the allegedly abnormal excretion of urinary steroids in chronically ill or debilitated patients have been discussed elsewhere (p. 223, 227).

[3] Selye B3035/46.
[4] Goldin et al. B39233/49.
[5] Van Hoosen B40920/47.
[5a] Nauts et al. B47668/46.
[6] Boutwell et al. B39202/49.
[7] Selye 94572/49.
[8] Spies et al. B45105/49.
[8a] Taylor and Morris B46977/50.
[8b] Bonner et al. B46956/50.
[8c] Reifenstein et al. B46311/49.

In mice receiving "sarcoma 37" implants, the "spontaneous regression and sloughing" could be increased by adreno-cortical **extract,** but the results were not striking. This same extract exerted no demonstrable effect upon the growth of definitely established methylcholanthrene-induced sarcomas.[9]

When tumor grafts were minced with adrenal gland tissue and the mixture subsequently implanted into susceptible hosts, the growth of rat "sarcoma 231" was prevented or retarded. Minced pituitary gland tissue has a similar, but less pronounced effect; other tissue proved inactive. It was concluded that the effect of adrenal tissue upon the malignant growth "might be due to a direct action of adrenal tissue on a tumor such as lysis of the cells or to a secondary action such as the influence of the adrenal medulla on the blood-vessels of the host".[10] Since both adrenaline (in the adrenal) and vasopressin (in the pituitary) cause local necrosis, even of normal cells, it is very probable that the anti-tumorigenic effect was merely the result of local non-specific tissue damage under these circumstances.

Summary. — Various procedures (toxic drugs, malnutrition, hypophysectomy, adrenalectomy), which inhibit anabolism and cellular growth in general, tend to counteract the growth of neoplastic tissue. There is no definite evidence to indicate that the hormones produced during the G-A-S, particularly ACTH or cortisone have any true anti-tumorigenic action, with the possible exception of neoplasms formed from lymphatic tissue which is notoriously sensitive to destruction by gluco-corticoids.

[9] Diller et al. B41830/48.

[10] Lewis et al. B41834/49.

MALFORMATIONS

Among the infants of women who acquire systemic **infections** during pregnancy, the incidence of congenital malformations appears to be significantly increased.[1]

In this connection it is interesting that various congenital anomalies have been produced in the rat by injection of trypan blue and other **toxic agents** during gestation. These findings, as well as a detailed survey of the pertinent literature concerning the influence of maternal stress upon the development of the embryo, led to the conclusion that the non-specific action of diverse damaging agents can cause malformations in the offspring,[2] perhaps through the G-A-S mechanism.[2a]

It remains to be shown whether the hypophysis-adrenal system plays a part in such embryonic malformations. **Adreno-cortical extract,** injected under the chorio-allantois of young chick embryos, produces corneal changes simulating keratoconus as seen in clinical pathology. In many cases this was accompanied by generalized edema, liver necrosis, gastroschisis with ectopia of the viscera, but the corneal anomaly was the most constant.[3] Corresponding experiments in pregnant mice and rats gave less clear-cut results.

[1] Grönvall and Selander B37882/47. Ingalls and Davies B37883/47. Lévy-Solal et al. B43976/47. Loewe-Lyon B41801/48.

[2] Gillman et al. **B26480/48.**

[2a] Leroy B48086/49.

[3] Dalton et al. A30864/40.

It is also noteworthy in this connection that hypoglycemia produced by insulin in 5-day chick-embryos frequently results in micromelio. This effect is further enhanced by simultaneous administration of adreno-cortical extracts.[4]

Summary. — The comparatively frequent occurrence of malformations in women who acquire infectious diseases during pregnancy, as well as in animals exposed to various stressors during gestation, suggests that the G-A-S may be responsible for certain types of congenital anomalies. Overdosage with adreno-cortical extracts causes a variety of malformations, especially in chicks, but it has not yet been definitely proven that these are the direct results of the corticoids contained in the extracts. Further research will be needed to ascertain whether the increased incidence of malformations among the offspring of individuals exposed to stress during pregnancy is related to the hypophysis-adreno-cortical mechanism.

[4] Zwilling B45253/48, B46237/48.

ELECTRIC POTENTIAL

It may be taken as a well established fact that there are marked differences between the electric charge of various organs, between the cells and the interstitial fluid around them, and even between various parts of a single cell. In general, it may be said that interstitial fluid, blood and connective tissue carry a negative charge, while parenchymatous organs are positively charged. It will be noted that K, Mg and PO_4 predominate in tissues of relative positivity, Na, Ca and Cl in structures having a relatively negative charge. As a result their low dielectric constant cell-membranes act as insulators. Hence a considerable difference in the electric potential can develop between parenchymatous organs on the one side and the surrounding interstitial tissue-fluid and blood on the other.[1]

It has been possible to estimate the electric potential of different organs, and even of individual cells, by the use of micro-electrodes or by dyes which carry varying electric charges. With the former method one measures the potential by connecting a micro-electrode on the one hand with a living cell and on the other with an instrument suitable for the measurement of minute amounts of static electricity; the latter technique is based on vital staining of tissues, in agreement with Coulomb's law according to which bodies of similar electric charge repel, while those of opposite charge attract each other. Considerable work has been done with these and other methods to tabulate the different electric potentials of various cells under normal and pathologic conditions.[2]

It is generally agreed that cells with a positive charge tend to lose it (as well as their K, Mg and PO_4) under the influence of various non-specific damaging agents (e.g., anoxia, anesthesia, trauma). This derangement is allegedly one of the major factors responsible for the loss of the characteristic

[1] Keller **B37494/46.**

[2] Fischer B37697/31, B37696/32, Keller B37698/32, B37695/35, B37694/36, B37700/36, **B37699/38.**

"selective permeability" of cell-membranes, which occurs in the course of the so-called "serous inflammation".[3] Presumably the same is true of the A-R.

It is regrettable that in recent years comparatively few investigators have used these techniques. Judged by the scarcity of available data concerning this subject, it would appear highly rewarding to examine systematically the changes in electric potential that are occasioned by the G-A-S.

Summary. — Interstitial fluid, blood and connective tissue carry a negative, parenchymatous organs a positive electric charge; thus a difference in electric potential exists between them. The structures carrying a negative charge are usually rich in Na, Ca and Cl, while those with a positive charge contain more K, Mg and PO_4. Cells with a positive charge tend to lose it under the influence of stressors and at the same time, release their K, Mg and PO_4. This change is reputedly a fundamental factor of the derangement in membrane permeability characteristic of "serous inflammation" and the A-R.

Up to the month of May, nineteen hundred and fifty, this is all I have learned, that deserves to be recounted, about the General-Adaptation-Syndrome and the Diseases of Adaptation.

I rather suspect there will be much more to tell next year — and the year after that; while part of what I think I know I shall believe no longer.

If so, you will hear from me again, for I shall always enjoy contemplating this subject.

[3] Eppinger **B37085/49.**

GENERAL SUMMARY

With the concept of the G-A-S, we have attempted to integrate a number of seemingly quite unrelated observations into a single unified biologic system.

In the historic introduction to this book (cf. pp. 2 ff.) we mentioned, among other things, the work of Claude Bernard, who showed how important it is to maintain the constancy of the *"milieu intérieur"*, Cannon's concept of *"homeostasis"*, Frank Hartmann's *"general tissue hormone"* theory of the corticoids, Dustin's observations on the *"caryoclastic poisons"*, the *"post-operative disease"*, the curative action of fever, foreign proteins, and of other *"non-specific therapeutic agents"*, the *"nephrotoxic sera"* of Masugi and the *"Goldblatt clamp"* for the producion of experimenal renal hypertension.

At first sight, it would seem that all these observations have little in common and that there is no reason to attempt their integration into a unified system of physiologic and pathologic events. Yet, this book — and indeed most of the author's research work — has been devoted to the construction of bridges between these and many additional facts, since they were thought to be interconnected in Nature. Through the comprehension of their unity, we hoped to learn how to use them better for the understanding of life and the treatment of disease.

The keynote of this unification was the tenet that all living organisms can respond to stress as such and that, in this respect, the basic reaction pattern is always the same, irrespective of the agent used to produce stress. We called this response, the General-Adaptation-Syndrome, and its derailments, the Diseases of Adaptation.

Anything that causes stress endangers life, unless it is met by adequate adaptive responses; conversely, anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life and every vital organ and function participates in them. In order to present a well-proportioned outline of the G-A-S it was necessary, therefore, to peruse every branch of physiology, biochemistry, pathologic anatomy and clinical medicine in search of the "stress factor" in all aspects of normal and abnormal life. — This is our apology for the length and complexity of this volume.

It will take many years, indeed many generations, before the details of the G-A-S are satisfactorily elucidated. In fact, we shall never truly "understand" this phenomenon, since the complete comprehension of life is beyond the limits of the human mind. But there are many degrees of "elucidation". It seems that now the fog has been just sufficiently dispersed to perceive the G-A-S through that measure of "twilight", which permits us to discern the grandeur of its outlines, but fills us with the insatiable desire to see more.

We realize that many lines in our sketch will have to be hesitant, some even incorrect, if we try to put on paper now what we still see only vaguely. But a preliminary map — albeit largely incomplete and partly inaccurate — is needed *now* by those eager to exploit this field which holds so much promise for all who

suffer from stress! We hope that these pioneers in unchartered territories will accept my partial and distorted map, in the spirit in which it is offered, to complete and rectify it.

It is in this sense that I should like the reader to consider the following synopsis of what I think I see.

PRINCIPAL FACTS AND THEORIES UPON WHICH THE G-A-S CONCEPT IS BASED

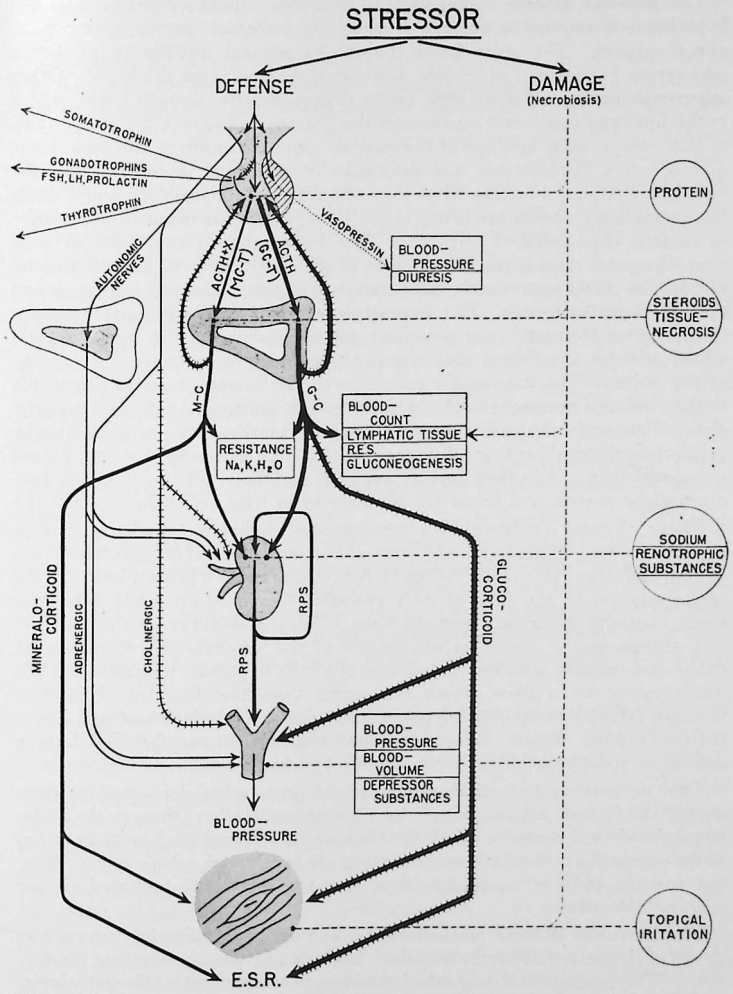
Under this same heading, in the introductory section of this book (cf. pp. 5 ff.) we merely enumerated a few facts and theories, which we considered to be fundamental for the formulation of our concept. Now after having discussed pertinent data extensively, we shall attemp to integrate all our facts and theories into a unified system.

Apart from the many specific defense reactions (e.g., formation of specific antibodies, adaptation to cold, habituation to morphine, hypertrophy of much-used muscle groups) there is an integrated syndrome of closely interrelated adaptive reactions to non-specific stress itself; this has been termed the **"General-Adaptation-Syndrome"** (G-A-S). It develops in three stages: the **"Alarm-Reaction"** (A-R), the **Stage of Resistance** (S-R) and the **Stage of Exhaustion** (S-E). Most of the characteristic manifestations of the A-R (tissue catabolism, hypoglycemia, gastrointestinal erosions, discharge of secretory granules from the adrenal cortex, hemoconcentration, etc.) disappear or are actually reversed during the S-R, but reappear in the S-E. This suggests that the ability of living organisms to adapt themselves to changes in their surroundings, their adaptability, or **"adaptation energy"**, is a finite quantity; its magnitude appears to depend largely upon genetic factors.

In the G-A-S, the manifestations of passive, non-specific **damage** are intricately intermixed with those of active **defense.** This is an inherent characteristic of the stress, which elicits the G-A-S. In the biologic sense stress is the interaction between damage and defense, just as in physics tension or pressure represent the interplay between a force and the resistance offered to it.

In addition to damage and defense, every stressor also produces certain **specific actions** (e.g., anesthetics act upon the nervous system, diuretics upon water metabolism, insulin upon the blood-sugar), quite apart from their stressor effects. Hence the G-A-S never occurs in its pure form, but is always complicated by superimposed specific actions of the eliciting stressors. In contemplating any biologic response (e.g., a spontaneous disease, an intoxication, a psychosomatic reaction), it is usually quite difficult to identify individual manifestations as being due respectively to: damage, defense or specific actions of the provocative agent. Only non-specific damage and defense are integral parts of the G-A-S, but the specific actions of the eliciting stressors modify the course of the resulting G-A-S (e.g., the glycemic curve will deviate from the characteristic pattern if insulin is used as the stressor agent; the neurologic manifestations will be atypical if the G-A-S is provoked by ether). In this sense they act as **"conditioning factors"**. Certain circumstances, not directly related to the stress situation, are also prone to alter the course of the G-A-S. Among these, heredity, pre-existent disease of certain organ systems and the diet are especially important.

The adjacent schematic drawing disregards the specific actions of stressors, since they are not part of the G-A-S. It attempts to depict only the main pathways through which non-specific stress itself affects the organism and the manner in which such reactions are conditioned.



Defense

The systemic defense measures, against both general and localized (topical) injuries, are coordinated through the hypothalamic vegetative centres and the hypophysis. The **initial pathways** through which stressors act upon these

centers are not yet known. Probably, either humoral or nervous impulses, coming from the site of direct injury, can induce the hypothalamus-hypophysis system to gear the body for defense. Subsequently both of the two great integrating mechanisms, the nervous and the endocrine system, are alerted.

The nervous defense mechanism. — Nervous impulses descend from the hypothalamic vegetative centers, through the autonomic nerves, to the peripheral organs. The splanchnics induce the **adrenal medulla** to discharge adrenergic hormones (adrenaline and nor-adrenaline) into the blood. **Other adrenergic nerves** influence their target organs directly, through fibers, which in the final analysis again act through the liberation of adrenergic compounds, in this case at their endings in the effector organs themselves (blood vessels, glands, etc.). Presumably the discharge of adrenergic hormones into the circulation is most effective when they are needed throughout the body, while the sympathetic nerves are better suited to impart similar impulses selectively, to certain circumscribed territories. The most conspicuous results of such neuro-humoral discharges are changes in the contractility of smooth muscle. Due to an adrenergic vaso-constriction, peripheral resistance increases and the blood-pressure rises. This hypertensive response may be further accentuated by an increased cardiac volume and the opening of the *"renal shunt"*, which deviates blood from the cortical glomeruli to the juxtamedullary region of the kidney. This neurogenic activation of the "shunt" is quite comparable to that induced by mechanical interference with the arterial inflow (Goldblatt clamp, "endocrine kidney" operation) into the kidney, hence it augments the production of renal pressor substances (RPS). The latter also cause peripheral vasoconstriction; thus they further augment peripheral resistance in the cardiovascular system and hence the blood-pressure rises (cf., below).

There is some evidence of a simultaneous **cholinergic discharge** during systemic stress. Concurrent activation of both agonists and antagonists occurs in many effector systems during the G-A-S. Presumably it helps to stabilize the target organs, in the face of very powerful stimuli which might otherwise cause excessive deviations from the norm. This concurrent tension of agonists and antagonists is somewhat reminiscent of the simultaneous contraction of flexor and extensor muscles, for instance in a limb, to prepare it against possible displacement by a blow which may come from any direction. However, damage (shock) endangers life particularly through vasodepressor and hypotensive actions, hence, the predominant response during the G-A-S is a defensive (prophylactic) vasoconstriction and hypertension.

The nervous system also participates in many other defensive reactions during the G-A-S, e.g., the regulation of *water metabolism* (through the hypophyseal stalk and posterior-lobe), the *blood-sugar* (through the hepatic branches of the sympathetic division), and the *blood-count* (through splenic contraction), but for the sake of simplicity, these are not specifically indicated in our schematic drawing.

The hormonal defense mechanism. — The principal endocrine response to stress is characterized by the so-called *"shift in anterior-lobe hormone production"*. This consists in a diminished secretion of **somatotrophin, the gonadotrophins** (FSH, LH, prolactin) and thyrotrophin — which are not essential for the maintenance of life during conditions of emergency — accompanied by an increase in the secretion of **ACTH.** Apparently the anterior-lobe is unable to produce all its hormones at an optimal rate, if it is called upon to discharge extraordinarily large amounts of corticotrophin.

ACTH is a "gluco-corticotrophic" (G-CT) hormone. It induces the adrenal cortex to produce predominantly **gluco-corticoids** (G-C), e.g., "compound F", cortisone. The latter act upon the blood-count (lymphopenia, eosinopenia, polymorphonuclear leucocytosis), the thymico-lymphatic tissue (lympholysis), the reticulo-endothelial system (increased phagocytosis and antibody formation) and gluconeogenesis (transformation of non-sugars into carbohydrates).

The gluco-corticoids presumably influence *resistance* in many additional ways, which have not yet been fully analyzed. Through all these actions such steroids help to maintain adrenalectomized animals, even during exposure to stress.

All gluco-corticoids so far examined possess some *mineralo-corticoid activity* (actions upon Na, Cl, K and water metabolism); thus they resemble the pure mineralo-corticoids, but the latter are much more potent in this respect and possess no gluco-corticoid action. Hence, changes in mineral and water metabolism, observed after the injection of ACTH, do not necessarily reflect the production of pure mineralo-corticoids by the adrenal.

The action of gluco-corticoids upon the *kidney* has not yet been extensively studied. However, preliminary investigations show that they cause marked hyperemia of the glomeruli and may render the latter permeable to proteins and even blood. Heavy overdosage with gluco-corticoids can produce severe hyalinization and disintegration of glomeruli. This is followed by a rise in blood-pressure, presumably mediated through the RPS system. In this respect, gluco-corticoids and mineralo-corticoids may mutually synergize each other.

The gluco-corticoids inhibit the production of *arteriosclerotic* changes (especially periarteritis and hyalinosis). In this respect they antagonize the effects of mineralo-corticoids.

The gluco-corticoids generally inhibit excessive proliferation of *fibrous tissue*, the formation of *intercellular protein deposits* (e.g., hyalinosis, collagen disease, allergies) and excessive granulomatous defense reactions against those local irritants which stimulate fibroplastic inflammatory reactions in mesenchymal tissue. They also tend to decrease the *erythrocyte sedimentation rate* (*ESR*), through their effect upon the blood-proteins. In all these respects they act as antagonists of the mineralo-corticoids.

The mechanism of the marked *anti-allergic and anti-histaminergic* actions of gluco-corticoids has not yet been elucidated. It may depend upon the breakdown of the proteins which store histamine as a protein-histamine complex.

Many data suggest that under conditions of stress mineralo-corticoid production is likewise increased. Such a rise can also be elicited by certain impure, **mineralo-corticotrophic (M-CT),** anterior-pituitary extracts, for instance lyophilized anterior-pituitary tissue (LAP). Threshold doses of LAP are further activated in this respect by simultaneous administration of ACTH. Apparently the action of the latter can be qualitatively altered by some factor ("X") present in crude pituitary extracts and LAP. This *"X factor"* appears to be a specific pituitary principle, as it has not been found to occur in similar preparations of other tissues (e.g., liver). The "X factor" is manifestly not ACTH, but it may be identical with one of the other, already known, hypophyseal hormones. It could also be a special hypophyseal principle, not hitherto identified. Be this as it may, it has now definitely been established that certain pituitary extracts produce a gluco-corticoid type, others a mineralo-corticoid type of reaction. Furthermore, in response to stress, the pituitary itself may

discharge predominantly gluco-corticotrophic or mineralo-corticotrophic principles.

The mineralo-corticoids share with the gluco-corticoids the ability to increase the general *resistance* of adrenalectomized animals. They also cause severe lesions in the *kidney*, if large quantities of them are given over a long time. There is distention of the convoluted tubules, proliferation of the spiral segments, hyalinization of the glomeruli, proteinuria, hyaline-cast formation and, eventually, nephrosclerosis.

It is highly probable that mineralo-corticoids increase RPS production especially through some direct functional effect upon the convoluted tubules. Even the subsequent morphologic changes in this part of the nephron precede the development of glomerular sclerosis. Eventually however, the gradual constriction of the glomerular capillary bed acts somewhat like the Goldblatt clamp or the "endocrine kidney" operation and, simultaneously with the inhibition of glomerular filtration, increases the endocrine activity of the nephron. At the same time the inactivation of RPS is impeded and a hormonally induced renal hypertension ensues.

Presumably, both stimulation of RPS formation and inhibition of RPS destruction is thus induced by mineralo-corticoids. This affects the blood-vessels. At first the resulting excess of RPS causes a *functional vaso-constriction* with an increase in peripheral resistance and blood-pressure. More prolonged overdosage with mineralo-corticoids results in *arteriosclerotic changes* (especially periarteritis nodosa and hyalinosis), with a consequent permanent increase in peripheral resistance and blood-pressure.

In this respect, mineralo-corticoids and gluco-corticoids mutually antagonize each other, but since (at least at certain dose levels) their actions upon the kidney are synergistic, it depends upon the "conditioning" circumstances whether the administration of gluco-corticoids, to animals overdosed with mineralo-corticoids, increases or decreases the *blood-pressure*. (Cf. also conditioning effect of sodium and renotrophic substances, below.)

There is no definite evidence to prove that either type of corticoid has any *direct vasopressor effect*. Addition of corticoids to perfused vessel preparations does not cause them to contract. Nevertheless, mineralo-corticoids can augment the blood-pressure even in the absence of the kidney, presumably by raising the *blood-volume* through their effect on mineral and water metabolism.

Both types of corticoids act back upon the anterior-lobe and inhibits its ACTH production, through the so-called phenomenon of *"compensatory atrophy"*. It is not yet known whether corticoids also impede the endogenous production of that "X factor" which renders ACTH mineralo-corticotrophic. However, this is very probable, since otherwise ACTH therapy would only aggravate conditions characterized by symptoms of mineralo-corticoid overdosage. If the production of the "X factor" is inhibited in the same manner as that of ordinary ACTH, then the therapeutic action of ACTH is readily explicable. In both instances the pituitary is exposed to an excess of gluco-corticoids. The latter are even more potent in eliciting the "compensatory atrophy" phenomenon than the mineralo-corticoids. Consequently, endogenous corticotrophic stimuli (including "X-factor") are virtually eliminated and the exogenously administered, predominantly gluco-corticotrophic, ACTH acts uninfluenced upon the adrenal cortex.

There is much to suggest that at least certain types of stress (e.g., emotional stimuli) can increase the production of antidiuretic hormone, which is probably identical with **vasopressin.** This effect is undoubtedly mediated by nerve tracts descending from the hypothalamus to the posterior-lobe, since (unlike the discharge of ACTH) it is abolished by transection of the hypophyseal stalk.

Vasopressin exerts important effects upon the blood-pressure and diuresis; these may be superimposed upon the typical reaction pattern during the G-A-S. However the rôle of vasopressin secretion during systemic stress has not yet been adequately investigated.

Damage and Other Factors Conditioning Defense

As we have said before, many non-specific actions of stressors merely represent manifestations of damage and are not mediated through either the humoral or the nervous defense systems outlined above. These changes appear to result from **necrobiosis** of cells not sufficiently protected by the systemic defense mechanism. Thus, *tissue catabolism* occurs under conditions of stress even in the absence of the pituitary, the adrenals or the sympathetic nervous system. Although gluco-corticoids enhance catabolism, especially of readily dispensable proteins (e.g., that of the thymus, the lymph-nodes and connective tissue), extensive losses of body protein, fat and carbohydrate can occur even after adrenalectomy.

Catabolites, thus produced, can condition the defensive chain-reaction of the G-A-S at various links. We have seen that *protein* tends to favor the mineralo-corticotrophic type of hypophyseal discharge, that *sodium* increases, while *renotrophic steroids* decrease, the sensitivity of the kidney to overdoses of mineralo-corticoids, that topical *chemical irritation* augments the fibroplastic and hyalinosis-producing action of mineralo-corticoids and so forth. There is every reason to believe that endogenously liberated protein (or amino-acids), sodium, renotrophic steroids and irritating metabolites, would influence such hormone actions in the same manner as these substances do when they are exogenously introduced into the body. The intensity and the quality of such "endogenous self conditioning" of the G-A-S largely depends upon the body's reserve of these metabolites and the intensity with which they are discharged into the blood. Presumably, this in turn is influenced by heredity, species differences, previous exposure to stress, the nutritional state of the organism, etc.

We saw that the **specific actions of individual stressors** may likewise act as conditioning factors. Thus agents causing intense renal damage can sensitize the body to the pressor effects of the G-A-S, somewhat in the same manner as partial nephrectomy does; pyrogens, histamine and other stressors capable of causing severe vascular paralysis will selectively "decondition" the arterial tree to the pressor action of endogenous RPS; microbes, allergens or local mechanical trauma can stimulate the tissues which come into direct contact with them (somewhat like the formalin or mustard in our "topical irritation arthritis" test) to the formation of a fibroplastic and hyalin-containing granuloma tissue.

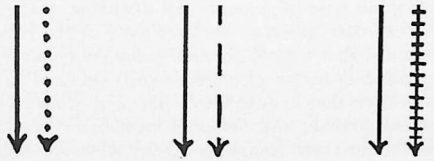
Such conditioning factors affect the defense mechanism at different points and may either increase or decrease the efficacy of any one among its individual components. Hence, it is evident that the essentially stereotypical defense-pattern of the G-A-S can manifest itself in widely different ways, depending upon such conditioning factors.

This is particularly important for the understanding of the diseases of adaptation. Unless conditioning factors could considerably alter the reaction-pattern to stress, it would be impossible to ascribe rheumatoid arthritis, periarteritis nodosa, allergies, certain types of diabetes, or hypertension to the same causative agent, namely to systemic stress. The concept *that such widely different maladies should result from the same cause* has often been considered to be quite contrary to accepted views concerning the causation of disease. Since this tenet is rather fundamental for our interpretation of the diseases of adaptation, it deserves special attention.

Let us point out firstly, that such an assumption is *not without precedent in medicine*. For example, excessive production of thyroid hormone may be associated with predominantly ophthalmic, metabolic or cardiac derangements. Before the tuberculosis bacillus had been isolated, it would have been considered most improbable that such dissimilar conditions as Pott's disease, phthisis of the lungs, miliary tuberculosis and the tuberculous lupus of the skin, are all caused by the same pathogen, yet, this is the case.

We have attempted to demonstrate that the polymorphism of the G-A-S symptomatology is due to two principal reasons. Firstly, every stressor has specific actions, in addition to its stress-producing ability. The former modify the response caused by stress as such; hence, the *polymorphism of the G-A-S manifestations can be due to specific effects of the evocative stressors.*

The following schema will illustrate this point. In all three figures the solid arrow represents stress, the other the "contaminating" specific actions.



Obviously, the end results of exposure to the three agents represented here could not be the same.

This type of "conditioning" may also be illustrated by an example taken from chemistry. All acids have many properties in common, yet the reactions of each member in this group are essentially different. The characteristics which they share are due to their acidity, the properties which distinguish them are the specific reactions of the carriers of this acid function. In pharmacology the stressor effect is what the drugs have in common, their other properties endow them with "specific pharmacologic actions". Both in chemistry and in pharmacology the specific properties condition that non-specific feature (acidity, stress) which the entire group shares. Hence, no two acids, — and no two stressors — act exactly alike. This may help to illustrate conditioning by specific properties of the stressor.

We have seen, however, that even exposure to the same stressor agent may result in qualitatively different responses. Here *polymorphism of the G-A-S manifestations is due to selective conditioning, by factors extraneous to the stressor.* This "peripheral conditioning" may occur at the various intermediate stations of the G-A-S or in the target organs themselves. We have compared this to the manifold effects one can obtain with the same electric current. During

an emergency, it may be necessary to supply more electricity for a community. This current will always be of the same quality and it will always travel along the same, pre-existent, main channels. Yet, depending upon the kind of emergency and the special needs of each district, both its quality and quantity has to be regulated locally in the periphery. Thus the same current can be used to produce mechanical work, sound, light of any color, heat or cold and indeed it may be shut out completely from a locality where it would represent a fire hazard. Of course, the more we approach the periphery of such an electric circuit, the more subject it will be to conditioning. Firstly, because the thin terminal wires can more easily be handled then the thick principal cables and secondly, because interventions anywhere along the line, above such a peripheral point, would affect the latter.

Essentially the same is true of the G-A-S. The more we approach the periphery, the more often do we note deviations from the standard G-A-S pattern. All stressors cause an ACTH discharge, but this may or may not be accompanied by the production of the "X factor", which is necessary for mineralo-corticotrophic actions. Interference at a lower level may cause even more selective deviations from the typical stress response. Thus, transection of the splanchnics may impede adrenaline discharge during the A-R, without interfering with any G-A-S manifestations except those resulting directly from hyperadrenalinemia. Possibilities for conditioning become ever more selective as we approach the peripheral target organs, each of which can be individually protected or sensitized to the typical actions of the G-A-S.

It is an inherent characteristic of most ramifying systems that side branches are more readily influenced than main lines. The following schematic drawing will help to illustrate this.

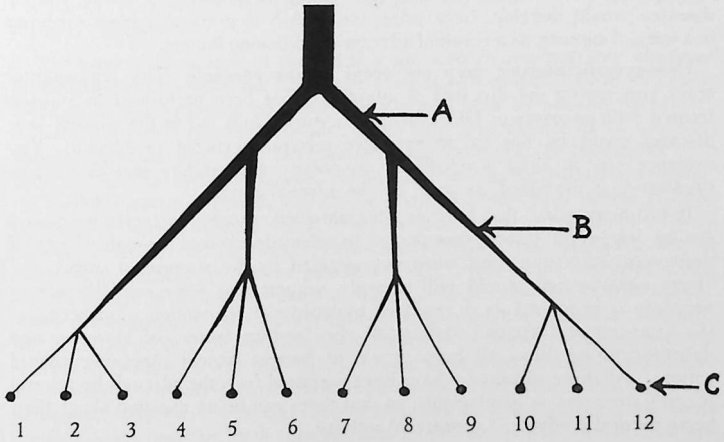


Illustration of selective conditioning in a ramifying system. Here 12 target organs received impulses through branches of a single main line. Conditioning at **A** would affect targets 7-12 without affecting targets 1-6. Conditioning at **B** permits us to single out targets 10-12 specifically. Conditioning at **C** influences only the one target organ marked 12.

PRINCIPAL CRITICISMS OF THE G-A-S CONCEPT

The general outlines of the G-A-S concept have not been challenged, but some of its aspects became the subject of much debate and criticism; these deserve special consideration here.

Why are the "diseases of adaptation" so polymorph in their manifestations if they are all due to stress? We mention this question only for the sake of completeness, since it has already been answered in the preceding section. We believe that the principal reasons for this polymorphism are the so-called "conditioning factors"; namely, the specific effects of the evocative stressors and other exogenous, or endogenous factors (heredity, pre-existent disease of certain organs, diet, previous exposure to stress, etc.) which can affect, selectively, certain pathways or target organs of the G-A-S response.

Why does exposure to the same stressor produce disease only in certain individuals? It is undoubtedly true that the same drug, microbe, emotional irritant or physical injury may produce a disease of adaptation in one person and be tolerated with impunity by another. It should be recalled, however, that the G-A-S is a useful, normal physiologic reaction to stress; only its derailments have been interpreted as diseases of adaptation. Hence, exposure to a stressor can be expected to produce such diseases only if the defense reaction is inadequate. Thus, for instance, in our experimental efforts to produce the hyalinosis-hypertension syndrome in rats by exposure to cold, we found it necessary to perform unilateral nephrectomies and to keep the animals on high-sodium, high-protein diets. All these conditioning circumstances failed to produce disease in the absence of stress, but upon exposure to cold, they caused a derailment of the G-A-S, with consequent cardiovascular lesions, nephrosclerosis and a rise in blood-pressure.

It is very probable that in man also, under the influence of stress, similar diseases would develop, only when the G-A-S is prevented from evolving in a normal manner, as a result of adverse conditioning factors.

Desoxycorticosterone may not occur in the adrenals. The fundamental work concerning the diseases of adaptation has been performed in animals treated with excesses of DCA. It is this work which led to the concept that diseases could be due to an excessive mineralo-corticoid production. Yet, evidence now at hand is insufficient to prove with certainty that desoxycorticosterone is produced, as such, by the adrenal cortex.

It will be recalled, that LAP (a mineralo-corticotrophic extract) also causes similar lesions in intact, though not in adrenalectomized animals. Even if desoxycorticosterone itself were not secreted by the suprarenal cortex, the above observations would still strongly suggest that some similarly acting principle is produced as a result of hypophyseal stimulation. Furthermore, the "amorphous fraction" of Kendall, the "sodium factor" of Hartman and desoxocortisone, have all been shown to possess typical mineralo-corticoid actions. All these substances have been prepared from the adrenals by several investigators and in good yields, so that there can be no question about their being natural products of suprarenal activity.

The doses of DCA used in the fundamental experiments on the "diseases of adaptation" may exceed the amounts produced endogenously, by the adrenal itself. This criticism has been voiced particularly with regard to the earliest experiments, in which DCA was given in the form of injections to non-sensitized animals. Subsequently, with the introduction of the pellet implantation technique, especially in animals sensitized by unilateral nephrectomy and/or high-sodium diets, much smaller amounts of the hormone proved to be disease producing.

It must be remembered, furthermore, that there is no objective reason to consider the pathogenic amounts of mineralo-corticoids as being beyond the limits of what could be produced in the body during stress. The quantities excreted in the urine of men who had received DCA, in doses conducive to hypertension, increased blood-volume, edema and renal damage, do not exceed those eliminated by patients after burns, traumatic injuries or acute infections. If we can judge by the amounts of gluco-corticoids required to produce remissions, in those spontaneous diseases which have been simulated in the animal by DCA overdosage, then this criticism appears to be even more unjustified. About 10 mg. of DCA per day given over a period of weeks, would certainly be pathogenic in man, while 80-100 mg. of cortisone are usually required to produce a pronounced remission, for instance, in rheumatoid arthritis or lupus erythematodes.

How can one reconcile the fact that the "rheumatic-allergic type" of disease is produced by corticoids in animals and nevertheless responds so favorably to corticoid therapy in man? This question hardly deserves much comment now, although it has often been asked, just after the introduction of cortisone into clinical practice. The original animal experiments — of necessity — had to be performed with DCA (a mineralo-corticoid) since this was the only adrenal steroid available in adequate amounts. Its effects upon many target organs are the reverse of those produced by gluco-corticoids (e.g., cortisone). As we now know, this is due partly to a peripheral antagonism at the level of the target organs themselves and partly, perhaps also to the inhibition by gluco-corticoids of mineralo-corticoid production, through the "compensatory atrophy" phenomenon.

The urinary elimination of corticoids is not always demonstrably abnormal in the diseases of adaptation. As we have repeatedly emphasized in this book, diseases of adaptation do not necessarily result from an absolute deficiency or excess of corticoids; they can also ensue as a consequence of an improper balance between gluco- and mineralo-corticoid secretion, or be caused by a state of *"relative hypocorticoidism"*. Thus, in our "topical irritation arthritis" the introduction of an irritant into the joint region produced a violent arthritis in perfectly normal animals, yet it failed to do so after pretreatment with an excess of ACTH or cortisone. This clearly shows that the adequacy of corticoid production can only be assessed in proportion to the pathogen which creates a need for such hormones. It is highly probable that pathogenic factors, which cause disease in individuals whose corticoid production remains "normal", would fail to do so if the adrenals responded with an increase in hormone discharge, commensurate with the increased requirements occasioned by an abnormal situation. Indeed, it is quite possible that many individuals who carry the pathogens (whatever these may be) of rheumatoid arthritis, allergies, lupus erythematosus, and so forth, can remain in perfect health throughout life because — through the G-A-S mechanism — they have rendered these potential pathogens quite innocuous. To use an analogy from an entirely different field, one might compare them with the typhoid or meningococcus carrier who lives in perfect harmony with the deadly germs present in his body.

It should be mentioned furthermore, that some evidence of an *anomaly in steroid metabolism* has been noted, in patients suffering from the rheumatic-allergic diseases, (e.g., increased pregnandiol excretion after the administration of progesterone, anomalies in 17-KS elimination).

Research along these lines has been handicapped principally due to the difficulty of assaying, blood or urine, specifically for mineralo-corticoid activity. However, several recently published improvements in the relevant techniques hold great promise as regards the elucidation of this important problem.

CLINICAL APPLICATIONS OF THE G-A-S CONCEPT

As regards clinical medicine, we feel that the principal value of the G-A-S concept is that, by helping to understand the rôle of the stress factor in disease, it enables us to adjust our therapeutic measures accordingly.

Non-specific therapy. — It becomes increasingly more evident that many of the time honored, though not spectacularly effective, non-specific therapeutic measures — such as fever therapy, shock therapy, parenteral administration of foreign proteins, blood-letting or mere starvation — are beneficial, largely, through the G-A-S. Often their principal value appears to be that they stimulate ACTH and gluco-corticoid production. Wherever this is so, it may be preferable in the future to inject ACTH or cortisone. In certain instances, however, non-specific therapy proved efficacious where ACTH failed. For instance, in mental patients, who did not respond to ACTH, it could be shown by subsequent shock therapy that they are benefitted by non-specific stress. Here, presumably certain specific changes, incident to the shock, act as conditioning factors of the hypophysis-adrenal discharge, or separately through other channels of the G-A-S (e.g., the nervous system or the catabolic response of the A-R).

There is a striking parallelism between the diseases empirically shown to respond to non-specific therapy and those which show dramatic remissions under the influence of ACTH and cortisone (e.g., rheumatoid arthritis, various inflammatory conditions of the eye, allergies). Through the use of the corticotrophic and corticoid hormones we are on the threshold of developing a modern version of non-specific therapy, which is much more effective than the old and lends itself better to a scientific analysis of its mechanism.

Dietary treatment of cardiovascular and renal diseases. — Diets poor in seasoning (spices, salt) and/or protein, have long been recommended in the treatment of hypertension, nephritis, nephrosis and allied conditions. However, the results were rarely spectacular and, in the absence of any convincing rationale which could justify their use, they have not been received with sustained enthusiasm. Purely empirical observations on a heterogeneous clinical material failed to show clearly even whether the detrimental effects of highly seasoned food are due to sodium, chloride or condiments in general. It also remained a subject of debate, whether certain vegetable proteins are more readily tolerated than meat and, especially whether — in the face of heavy urinary protein losses in renal disease — it is better to prescribe low-protein diets, to protect the kidney against overwork, or rations rich in protein, to substitute for the constant urinary losses.

A study of the mechanism through which stress causes cardiovascular and renal disease, has established certain definite facts concerning the rôle played by protein and minerals in the pathogenesis of the experimental replicas of

such maladies. If these data can be applied to the corresponding clinical diseases — and there is much reason to think that they can — then we shall soon be able to prescribe diets on a much more rational basis.

Now that we know how to reproduce these diseases in animals, it is comparatively simple to establish the pathogenic rôle of each dietary constituent, under rigorously controlled experimental conditions.

Corticotrophin and corticoid therapy. — Undoubtedly, the most important pertinent data are those derived from the clinical use of ACTH and cortisone.

Since only very limited amounts of these hormones have been available up to date, it is not yet possible to assess their scope accurately. However, it is precisely now that some general orientation in this field is most urgently needed. By way of a summary, let us say therefore, that (apart from their obvious utility in hypocorticoidism and anterior-pituitary deficiency) **ACTH and/or cortisone have been shown to be of value in the following conditions:**

Agranulocytosis,
Alcoholism,
Allergies, various, (in addition to those specifically mentioned here)
Allergic rhinitis,
Asthma,
Atopic dermatitis,
Blepharitis,
Choroideremia,
Choroiditis,
Conjunctivitis vernalis,
Dermatomyositis,
Drug sensitization,
Eczema,
Exfoliative dermatitis,
Erythema multiforme,
Fevers (apparently irrespective of etiology, though probably normalization of the temperature is not always an advantage),
Gouty arthritis,
Hay fever,
Hemolytic anemias of various kinds,
Herpes zoster,
Hodgkin's disease,
Idiopathic hypoglycemia,
Iritis,
Iridocyclitis,
Keratitis,
Leukemias (various),
Loeffler's syndrome,
Lupus erythematosus disseminatus,
Lymphosarcoma,
Nasal polyps,
Nephrosis,
Neurodermatitis,
Ophthalmologic conditions (especially those characterized by allergic and inflammatory manifestations),
Periarteritis nodosa,
Pneumonia (pneumococcus, "primary atypical"),
Psoriasis,
Retinitis (centralis, pigmentosa),
Retrobulbar neuritis,
Rheumatic fever,
Rheumatoid arthritis and spondylitis,
Serum sickness,
Tuberculosis of the larynx,
Ulcerative colitis,
Urticarias (various),
Uveitis,
Vasomotor rhinitis,

Preliminary data suggest that this type of treatment may also be of value in the following conditions:

Boeck's sarcoid,
Glaucoma,
Hepatitis,
Hypertension,
Hyperthyroidism (especially in normalizing the B.M.R. and reducing the exophthalmus),
Keloids,
Liver cirrhosis,
Myasthenia gravis,
Nephritis (especially if due to allergy),
Pemphigus,
Scleroderma,
Thromboangiitis obliterans (Buerger),

Available data suggest that ACTH and/or cortisone are of no value in:

Amyotrophic lateral sclerosis,
Carcinomas of most types,
Congestive heart failure,
Diabetes mellitus,
Multiple myeloma,
Poliomyelitis,

ACTH and/or cortisone may produce harmful effects in:

Acne vulgaris,
Congestive heart failure,
Cushing's syndrome,
Diabetes mellitus,
Hypertensive disease of certain types,
Nephritis of certain types,

Osteoporosis,
Peritonitis,
Septicemia,
Wound healing,

In this connection, it should also be emphasized that, under certain conditions, ACTH and/or cortisone may actually cause:

Acute pulmonary edema,
Ascites,
Marked decrease in resistance to infections,
Obscuring of the criteria of disease (e.g., fever and abdominal rigidity in peritonitis, the hematologic manifestations of systemic diseases, the acceleration of the pulse in acute infections, etc.)

PROBLEMS FOR FUTURE RESEARCH CONCERNING THE G-A-S

At this point it may be stimulating to contemplate some of the most important tasks that lie before us. However, in order to do so effectively, we must first consider the direction this type of work has taken during the last few years.

In the first printing of my "Textbook of Endocrinology",[1] I emphasized that: "For the species, the most important rôle of the hormones is reproduction, but for the individual, it is differentiation and adaptation. It becomes increasingly more obvious, furthermore, that the principal medical application of endocrinology is not the treatment of the primary, but of the secondary diseases of the endocrines. — Tumors and hyperplasias of endocrine glands, with consequent hormone overdosage, or destruction of incretory organs with the resulting hormone deficiency syndromes, are instructive, simple experiments of nature, which have taught us much about the endocrines. But these are rare diseases in comparison with the hormonal derangements resulting from maladaptation to stress."

"The main fatal syndromes of internal medicine (various cardiovascular, renal 'rheumatic' and old age diseases) may belong to this latter group; they are probably by-products of faulty hormonal adaptative reactions to a variety of non-hormonal pathogenic agents. The apparent cause of illness is often an infection, an intoxication, nervous exhaustion or merely old age, but actually, a break-down of the hormonal adaptation mechanism appears to be the most common ultimate cause of death in man."

Similar considerations led Albright to point out in his introduction to "The Endocrines" in Cecil's Textbook of Medicine[2] that: "The physician who calls himself an endocrinologist and confines his interests to such unfortunate members of society as might appear in the side-show of a circus, never realizes that pneumonia, a broken leg, and a bad burn involve important changes in adrenal cortical function (cf. 'alarm reaction' of Selye), that the disturbance in homeostasis occasioned by chronic renal insufficiency is ameliorated by a secondary hyperparathyroidism, that the somatotrophic action of testosterone propionate may be of use in many conditions other than male hypogonadism, and so on."

In his inaugural lecture at the Hôpital Bichat, in Paris, Laroche[3] stressed particularly, in connection with the experimental work on the G-A-S that: "These experiments throw a new light upon a series of maladies, which could not hitherto be related by pathologists to any particular hormonal derangement: certain hypertensions, certain types of chronic nephritis, the rheumatic affections, periarteritis nodosa, etc. Since these conditions can be elicited by a

[1] Selye 94572/47.
[2] Cecil A63152/43.
[3] B26357/48.

hormonal derangement, one wonders whether it would not be possible to effect their re-equilibration by means of other hormonal actions?"

In the corresponding section of the first monograph on the G-A-S, we pointed out that: "It would be tempting to survey all the diseases of unknown etiology from this new point of view and to determine whether those among them which apparently can be caused by a variety of agents, belong to the category of the diseases of adaptation".[4] — This has been accomplished, to the best of my ability, in the present volume. — Let us consider now some of those questions whose solution appears to be particularly rewarding when we survey the G-A-S concept, as it presents itself during the early months of 1950.

Adaptation energy. — Ever since 1937 I have been intrigued by the fact that an already acquired adaptation to a certain stressor agent is gradually lost in the course of chronic exposure. This means that the "adaptation energy" (or adaptability) of the organism is a finite amount. There is a singular similarity between the manifestations of the exhaustion stage, which ensues when adaptability is lost, and those of physiologic senility. No doubt, inestimable advantages would accrue to the practice of medicine if we succeeded in identifying "adaptation energy". — So far we can report no progress along these lines.

The physio-pathology of periodicity. — In addition to the irreversible exhaustion of senility, or of the "exhaustion stage" in the G-A-S, there is a temporary exhaustion or fatigue, which ensues after less prolonged exposure to stress. From this condition recovery occurs most readily as a result of rest.

Stress-reactions — such as the G-A-S — are optimally effective during short emergencies; perhaps largely, because most of the "stress hormones" (adrenergic substances, ACTH, corticoids, RPS) are well tolerated only during short periods and tend to cause severe complications if they act upon the body persistently over a long time. Thus, for example, the amounts of endogenous corticoids which spill over into the urine during a brief emergency (e.g., burns, emotional upsets, trauma, muscular work) are as high as those found in Cushing's disease, yet they do not produce "cushingoid" manifestations. The same is true of patients who receive large amounts of such hormones, during a short time, for medicinal purposes. The intermittent secretion of ACTH during various stress situations (infections, nervous stimuli, etc.) may also explain the comparative rarity of cushingoid changes in chronic disease, although here "deconditioning" metabolic changes probably also play a rôle. It may be rewarding to examine the mechanism of recovery from brief periods of overdosage with the "stress hormones" in order to learn how to avoid complications when they are therapeutically administered.

But there are many other data to stimulate interest in "periodicity".

A certain degree of cyclicity is nearly as characteristic of life as adaptability itself and the lack of periodicity, or rigidity, is almost equivalent to death. The female sexual cycle, the pulse, the sleep rythm with all the concomitant diurnal variations, the interchange between activity and rest, between work and play, the periodic renewal of cells in various organs are all indispensable for the maintenance of normal life. Stressors tend to disrupt this periodicity in many ways. It would be interesting to examine the possible relations between the diseases of adaptation due to stress and what might be called the "diseases of periodicity".

[4] Selye B1204/46.

From time to time we feel the urge to re-organize our classifications in medicine, even if nothing really new is added — just as we re-arrange the contents of our desk-drawers. It gives us a chance to eliminate the useless objects and to put the most useful ones into accessible positions. It may even call to our attention some long-forgotten item, which we banished into obscurity at a time when we failed to realize its, now so obvious, utility.

We found it of interest to re-arrange medicine, in this book, according to the G-A-S concept, but it may be equally, or even more, fruitful for some future investigator to re-arrange them as "diseases of periodicity".

The problem of the "first mediator". — In the many chapters of this volume we repeatedly had occasion to deplore the paucity of information concerning stimuli which, during stress, induce the pituitary to discharge ACTH. Transection of the stalk (with all its nervous and blood-vessel connections between hypophysis and hypothalamus) does not necessarily impede this response. The nervous pathways between the hypothalamus and the pituitary may be of importance in the event of exposure to purely neurogenic stressors; it remains to be seen, however, what carries the "stress message" to the anterior-lobe, from a burned skin, a traumatized limb, or tissues damaged by systemic infections and intoxications. We expressed the opinion that perhaps an ACTH discharge could be caused by any derangement in the chemical or physical characteristics of the blood, but this is merely a hypothesis. Further work along this line is badly needed.

The possible therapeutic value of G-A-S components, other than adrenaline, ACTH and gluco-corticoids. — Up to now, attention was principally focused upon the utility of the adrenaline and gluco-corticoid discharges, the former mediated by the sympathetic, the latter by ACTH. It is highly probable that many other manifestations of the G-A-S participate in raising resistance. In this connection, one might think of nor-adrenaline, mineralo-corticoids, antidiuretic hormone (vasopressin) acetylcholine, histamine, the products of lympholysis and even endogenous anti-histaminics.

How perfect is the correlation between gluco-corticoid and anti-arthritic activity? — Up to the present time all our observations suggest that the power of a compound to inhibit rheumatoid arthritis or "topical irritation arthritis", to cause thymico-lymphatic involution, eosinopenia, glycogen deposition in the liver and to antagonize certain manifestations of the "hyalinosis syndrome" are all correlated activities. In the terms of steroid pharmacology, this would mean that these are subordinate actions of the gluco-corticoid potency, just as vaginal cornification, uterine estrus and testicular atrophy are subordinate actions of the folliculoid (estrogenic) potency. It is not certain, however, that this apparent lawfulness will apply to all steroids which may become available in the future. There is some reason to believe that cortisonediene (a compound differing from cortisone by the introduction of a second double-bond at C_{6-7}) possesses certain gluco-corticoid activities, without being capable of causing a remission in clinical rheumatoid arthritis. Further elucidation of these aspects of steroid pharmacology would undoubtedly extend the scope of pharmaco-therapy in the diseases of adaptation.

How perfect is the correlation between mineralo-corticoid and hyalinosis activity? — In general, preparations with marked mineralo-corticoid actions (NaCl retention, K elimination, diuresis) are also most effective in producing experimental hyalinosis. However, in comparing the actions of LAP, desoxocortisone and desoxycorticosterone, this parallelism does not appear to be perfect. Furthermore, at very high dose levels, in certain vascular territories (e.g., kidney), even gluco-corticoids can cause hyalinosis although in other target organs they inhibit such changes, even at the same dose levels. We wish to stress the need for a more profound analysis of the correlation between mineralo-corticoid and hyalinosis activity especially since, for the sake of simplicity, in the body of this volume we tended to describe these properties as strictly interdependent. We felt that this is justified, as a temporary measure, in order to avoid further complication of our presentation, especially since there is no convincing evidence to the contrary. It will be kept in mind, however, that up to now we do not have definite proof that the characteristic effects upon mineral metabolism and hyalin deposition are but two subordinate actions of the mineralo-corticoid potency.

Selective conditioning in general. — We saw that some factors (diet, drugs, etc.) can selectively increase or decrease the action of stress hormones upon certain organs. In order to accentuate the desirable and to minimize the undesirable effects of ACTH and cortisone, it is imperative to learn more about the activities of such "conditioning factors".

Selective conditioning of the adrenal response in particular. — The possibility of influencing the adrenal, at will, to produce different kinds of hormones, deserves special mention. The adrenal cortex can produce a variety of compounds, namely, mineralo-corticoids, gluco-corticoids, testoids, folliculoids and perhaps even "lipo-corticoids". We have shown furthermore that the morphologic response of the adrenal cortex can also be qualitatively altered by conditioning factors. We concluded that the pharmacology of the adrenal cortex is not merely limited — as has hitherto been thought — to a more or less intense stimulation by ACTH. It would be of the greatest interest to learn more about the factors which permit us to induce the adrenal cortex to respond in qualitatively different ways.

In this respect the recently discovered "X-factor", which appears to be present in impure APE and LAP, is of especial interest. It may be a new hormone or a mixture of already identified anterior-lobe principles. In any case, we shall have to attempt its identification in order to understand how the hypophysis can react to stress by discharging mineralo- and gluco-corticoids in variable proportions.

The recent demonstration that nor-adrenaline is produced by the adrenal medulla raises the possibility of its participation in emergency reactions. Up to now only adrenaline has been considered in this connection. Are there factors which can condition the adrenal medulla to produce either adrenaline or nor-adrenaline predominantly?

Selective hypocorticoidism. — The problem of selective hypo-corticoidism is closely related to that previously discussed. The syndrome produced by excess mineralo-corticoids has often been compared to that of adrenal insufficiency. In both instances there is a tendency to develop hypoglycemia, a predisposition for arthritis, a decreased resistance to various types of stressors and, under certain circumstances, thymico-lymphatic hyperplasia. In these respects, manifestations of hypocorticoidism resemble those of a mineralo-corticoid excess. On the other hand, hypertension and hyalinosis are only characteristic of the latter. The relationship between complete hypocorticoidism (as caused by adrenalectomy) and selective hypo-gluco-corticoidism (as induced by mineralo-corticoid overdosage), requires further study.

Why is RPS maximally produced when it is **minimally detoxified ?** — It has been noted that conditions which cause the kidney to produce an excess of RPS, also interfere with its ability to detoxify such pressor substances. Indeed there appears to be a rather close inverse parallelism between RPS production and RPS detoxification. Perhaps such compounds as DCA and such interventions as the "endocrine kidney" operation, change the direction of a reversible chemical reaction between RPS and some inactive precursor. If in the body the total amount of RPS plus its precursor were fairly constant, factors which would tend to direct the process towards RPS production would then automatically diminish its inactivation. This is but one of many possible explanations of the observed facts, but in view of the great practical importance of renal hypertension, the field certainly deserves a systematic analysis.

Why is ACTH (or cortisone) capable of producing remissions both in granulocytic anemias and in agranulocytosis ? — Perhaps here granulocytosis and agranulocytosis are merely secondary manifestations of a response to some evocative agent, whose stressor effect is mitigated by gluco-corticoids. The condition is apparently comparable to the rise in body temperature occasioned by cortisone in Addisonian hypothermia, although the same compound depresses fever caused by a variety of pathogens. The mechanism of such dual responses remains to be elucidated.

Is the similarity in the pharmacologic effects of adrenergic and corticoid compounds merely coincidental ? — Adrenergic compounds and corticoids share a number of actions, such as the ability to produce hyperglycemia and hypertension, to increase muscular efficiency and to antagonize certain types of allergic reactions. It may be significant that such varied effects are shared by hormones of the adrenal cortex and medulla, but the cause and purpose of these similarities — as those of the morphologic proximity between adrenal cortex and medulla — remain obscure.

Other miscellaneous problems. — The inhibition of *wound healing and regeneration* by gluco-corticoids raises the possibility that mineralo-corticoids may act inversely, but this remains to be shown.

The frequent occurrence of *purulent infections* (e.g., pulmonary, renal or hepatic abscesses) in animals and the occasional development of peritonitis in man treated with large doses of gluco-corticoids, suggests that these hormones may be useful tools in the analysis of inflammations in general.

The rôle of the corticoids in the pathogenesis and therapy of *hypertension, eclampsia, peptic ulcer, psychosomatic derangements,* various types of *tumors,* etc. has merely been suggested by the experiments completed up to date. Further work along these lines would be highly desirable.

ACTH and cortisone substitutes are urgently needed for therapeutic purposes. The possibility of synthesizing ACTH from its constituent amino-acids is now under investigation and it is quite possible that certain steroids of cortisone-like structure may help to decrease the high cost and increase the availability of these useful compounds.

It will also be necessary to explore systematically those drugs which could act as *gluco-corticoid synergists,* in certain specific instances. Some such problems have already been discussed under the heading of "conditioning", but many cognate applications come to mind. For instance, it might be useful to depress granuloma formation in tuberculosis and other infectious diseases in order

to expose micro-organisms to the destructive effect of antibiotics. It should be explored whether, in the absence of encapsulation and granuloma formation, micro-organisms would be more readily attacked by anti-microbial agents.

The necessity for specialists in adaptation and problems of stress. — Finally, we should like to emphasize that the science of adaptation is beginning to develop into a separate branch of medicine. Apart from specialists in certain techniques (surgery, x-ray, laboratory diagnosis) and target organs (heart, gastrointestinal tract, skin, eye), we will need the specialist in stress and adaptation.

Just like his colleagues in other disciplines, he will have to borrow from cognate fields. The ophthalmologist has to acquaint himself with certain aspects of surgery, internal medicine, allergy, etc.; the cardiologist must know a good deal about x-ray findings, the physics involved in electrocardiography, etc. Similarly, the stress specialist will have to devote a good deal of his time to the study of internal medicine, experimental physiology and pathology, allergy, neurology, endocrinology, and so forth. Nevertheless, the immensity of the subject-matter related to stress-problems will undoubtedly require the training of specialists who may be consulted in connection with diseases in which the stress factor plays a predominant part.

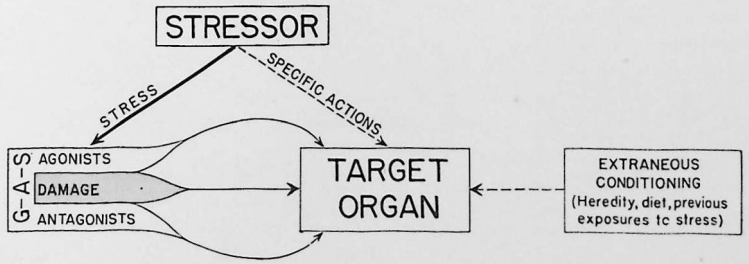
DIAGRAMMATIC SYNOPSIS OF THE G-A-S CONCEPT

And now in these last few paragraphs of the book, I should like to summarize concisely what appears to me its most important outcome.

All agents can act as stressors producing both stress and specific actions. No agent can produce one without the other. The specific actions affect the target organs in a variety of ways. Stress acts only through the G-A-S. It causes defense and damage.

The defense mobilizes agonists and antagonists which, through their interaction on the target organ, stabilize the latter and adjust its response to injury. But stress also invariably causes some degree of damage, through the G-A-S. This likewise affects the target organ, though not through the humoral and nervous mediators of non-specific defense.

Factors extraneous to the G-A-S (e.g., heredity, diet, previous exposure to stress) can condition these responses. Thus in the final analysis the reaction of the target organ will depend upon the specific actions of the stressor, the effects of the resulting G-A-S (agonists, antagonists, non-specific damage) and extraneous conditioning factors. This explains how the essentially stereotypical G-A-S response can lead to a variety of polymorph syndromes and why so many apparently unrelated diseases are amenable to therapy by "stress hormones".



Disease consists of two components, damage and defense. Up to now medicine attempted to attack almost only the damaging pathogen (to kill the germs, to excise tumors, to neutralize poisons).

As regards defense, hitherto, medicine limited itself to such vague advice as the usefulness of rest, wholesome food, etc. A study of the G-A-S suggests that henceforth we will be able to rely upon much more effective means of aiding adaptation to non-specific local or systemic injury, by supplementing the natural defensive measures of the G-A-S, whenever these are sub-optimal.

INDEX

To facilitate the use of this index, block numerals (e.g., **12**) refer to principal discussions of a subject, bracketed numerals [e.g., (12)] to illustrations and ordinary Roman numerals (e.g., 12) to all other parts of the text.

Greek letters (e.g., α, β, γ, δ, Δ), numbers which form part of indexed words and short connecting words (e.g.: in, the, of, for, from, to, as) are omitted in determining the alphabetic position of entries in this index.

When a "target organ" **A** is influenced by a stimulus **B**, this is indicated by an arrow pointing from **B** to **A** thus: **B → A**, instead of the usual cumbersome entry: "**A**, effect of **B** upon". Conversely, the effect of **A** upon **B** is indicated by the entry: **B ← A**, while a general discussion of the interrelation between **A** and **B** is indexed thus: **A ⇆ B**.

If two stimuli **B** and **C** act upon the same target organ **A**, this is usually indexed: **A ← B + C** or **B → A ← C**.

It is, of course, impossible to index highly complex interactions under each stimulus or target involved (and all their synonyms), but entries have been so selected that it will be rarely necessary to search for a specific item under more than two possible headings.

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In general, the same bibliographic procedure was employed here as in the Encyclopedia of Endocrinology (Selye A57606/43, B3035/46) to which the reader is referred for a more detailed discussion of this system. Suffice it to state here that in the text small exponential numbers (which do not interfere with readability) refer to footnotes. The latter list the author, the accession number and (after a stroke) the last numerals of the year of publication, of all communications to which reference is made. Thus without having to turn the page, the reader can immediately see whose work is being considered and whether this is of recent date. The full reference is obtained by consulting the corresponding accession number, among this author's publications, in the present section.

For instance, a footnote in the text "Abbott et al. B29501/46" refers to the first publication listed below. Numbers followed by the sign "/ND" indicate not dated communications or previously unpublished observations. In the list below, block numerals are used to designate extensive synoptic publications concerning the field indicated in the title; in the footnotes the most detailed surveys of the subject in the corresponding text are so designated.

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