The Story

OF THE

ADAPTATION SYNDROME

●

"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."

[From the foreword of "STRESS." Acta Med. Publ., Montreal (1950)]

BY THE SAME AUTHOR:

"**STRESS** (The Physiology and Pathology of Exposure to Stress)," 1950.

"ANNUAL REPORT ON STRESS," 1951.

"ANNUAL REPORT ON STRESS," 1952 (in preparation).

"TEXTBOOK OF ENDOCRINOLOGY," 2nd Edition, 1949.

"THE STEROIDS" (4 Volumes), in Encyclopedia of Endocrinology, 1943.

"OVARIAN TUMORS" (2 Volumes), in Encyclopedia of Endocrinology, 1946.

ACTA INC., Medical Publishers, 5465 Decarie Blvd., Montreal, Canada.

●

"TRATTATO DI ENDOCRINOLOGIA," Italian translation of "Textbook of Endocrinology" by Professor Cesare Cavallero, 1952.

CASA EDITRICE AMBROSIANA, Milano, Corso S. Gottardo 21/8.

●

"ENDOCRINOLOGÍA," Spanish translation of "Textbook of Endocrinology" by Professor José Mª Cañadell, 1952.

SALVAT EDITORES, S.A.,
Barcelona, Madrid, Buenos Aires, México, Río de Janeiro.

●

"ON THE EXPERIMENTAL MORPHOLOGY OF THE ADRENAL CORTEX" in American Lectures in Endocrinology, 1950. [In collaboration with H. Stone.]

CHARLES C. THOMAS, Publisher, Springfield, Illinois, U.S.A.

The Story

OF THE

ADAPTATION SYNDROME

(TOLD IN THE FORM OF INFORMAL, ILLUSTRATED LECTURES)

by

HANS SELYE

M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada)

Professor and Director

of the

Institut de Médecine et de Chirurgie expérimentales

Université de Montréal

◆

ACTA, INC.
MEDICAL PUBLISHERS
MONTREAL, CANADA

by

HANS SELYE

PRINTED IN CANADA

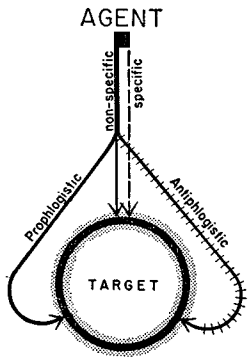
Ce livre
est très affectueusement
dédié à
Gabrielle, Michel et Jeannot
qui ont si patiemment partagé
avec l'auteur
le stress dû à ces leçons.

LEITMOTIV

The principal handicap in the understanding and appraisal of the adaptation syndrome concept is to be found not among the facts, but among the thoughts upon which it is based. It may help you to follow the complex story of stress, which I am about to relate, if you always bear in mind that it rests upon the few, simple, fundamental tenets illustrated by the adjacent diagram.

All **agents,** which act upon the body or any of its parts (**target**), exert dual effects:

(1) Specific actions (**interrupted arrow**); for instance, ether causes anesthesia, Salmonella typhi produces typhoid fever.



(2) A non-specific stereotypical reaction of stress, which manifests itself in the form of the general adaptation syndrome (**three-branched arrow**). — Stress affects the target directly. The topical tissue injury caused by a burn, the immediate effects of microbes upon cells are cases in point (**straight branch of solid arrow**), but some of its actions are mediated through humoral or nervous pathways (**curved branches of arrow**).

The principal humoral pathways lead through the anterior pituitary and the adrenal cortex, which produce essentially "adaptive"hormones. Among these, ACTH and the **antiphlogistic**-corticoids (e.g., cortisone) inhibit, STH and the **prophlogistic**-corticoids (e.g., DCA) stimulate inflammatory responses to injury.

The fundamental reaction-pattern to topical stress is "inflammation," to systemic stress, "shock." Various combinations of these two basic responses constitute the essence of most diseases.

The regulation of tissue reactivity, for instance through "adaptive hormones," often determines whether the body succumbs to disease or resists a potential pathogen by means of adaptation. Other humoral agents and the nervous system also participate in the adaptation syndrome, but the nature of their pertinent actions is not yet sufficiently understood to deserve a detailed consideration at the present time.

All the effects of biologic agents, and particularly those of the adaptive hormones, largely depend upon "conditioning factors" (**shaded area**), some of which are external (diet, temperature, light), others internal (heredity, constitution, previous exposure).

Thus a state of stress is produced in the body through multiple pathways, its effects being always modified by the variable specific actions of the eliciting agent and by the conditioning factors, the "terrain," which is different in every individual. These conditioning factors can selectively affect the individual pathways. This accounts for the variable manifestations of what, in essence, is but a single stress-response.

The adaptation syndrome in itself is not pathogenic; on the contrary, it is an indispensable physiologic defense reaction to damage as such. However, this — like any other biologic response — is not always optimally effective; its imperfections (e.g., an absolute or relative excess or deficiency of one or more adaptive hormones) play an important part in the pathogenesis of most diseases. The maladies, in which such inadequacies are even more important than the specific actions of the pathogen itself, are considered to be primarily "diseases of adaptation."

Now the great problem in endocrine physiology is no longer:

"What do the hormones do?" but **"What adaptive reactions do they influence!"**

Now the great problem in endocrine pathology is no longer:

"Which diseases are caused by the excessive function or destruction of an endocrine gland?" but **"In which diseases has the endocrine status a decisive influence!"**

Indeed, even apart from endocrinology, the principal endeavor of medicine in general is beginning to change. It is no longer the search for specific pathogens and for specific remedies with which to eradicate them. We always used to accept as a self-evident fact, that each well-characterized individual disease must have its own specific cause. This tenet is self-evident no longer. It becomes increasingly more manifest that an agent does or does not produce disease, depending upon a variety of conditions, some of which have now been definitely identified as being determined by the "adaptive hormones."

There begins to emerge a new and somewhat more complex pathology in which **the main objects of our study are no longer individual "pathogens," but rather "pathogenic situations."**

GLOSSARY OF TECHNICAL TERMS AND ABBREVIATIONS USED IN THESE LECTURES

A-C = antiphlogistic corticoid (probably synonymous with G-C).
ACTH = adreno-corticotrophic hormone or corticotrophin.
Adaptive hormones = hormones which are particularly important during the G-A-S (e.g., ACTH, STH, corticoids, adrenaline, nor-adrenaline).
Antiphlogistic corticoid (A-C) = corticoid particularly effective in inhibiting inflammation.
Antiphlogistic hormones = hormones particularly effective in inhibiting inflammation.
A-R = alarm reaction.
A-R changes = changes characteristic of the A-R.
Conditioning factors = factors which have little or no activity but can significantly alter a response to a stimulus (e.g., sodium can act as a conditioning factor of DCA activity).
Corticoids = substances simulating the activity of adrenal cortex. E.g.:
Corticosterone (Kendall's cpd. "B", Reichstein's cpd. "H", 11-21-dihydroxy-progesterone).
Cortisone (Kendall's cpd. "E", 17-hydroxy-11-dehydro-corticosterone).
Dehydrocorticosterone (Kendall's cpd. "A", 17-desoxy-cortisone).
Desoxocortisone (Reichstein's cpd. "S", 11-desoxy-17-hydroxy-corticosterone).
Desoxycorticosterone (Kendall's desoxy cpd. "B", 21-hydroxy-progesterone).
Hydrocortisone (Kendall's cpd. "F", Reichstein's cpd. "M", 17-hydroxy-corticosterone).
DCA = DOCA, desoxycorticosterone acetate: see "Corticoids" above.
Desoxocortisone: see "Corticoids" above.
Diseases of adaptation = diseases in which an inadequacy of the adaptation syndrome plays a particularly important rôle. In general, the term should be reserved for those maladies in which the maladaptation factor is more important than the eliciting pathogen itself. No disease is purely a disease of adaptation, any more than it could be purely a disease of the heart or an infectious disease without overlap with other nosologic groups.
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 ceases to secrete urine but continues to produce RPS.
"First mediator of damage" = hypothetical substance(s), originating in the directly injured area, which transmits the message of stress from the directly injured area to other parts of the body and causes systemic manifestations of damage or shock.
"First mediator of hormonal defense" = substance(s) originating in the directly injured area, which transmits the message of stress to the pituitary and causes an ACTH discharge. It is possible that the first mediator of damage is identical with this first mediator of hormonal defense.
Folliculoids = compounds simulating the hormonal activity of an ovarian follicle.
G-A-S = General Adaptation Syndrome. A triphasic, non-specific, adaptive reaction comprising: (1) the alarm reaction, (2) the stage of resistance, (3) the stage of exhaustion.
G-C = gluco-corticoid (probably synonymous with A-C).
Gluco-corticoid (G-C) = corticoid particularly effective in raising the liver glycogen and blood-sugar concentration (e.g., cortisone, hydrocortisone).
Hydrocortisone: see "Corticoids" above.
Kendall's compounds: see "Corticoids" above.
LAP = lyophilized anterior-pituitary tissue. A crude preparation which was used in the first experiments designed to show that pituitary extracts have an effect upon inflammation. LAP has a pronounced prophlogistic effect; as we presume, mainly because of its high STH content.
Luteoids = compounds simulating the hormonal activity of the "corpus luteum."
M-C = mineralo-corticoid (probably synonymous with P-C).
Mineralo-corticoid (M-C) = corticoid particularly effective in causing sodium retention and potassium loss (e.g., DCA, desoxocortisone).
Non-specific agents = agents which affect many targets and are devoid of the ability to act selectively upon any one.
Non-specific changes = changes which can be elicited by many agents.
P-C = prophlogistic corticoid (probably synonymous with M-C).
Prophlogistic corticoid (P-C) = corticoid particularly effective in facilitating inflammation.
Prophlogistic hormones = hormones particularly effective in facilitating inflammation (e.g., STH, DCA, desoxocortisone).
Reichstein's compounds: see "Corticoids" above.
RPS = renal pressor substance(s).
Specific agents = agents which affect only a very limited number of targets with great selectivity.
Specific changes = changes which can be elicited only by a very limited number of agents.
STH = somatotrophic hormone or "growth hormone." The term is used in these lectures to indicate the activity of the most purified STH preparations now available.

It must be emphasized that we have no definite proof that any available STH preparation is entirely pure. All our extracts exhibit both diabetogenic and growth-promoting properties. Although it is now generally held that STH is the diabetogenic hormone, it is also possible that the available preparations contain two principles: one growth-promoting, the other diabetogenic. Should this be so, we do not know which of these two principles would be responsible for the prophlogistic activity. Indeed, this inflammation-facilitating hypophyseal factor (which was originally designated as the "X-factor" of our LAP preparations) may even turn out to be a third principle, independent of both of the above mentioned properties of STH preparations. In these lectures, this prophlogistic factor is referred to as STH only because it is most plentiful in the most actively growth-promoting pituitary fractions and because it would be impractical to repeat the above explanation each time we make reference to this hormonal activity.

Stress = the sum of all non-specific biologic phenomena (including damage and defense). It may be local or topical (as exemplified by inflammation) or systemic (as exemplified by the G-A-S).
Stressor = an agent capable of producing stress. We distinguish the systemic stressor — alarming stimulus (an agent capable of producing a G-A-S) — from the topical stressor (an irritant which causes inflammation).
Target = that which reacts to a stimulus. Both structural (e.g., heart) and chemical (e.g., blood-sugar) receptors of stimuli are thus designated.
Testoids = compounds simulating the hormonal activity of the testis; also known as androgens or "male hormones".
TTH = thyrotrophic hormone.
"X-factor" of LAP = the prophlogistic factor(s) in crude pituitary preparations, such as LAP. (See also "STH" above).

TABLE OF CONTENTS

Leitmotiv ... 8

Glossary of Technical Terms and Abbreviations Used in These Lectures ... 10

FIRST LECTURE

Evolution of the Stress Concept. — Purely Descriptive Characterization of the Adaptation Syndrome ... 15

SECOND LECTURE

Dynamics of the Adaptation Syndrome. — Rôle of the Adrenal Cortex and of the Anterior Pituitary ... 44

THIRD LECTURE

The Diseases of Adaptation. — Effects of Overdosage with DCA and LAP(STH) ... 71

FOURTH LECTURE

How, Depending upon "Conditioning" Circumstances, the Same Adaptation Syndrome Can Produce Various Diseases. — The "Endocrine Kidney." — Clinical Use of Adaptive Hormones ... 101

FIFTH LECTURE

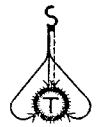
Overdosage with Antiphlogistic Hormones. — Interactions between the Various Adaptive Hormones. — "Conditioning" of Adaptive-Hormone Actions by (Systemic or Topical) Stress Itself. — The Therapeutic Value of Prophlogistic Hormones ... 133

SIXTH LECTURE

An Illustrated Catalogue of the Facts Brought to Light by the Adaptation Syndrome Concept and an Enumeration of the Doubts It Raised ... 158

SEVENTH LECTURE

General Summary and Outlook ... 203



INTRODUCTION

This booklet is a brief summary of my work on the adaptation syndrome; as such, it is intentionally quite subjective and personal.

I hope my readers will forgive its unusual informality, but it is compiled from only slightly edited wire-recordings of my lectures. In this way I hoped to preserve the spontaneity inspired by direct contact with the diverse groups of physicians and medical students in Canada, the U.S., Europe and South America, who asked me to tell them about the results of my pertinent experiments and the thoughts that induced me to perform them. These lectures and the subsequent discussions provided a most useful opportunity to appraise the points of view of colleagues, whose national backgrounds and special fields of medical training were extremely varied.

It is my impression that the rapid growth of interest in the physiology and pathology of the "Stress Syndrome" was much more effectively stimulated by these informal, unprepared lectures, than by my laboriously compiled, extensive monographs which attempted to present the entire relevant literature in a systematic manner.

For these reasons, I should like to maintain the informal character of my lectures in the present booklet, limiting my material almost entirely — as I did in my lectures — to observations made by my co-workers and myself; that is, to data about which I have first-hand information.

My teacher, Professor Arthur Biedl of Prague, once told me:

"In order to lecture well, you must never attempt to use more than one or two percent of what you know about a subject, and in medicine you never really know anything that you have not actually discovered — or at least checked — yourself."

I tried to follow this precept in all my lectures and will attempt to go on doing so in these pages.

My efforts to interpret experimental observations have led to the formulation of hypotheses, which in turn suggested other experiments. I shall describe these trends of thought also, because they bring light into what would otherwise merely be a dry enumeration of disconnected, and hence confusing, facts. Hypotheses (whether right or wrong) have always been the supreme directors of scientific effort; they — just as geographic maps — are of no value in themselves, yet, without them, the important facts they embrace would remain inaccessible to us.

In view of what I said, it is obvious that this booklet includes only what I happen to consider most important among the things I happen to know about stress. Hence it can make no pretense either at objectivity or at completeness. Those among my readers who wish to appraise the problem objectively, on the basis of all available pertinent data, are advised to consult the original publications upon which this review is based. They will find about 8000 of them quoted in my monographs "Stress" [1] and "Annual Reports on Stress." [2, 3]

(1) Selye, H.: "Stress (The physiology and pathology of exposure to systemic stress)." Acta Med. Publ., Montreal (1950).

(2) Selye, H.: "First Annual Report on Stress." Acta Med. Publ., Montreal (1951).

(3) Selye, H.: "Second Annual Report on Stress." Acta Med. Publ., Montreal (1952).

FIRST LECTURE

Evolution of the Stress Concept. Purely Descriptive Characterization of the Adaptation Syndrome.

Ladies and Gentlemen!

Tone of these lectures.

IT HAS BEEN SAID THAT: "Science is always most completely assimilated when it is in the nascent state" (James Clark Maxwell). I shall therefore try to present a branch of science to you just as it was born, discussing observations and theories in the order in which they presented themselves to us in the laboratory and in the clinic. This way, my account will give me an opportunity to re-live, and thus to share with you, that great intellectual satisfaction that comes from forcing one's way, step by step, into the confidence of Nature, by showing that we understand her.

You asked me to tell you the "Story of the Adaptation Syndrome," and that is just what I propose to do. Any attempt to cover the entire pertinent literature systematically in a brief lecture series would be futile. Besides, those interested in detailed information, concerning a specific point, would wish to consult the original publications anyway. However, the time allotted to me should suffice to outline the most striking

events in the history of this investigation and to give you a bird's eye view of the picture as a whole, as we see it today.

Of course, only a small portion of this work was performed by our group in Montreal. Yet, I hope to give you a fairly accurate eyewitness account of its growth, for at least I can say: "I was there." I was there to watch as this field emerged from the unknown and as it went through the first stages of its development. We carried out some experiments ourselves, and lecturing engagements, such as the present one, permitted me to visit almost every major research center in the world where pertinent work was under way. Furthermore, many students of stress come to our Institute in Montreal from other countries, in order to discuss and demonstrate their relevant observations. All this helped me to keep in close touch with this field.

The human mind always finds it intriguing (and sometimes instructive) to follow the steps by which a mystery is gradually solved. The stress-problem is still far from its final solution, but much progress has been made along these lines during the comparatively short period of the last 16 years.

For all these reasons, I believe it will be both more entertaining and more profitable to follow these developments in their historic evolution, rather than to give a purely factual account of the data now known.

To start with, let us try to recapture the spirit of the days when you could still browse through all the current medical journals without encountering the terms: "non-specific stress," "corticoids," "general adaptation syndrome," "diseases of adaptation" — or even "Selye," as far as that goes.

I am often asked just what made me think of the adaptation syndrome in the first place.

A youngster's first general impressions of medicine.

In retrospect, after so many years, it is rather difficult to single out precisely the beginning of a long trend of thoughts. As far as I can recall, non-specific reactions always held a singular fascination for me, because they were generally neglected and rejected from the focus of attention.

I clearly remember, for instance, one of the first lectures in internal medicine which I attended, in 1925, as a medical student at the German University of Prague. We were shown several patients in the earliest stages of various infectious diseases. As each case was brought into the amphitheater, the Professor carefully pointed out that the patient felt and looked ill, had a coated tongue, complained of more or less diffuse pains and aches in his joints, gastro-intestinal disturbances with loss of appetite and loss of weight (with an increased elimination of nitrogen, phosphates and potassium). Less constantly, but still very often, there was fever (with signs of euphoria, excitement or depression), an enlarged spleen or liver, proteinuria, an inflamed tonsil, a skin rash, etc. However, to all this he attached very little significance.

Then he enumerated a few "characteristic" signs, which, should they subsequently appear, may help the diagnosis of a specific disease. These, we were told, are the changes to which we must give all our attention. At present they happen to be absent, but until they will appear, not much can be done for the patient, since without them it is impossible to formulate a definite diagnosis or recommend efficient therapy. He was obviously not interested in the many changes which were already manifest, because they were "non-

specific" and hence "of no use" to the physician.

Since these were my first patients, I was still capable of looking at them without being biased by current medical thought.

I could understand that our professor had to find specific disease-manifestations in order to identify the particular pathogens from which these patients suffered. This, I realized, is necessary so that suitable drugs might be prescribed, medicines having the specific effect of killing the germs, or neutralizing the poisons, that made these people sick.

However, it impressed me, the novice, much more that only a few signs are actually characteristic of any one disease; most of them are common to many, wholly unrelated, maladies — or even to all diseases.

Why is it, I asked myself, that such widely different pathogens as those of measles, scarlet fever or influenza, share with a number of drugs, allergens, etc., the properties of producing the above mentioned "non-specific syndrome"? Yet, I learned that they do share them, they share them to such an extent that at an early stage a differential diagnosis may even be impossible.

The syndrome of "just being sick."

I can still clearly remember today — after more than a quarter of a century — the extraordinarily profound impression that this consideration made upon me at the time. I could not understand that, since time immemorial, physicians should have attempted to concentrate all their efforts on the recognition of individual maladies and the discovery of specific drugs, suitable only for the treatment of individual diseases, without giving any attention to the "syndrome of just being sick." Surely, if it was important to find remedies which help against one disease or another, it would

be ever so much more necessary to learn something about the mechanism of being sick, and the means of treating that "general syndrome of sickness," which is apparently superimposed upon all specific diseases!

However, an 18-year-old medical student has neither the training nor the facilities for pursuing such a thought further and, after a while, as I learned more and more about medicine, the many specific problems of diagnosis and therapy began to blur my vision for the non-specific. The former gradually assumed an ever increasing importance and pushed the entire concept of "being sick" out of my consciousness into that hazy category of the purely dialectic questions, which are obviously without issue and not worth bothering about.

Not until 10 years later, in 1935, did these same questions confront me again, although now under entirely different circumstances. At that time, I was working in the biochemistry department of McGill University on the physiology of the maternal placenta. I had just been assigned my first graduate student, Tom McKeown (now professor of social medicine at the University of Birmingham). I was then working on neuro-endocrine correlations during pregnancy and had succeeded in interesting McKeown to collaborate with me along these lines.

Non-specific derangements of sexual cyclicity.

As an incidental observation, we noted that some of our experimental animals exhibited anomalies of the sexual cycle following treatment with pituitary or placental hormone preparations. They showed no vaginal estrus and went into what is called a condition of "pseudo-pregnancy."

Before we could go much further in the analysis of this phenomenon, it became obvious, however, that this was in no way a characteristic effect of the preparations

that were employed. A perusal of the older literature, as well as some experiments which we performed to clarify this phenomenon, soon showed that overdosage with desiccated thyroid, various vitamin deficiencies, starvation, adrenalectomy and other damaging procedures can all cause such a failure of follicle maturation and a derangement of the sexual cycle. Thus it became obvious that the phenomenon is entirely non-specific and hence, we promptly lost interest in it.

Nevertheless, in an effort to interpret the mechanism of this sexual derangement, we concluded that it must be some manifestation of "non-specific stress," mediated through the pituitary and the glands which are under hypophyseal control. We thought it probable that a number of agents, through some condition of non-specific stress, may so affect gonadotrophic hormone production by the pituitary that insufficient amounts of follicle stimulating hormone are secreted and the cyclic production of ova and estrous changes cannot go on.

First use of the term "stress."

This was the first time that we used the word "stress" in its present connotation, as a state of non-specific tension in living matter, which manifests itself by tangible morphologic changes in various organs and particularly in the endocrine glands which are under anterior pituitary control. Yet these experiments have largely been overlooked and this is hardly surprising, since they were described in the appendix of a paper entitled "Studies on the physiology of the maternal placenta in the rat," [1] a title hardly suitable to call attention to this kind of work.

[1] Selye, H. and T. McKeown: "Studies on the physiology of the maternal placenta in the rat." Proc. Roy. Soc., London, series B. *119*:1 (1935).

A little later during this same year, I stumbled upon the "stress problem" again in connection with entirely unrelated studies. Quite independently of our histo-physiologic placenta studies, an active research program concerning the hormones of the placenta, ovaries and pituitary was being directed in the same department by my chief, Professor J. B. Collip. Within the frame of this project, it was my task to assay many glandular extracts, for their possible sex-hormone effects, on ovariectomized or hypophysectomized rats, using mainly histologic criteria as indicators of potency.

The technique of hypophysectomy.

I was entrusted with this part of the departmental research program, because my earlier training happened to be mainly in the fields of experimental surgery and morphology. Although, a few years earlier, Philip Smith had already succeeded in hypophysectomizing rats, the method he used required extraordinary surgical skill and was far too time-taking and risky for routine bio-assay purposes. It had taken me most of my time during 1932-1933 to develop the greatly simplified technique which is now in general use. It is therefore understandable that, during the succeeding years, I was particularly anxious to employ it somehow in the study of the numerous endocrinologic problems, which can be solved only by experimentation on large numbers of hypophysectomized animals. The identification and separation of individual anterior pituitary hormones and a systematic study of the manifold interactions between the hypophysis and the gonads, might be mentioned as examples of the kind of topic that occupied the center of our interest during those years.

As a background for "The Story of the Adaptation Syndrome," perhaps the most important result of

these investigations was the identification of what we now consider the principal "adaptive hormones" of the anterior lobe. Up to that time, it had been known only that hypophysectomy causes involution of the adrenal cortex and cessation of growth, while pituitary implants or crude extracts restore the growth rate and adrenal structure to normal. It was impossible to demonstrate with certainty, however, whether these effects were exerted through specific separate hormones of the anterior lobe. Using various pituitary extract fractions prepared by Professor Collip, we could show on my hypophysectomized rats, on the basis of histologic criteria, that fractions capable of actively stimulating growth did not exert any appreciable degree of adrenal cortical, gonadal or thyroid stimulation. Conversely, other extracts were capable of more or less selectively stimulating the adrenal cortex. From this we concluded that the "growth" or somatotrophic hormone, as well as the adrenocorticotrophic hormone of the anterior lobe, must be chemically distinct entities.[2]

The search for a new hormone.

Then, in the course of 1935, certain theoretic considerations led me to suspect that in addition to the so-called folliculoids (or "estrogens") and luteoids (progesterone) — which were already known at that time — the ovary might produce hormones having qualitatively different actions. I shall not detain you with a description of the reasons for this belief; it subsequently turned out to be erroneous anyway. Yet, — embarrassing as this may be — I must mention it since it was not a well-planned, systematic study, but an accidental observation, made in the course of experiments inspired by this faulty theory, that eventually led to the discovery of the adaptation syndrome.

(2) Collip, J. B., H. Selye and D. L. Thompson: "Beiträge zur Kenntnis der Physiologie des Gehirnanhanges." Virchows Arch. f. path. Anat. *290*:23 (1933).

As it is customary in sex hormone studies, we had to inject both ovariectomized and hypophysectomized rats with the extracts of ovaries and placentae, which we suspected might contain the "new ovarian principle." Then, we examined the organs of these animals to see whether any of the changes produced would be different in kind from those normally elicited by the known ovarian hormones.

A peculiar triad of manifestations.

Much to my satisfaction, such lesions were immediately obvious, using even the most impure extracts. In ovariectomized rats, these preparations caused: (1) a considerable adreno-cortical enlargement (with a discharge of the secretory granules from the cortical cells and intense mitotic proliferation, especially in the zona fasciculata), (2) acute involution of the thymico-lymphatic apparatus and (3) the appearance of bleeding ulcers in the stomach and duodenum. Hypophysectomized rats did not tolerate these extracts well and never responded with adreno-cortical stimulation or thymico-lymphatic atrophy; however, many of them developed gastro-intestinal ulcers.

This peculiar triad of manifestations (adreno-cortical stimulation, thymico-lymphatic atrophy and gastro-intestinal ulcers) could not be reproduced with any of the known ovarian hormones; hence, it was rather tempting to attribute it to the presence in the ovary of some additional, hitherto unidentified, principle or principles—presumably of hormonal nature.

The great happiness.

You may well imagine my happiness! At the age of twenty-eight I seemed to be already on the track of a new hormone and had a perfect bio-assay method

which would serve as a basis for its, no doubt imminent, isolation.

Unfortunately, this happiness was not to last long.

That both ovarian and placental extracts gave positive results, as judged by the above indicators, did not worry me much; after all, we knew that the placenta also produces ovarian hormones. We were somewhat confused, however, when we subsequently found that anterior pituitary extracts likewise produce such changes — and that even in ovariectomized rats. The gonadotrophic sex hormones of the pituitary (FSH, LH), which had already been identified by that time, were supposed to act only through the intermediary of the gonads. Yet, even this was not too disturbing, since mine was supposed to be a new hormone. As far as we knew it might be elaborated by several endocrines, and could act directly.

However, when, a little later, it became evident that extracts (or even mere implants) of the kidney, skin, spleen or any other organ would produce the same syndrome, I became puzzled. Was the causative factor some kind of a "tissue hormone," an ubiquitous biologic principle (such as histamine, or products of proteolysis) that might arise from almost any cell?

Another confusing finding was that all our efforts to purify the active extracts led to a diminution of potency. The crudest preparations, and mere tissue implants, were invariably the most active.

The great disappointment.

I shall never forget one particularly dark rainy afternoon, during the spring of 1936, when the great disappointment came. I was sitting in my small laboratory brooding about the ever increasing volume of data which by now had made it improbable that my "active principle" could be a new hormone. Yet, the

changes produced with these extracts were very real and constant. There must have been something in these preparations to account for such characteristic effects. But what was it?

It was then that a horrible thought occurred to me: for all I knew, this entire syndrome could be due merely to the impurity and toxicity of my extracts.

In this case, of course, all my work meant nothing. I was not on the track of a new ovarian hormone, indeed not even dealing with any specific "ubiquitous biologic principle," but merely with damage as such.

Formalin is also effective.

At that very moment, my eyes happened to fall upon a bottle of formalin, which was kept on a shelf together with many other histologic fixatives, in front of my desk. Formalin is, of course, a particularly damaging substance, which precipitates the proteins of all living cells, thus "fixing them" for histologic study. If my syndrome was really due only to tissue damage, I should be able to reproduce it by injecting rats with a diluted formalin solution. This, I immediately proceeded to do, and within forty-eight hours, when these animals came to autopsy, they showed adrenocortical enlargement, thymico-lymphatic atrophy and gastro-intestinal ulcers of greater intensity than I had been able to produce with any extract.

I do not think I have ever been more profoundly disappointed!

Suddenly all my dreams of discovering a new hormone were shattered. All the time and all the materials that went into this lengthy study were wasted. I tried to tell myself: you must not let this sort of thing get you down; after all, fortunately nothing was published about the "new hormone," so that no confusion was created in the minds of others and there was nothing

to retract. I tried to tell myself over and over again that such disappointments are inevitable in a scientist's life; occasionally anyone can follow a wrong track and it is precisely the vision necessary to recognize such deviations that characterizes the reliable investigator. But all this gave me very little solace and, indeed, I became so depressed that for a few days I could not do any work at all. I just sat in my laboratory meditating about how this could have been avoided and what was to be done now.

Eventually I decided that, of course, the only manly thing to do was to admit defeat, forget this unfortunate affair as rapidly as possible and return to some of the more orthodox endocrinologic problems that had occupied my attention before I was side-tracked into this adventure. Among these were: hormonal correlations during pregnancy and lactation, the physiology of parathyroid hormone, the identification of anterior pituitary hormones and anti-hormones. These were also interesting topics, and in any of these fields I had the singular advantage in Montreal of being able to count on the guidance and co-operation of one of the great masters of hormone research, my chief, Professor Collip, who worked on these topics from the biochemist's point of view. Yet, somehow I could neither dismiss this finding nor pull myself together to do anything else in the laboratory for several days.

The ensuing period of introverted contemplation turned out to be the deciding factor in pointing the way for all my subsequent scientific efforts.

A new point of view.

As I continued to go over my ill-fated experiments and their possible interpretation, it suddenly struck me that one could look at them from an entirely different angle. If there is such a thing as a single non-

specific reaction of the body to damage of any kind, this may be worthy of study for its own sake. Indeed, the elucidation of such a stereotypical "syndrome of response to injury as such" may be much more important than the discovery of yet another sex hormone.

As I repeated to myself: "a syndrome of response to injury as such," gradually my early lecture-room impressions of the clinical "syndrome of just being sick" began to reappear dimly out of my subconscience, where they were buried for so many years. Could it be that these manifestations in man (the feeling of being ill, the diffuse pains in joints and muscles, the gastro-intestinal disturbances with loss of appetite, the catabolism, etc.) were in some manner clinical equivalents of the experimental syndrome (adreno-cortical stimulation, thymico-lymphatic atrophy and gastro-intestinal ulcers) that I had produced with such a variety of toxic substances in the rat?

Could the "stress-anestrus" which Tom McKeown and I had studied a few months earlier, be the equivalent of the amenorrhea that occurs in women during exposure to infections, malnutrition or emotional strain?

If this were so . . . !

If this were so, the general medical implications of this syndrome would be enormous! Some degree of non-specific damage is undoubtedly superimposed upon the specific symptomatology of any disease and of any drug used to treat disease.

. . . non-specific injury would mask the characteristic effects of all diseases and remedies and . . .

If this were so, everything we had learned about the characteristic manifestations of disease and about the specific actions of drugs would be in need of revision. All the actually observed biologic effects of stimuli must represent the sum of their specific actions and of this non-specific response to damage that tends to mask the former!

. . . one might combat damage as such.

If this were so, it would mean that my first classroom impressions, about the one-sidedness of medical thinking, were quite justified and by no means purely academic points without practical issue. Evidently, if the "damage syndrome" is superimposed upon the specific manifestations of all diseases and remedies, a systematic inquiry into its mechanism should furnish us with a solid scientific basis for the treatment of damage as such.

Non-specific therapy . . .

It had long been known, empirically, that certain measures are useful to patients suffering from almost any disease. Indeed, such measures had been in use for centuries. One advises the patient to go to bed and to avoid both physical and mental exertions; one tells him to take an easily digestible diet and to protect himself against great variations in temperature, humidity or draught. Furthermore, in many quite unrelated maladies, certain "non-specific therapeutic agents" have been prescribed in the form of drugs (injections of foreign proteins, pyrogens or colloidal metals, shock-therapy with insulin or metrazol) or physical agents (such as electro-shock, exposure to cold or heat, balneologic and climatologic therapy, ultraviolet rays, diathermy, blood-letting). However, the indications for these measures had to be worked out purely by experience and many of them fell into disrepute because it was not clear why and how they would act. Others have been generally accepted, but — for these same reasons — their uses could not be extended beyond a few accidentally observed applications.

. . . might be objectively analyzed and scientifically improved.

Now, if we could prove that the organism has a general non-specific reaction-pattern with which it can meet damage caused by a variety of potential pathogens, this defensive response would lend itself to a

strictly objective, truly scientific analysis. By elucidating the mechanism of the response through which Nature defends herself against injuries of various kinds, we might learn how to improve upon this reaction whenever it is not optimal.

I was simply fascinated by these possibilities and immediately decided to reverse my plans for the future. Instead of dropping the stress problem and returning to orthodox endocrinology, I was now prepared to spend the rest of my life studying this non-specific response. — I never had any reason to regret this decision.

The voice of experience offers advice.

It may help the younger members in the audience, those who are struggling to find their proper medium for scientific endeavor, to point out that I often had to overcome considerable mental inhibitions in my efforts to carry on with this plan. Nowadays it is perhaps difficult to appreciate just how absurd this plan seemed to most people before we had more facts to substantiate it. For example, I remember one senior investigator whom I admired very much and whose opinion meant a great deal to me. I knew he was a real friend who seriously wanted to help me with my research efforts. One day — during these hectic weeks — he asked me into his office for a good heart-to-heart talk. He reminded me that for months now, he had attempted to convince me that I must abandon this futile line of research. He assured me that, in his opinion, I possessed all the essential qualifications of an investigator and that I could undoubtedly contribute something, even to the generally recognized and accepted fields of endocrinology, so why bother with this wild-goose chase?

I met these remarks only with my usual outbursts of uncontrolled juvenile enthusiasm for the new point of view; I outlined again the immense possibilities inherent in a study of the non-specific damage which must accompany all diseases and all but the mildest medications.

When he saw me thus launched on another enraptured description of what I observed in animals treated with this or that impure toxic material, he looked at me with desperately sad eyes and asked in obvious despair:

"The pharmacology of dirt."

"But, Selye, try to realize what you are doing before it is too late! You have now decided to spend your entire life studying the pharmacology of dirt!"

Of course, he was right. Nobody could have expressed it more poignantly; that is why it hurt so much that I still remember the phrase after some 17 years. Only that to me the "pharmacology of dirt" — i.e. the response to non-specific damage as such — seemed the most promising subject in medicine.

Yet, as time went by, I often doubted the wisdom of my decision. So few among the recognized, experienced investigators, whose judgement one could usually trust, agreed with my views and, after all, was it not silly and pretentious for a beginner to contradict them? Perhaps I had just developed a warped point of view, perhaps I was merely wasting my time?

Banting's tap on the shoulder.

In such moments of doubt, I derived considerable fortitude and courage from the fact that, right from the beginning, one of the most respected Canadian scientists, Sir Frederic Banting, was manifestly interested in my plans. At that time, he was often visiting university laboratories throughout the country

since he acted as an advisor to the Canadian National Research Council. When in Montreal, he often dropped in quite informally into my somewhat overcrowded little laboratory. There was not much space and he usually settled down on top of the desk listening with interest to my day-dreaming about the "syndrome of being sick." Nothing could have done me more good! He also helped to secure the first modest financial aid for this kind of research, but that was comparatively unimportant. More than anything in the world I needed his moral support, the reassuring feeling that the discoverer of insulin took me seriously.

I often wonder whether I could have stuck by my guns without his tap on the shoulder.

Plans for future research.

The next point to decide was how to go about studying this new syndrome.

Right from the start, a multitude of questions arose:

(1) To what extent is this syndrome really non-specific?

(2) Apart from those already observed, what other manifestations are part of it?

(3) How does it develop in time? Is the degree of its manifestations merely proportional to the magnitude of the damage at all times, or does the syndrome — like many infectious diseases — go through distinct stages in a certain chronologic order?

(4) To what extent are the manifestations of the non-specific syndrome influenced by the specific actions of the agents which elicit it?

(5) What could we find out about the mechanism, the "dynamics," of this reaction; that is, the pathways through which the various organ changes are elicited?

These and many other questions not only presented themselves quite spontaneously, but became immediately amenable to objective scientific analysis, as soon as the concept of the "non-specific syndrome" had crystallized. We were convinced that it was only a matter of time now to find the answers to all these questions, which could not even have been asked before the theory of a single "stereotypical response to damage" had taken a precise form.

How non-specific is this syndrome ?

I thought that our first query should be: just how non-specific is our syndrome? Up to now, we had elicited it only by injecting foreign substances (tissue extracts, formalin). Subsequent experiments showed that one can produce essentially the same syndrome with purified hormones (e.g., adrenaline, insulin), physical agents (e.g., cold, heat, x-rays), trauma (intense sound or light), hemorrhage, pain or forced muscular exercise; indeed, *we could find no noxious stimulus that did not elicit our syndrome.*

The first semantic difficulties.

It is at this point that I first became painfully aware of the purely semantic difficulties arising out of new points of view in medical research. Novel concepts require new terms with which to describe them. Yet most of us dislike neologisms, perhaps because, especially in the naming of clinical syndromes and signs, new names are so often proposed merely to give a semblance of a new point of view. Of course, a designation, if badly chosen or redundant, can confuse more than clarify. However, now we clearly needed terms for two things: firstly, for the non-specific reaction itself, and secondly, for its evocative stimulus.

My first paper on this subject, (which incidentally took up only 74 lines of a single column) came out

on the 4th of July(!) 1936 in the British journal "Nature." It was entitled: "A Syndrome Produced by Diverse Nocuous Agents." (3)

Stress hides behind a pseudonym.

By that time, yielding to adverse public opinion, I had temporarily abandoned the term "stress," as employed in the paper on the stress-induced anomalies of the sexual cycle. There was too much criticism of my use of the word "stress" for endocrine and other non-specific somatic reactions. I did not want to obscure the real issues by semantic squabbles and I hoped that "nocuous" or "noxious" would be considered less obnoxious than "stress" until the concept were better understood.

The "Alarm Reaction."

In this same paper, I also suggested the name "alarm reaction" for the initial response, as described above, arguing that it probably represents the somatic expression of a generalized "call to arms" of the body's defensive forces.

The "Stage of Resistance."

However, this alarm reaction evidently was not the whole response. Our first pertinent experiments immediately showed that upon continued exposure to any noxious agent capable of eliciting this alarm reaction — unless it kills within a day or so — a stage of adaptation or resistance ensues. In other words, no living organism can continuously be maintained in a state of alarm. If the agent is so drastic that continued exposure is incompatible with life, the animal dies during the alarm reaction within the first hours or days. If it can survive at all, this alarm reaction is necessarily followed by a second stage which we called the "stage of resistance." The manifestations of this second stage were quite different from — and in many instances, the exact opposite of — those which

(3) Selye, H.: "A syndrome produced by diverse nocuous agents." Nature, London. *138*: 32 (1936).

characterized the alarm reaction. For instance, during the alarm reaction, the cells of the adrenal cortex discharged their secretory granules into the bloodstream and thus became depleted of storage material; in the stage of resistance, on the other hand, the cortex became particularly rich in secretory granules. While in the alarm reaction, there was hemoconcentration, hypochloremia and general tissue catabolism, during the stage of resistance we noted hemodilution, hyperchloremia and anabolism with a return towards normal body weight.

The "Stage of Exhaustion."

Curiously, after still more prolonged exposure to any of the noxious agents we used, this acquired adaptation was lost again. The animal entered into a third phase, the "stage of exhaustion," whose symptomatology was in many respects strikingly similar to that of the initial alarm reaction.

All these observations led us to suggest that an additional all-embracing name for the entire syndrome was required. Since the latter appeared to be so evidently related to adaptation, we called the whole non-specific response the "General Adaptation Syndrome" (G-A-S), emphasizing that it evolves in the three stages:

1. — The alarm reaction (A-R)
2. — The stage of resistance (S-R)
3. — The stage of exhaustion (S-E).

Why general adaptation syndrome ?

We called this syndrome "general" because it is elicited only by those agents which cause a general condition of stress (in that they affect large portions of the body) and in turn it evokes generalized, that is, systemic defense phenomena.

We called it "adaptive" because it helps the acquisition and maintenance of a state of inurement.

We called it a "syndrome" because its individual manifestations are co-ordinated and even partly interdependent.

Now that we have got that far with the story of stress, let us stop for a moment to intercalate a few thoughts about research in general, considerations which I think it might be opportune to bring before you at this point.

Because you look at something you do not necessarily see it.

I see many young people in this audience, presumably students and recently graduated physicians. I suppose many among you would like to try your hand at medical research, but fear — as I did when I started — that the odds are too heavily against you. When one starts out in this career, it is somewhat discouraging to think that through so many centuries, so many outstanding investigators have explored the salient problems of medicine and hence, presumably most of the important things have been discovered already.

My students often tell me that, in their opinion, to make really interesting discoveries today, it is indispensable to have at one's command: large sums of money, modern laboratories equipped with all kinds of complicated, expensive machinery and preferably a large staff of highly trained assistants. They point out that nowadays it would be difficult to discover the adrenal glands as Eustachius did in 1563, by merely dissecting the fat around the upper pole of the kidney. We can no longer have the satisfaction of recognizing the relationship between pituitary tumors and the syndrome of acromegaly, because Pierre Marie had already done that in 1886.

Only the future will be able to tell us just how much good the adaptation syndrome has done for the understanding of disease, the relief of human suffer-

ing and the progress of medicine in general. But if in these respects it should prove of some value, I feel that you, the scientists of tomorrow, might derive encouragement from the knowledge that the G-A-S was found without any of the above mentioned laboratory luxuries, or even — had I had them at my disposal — the wisdom and experience that would have been necessary to use them.

Fortunately, it is not so much the existence of things that we do not know, or about which we are too uncertain, that handicaps our research, but the existence of things we do know and about whose interpretation we are quite certain . . . although it is false.

You will recall that the indices of stress, upon which the concept of the adaptation syndrome was based, were: adreno-cortical enlargement and hyperemia, gastro-intestinal ulcers, thymico-lymphatic atrophy and anomalies of the sexual cycle with failure of follicle maturation. Then came the realization that this syndrome is triphasic, with the initial appearance of marked acute manifestations (alarm reaction), their subsequent disappearance (stage of resistance) and finally a breakdown in the organism, with complete loss of resistance (stage of exhaustion). These were the facts upon which the note on: "A syndrome produced by diverse nocuous agents" was based. All these criteria are readily visible by naked-eye inspection; hence, a pair of scissors with which to open my rats was the only instrument required. The production of stress by trauma, starvation or the feeding of toxic substances, certainly necessitated no complicated apparatus. Let me assure you that exposure to cold was likewise no problem in Montreal during the major part of the year, especially in the McGill

Medical Building with its conveniently wind-swept flat roof. It is true I did use a syringe for the injection of formalin and even then I had a "staff" in the person of Mr. Kai Nielsen who, at that time, was an untrained laboratory assistant and helped me mainly by holding the rats and by the stabilizing effect of his always friendly, even-minded Scandinavian personality.

In the intervening years, I went to infinite trouble studying this same syndrome with every available modern weapon of histology, chemistry and pharmacology. I have been given the means to construct one of the best equipped Institutes of Experimental Medicine in the world and have acquired a large staff of highly trained assistants. Yet today, in 1952, as I look back upon the years that elapsed since those early observations in 1936, I am ashamed to say that, despite all this help, I have never again been able to add anything comparable in its significance to those first primitive experiments.

Mr. Nielsen.

I am glad to report that Mr. Nielsen is still with me today and has in the meantime learned a great many complex laboratory techniques. He is in charge of an entire team of technicians and — as my illustrations will testify — has also become an expert micro-photographer. Yet, in retrospect, when everything is said and done, I feel somehow that in 1936, when we were both young, as well as now in 1952, when we are a little less so, his undoubtedly enormous contribution to the study of stress was very simple. He always was, and still is, an utterly reliable, straight-forward person and a warm-hearted friend upon whose level-headed judgement one can count to keep things straight around the lab. Let me assure you that in the actual practice of research, these solid characteristics of an associate can be much more useful than the most highly trained staff of assistants; just as simple thoughts connecting simple observations often help you to come much closer to a real understanding of Nature, than if you put complexities in the way of an intimate contact with her.

What do you need in order to do research ?

At this stage of your careers you may not possess, or even know how to use, the intricate facilities of a modern research institution, but all of you may derive encouragement from the thought that you need but

your eyes to see a whole forest. It is only for the detection of some minute detail, for instance, a granule in a cell of one tree within this forest, that you require a microscope.

My advice is: try to look for the mere outlines of big things with your fresh untrained and unbiased minds. When you are older, you may no longer be able "to see the forest for the trees" — but then you will have the money to buy an electron-microscope and to hire an assistant who knows how to use it. If sufficiently pressed, he will discover some hitherto undescribed cell detail for you.

You may feel that all this had nothing to do with the adaptation syndrome about which you came to hear. Don't you believe it! On the contrary, to me these were the thoughts that really counted, and that is why I feel I must share them with you. If you come to think of it, the adaptation syndrome could have been discovered during the middle-ages, if not earlier; its recognition did not depend upon the development of any complicated pieces of apparatus, new techniques of observation, nor even upon much ingenuity or intelligence, as far as that goes, but merely upon an unbiased state of mind, a fresh point of view.

I think it is well for those on the threshold of a scientific career who have no complex machinery or even an extensive training at their disposal, to realize fully that there are two ways of detecting something that no one can see: one is to aim at the finest detail, by getting as close to the object as possible, with the best available analyzing instrument; the other is merely to look at it from a new angle, where it shows hitherto unexposed facets. The former requires money and experience, the latter presupposes neither of these; indeed, it is actually aided by the lack of prejudice and the absence of those established habits of thinking which tend to come after long years of study.

But let us get on with the story!

The term "Stress" emerges victorious . . .

By now, little by little, the main characteristics of the G-A-S had been recognized and named, but we still had no precise idea of the actual evocative factor and, of course, even less a suitable name to describe it. I spoke of "nocuous agents," but this term was soon found to be inadequate. Even such physiologic stimuli as a brief period of muscular work, excitement or a short exposure to cold, were sufficient to produce certain manifestations of an alarm reaction, for instance, an adreno-cortical discharge. Obviously, these could not be described as strictly "nocuous" agents, and hence a more precise designation was required.

In search for such, I again stumbled upon the term "stress," which had long been used in common English and particularly in physics to denote the sum of all forces (no matter what forces) which act against a resistance. For example, the changes induced in a rubber band during traction, or in a spring during pressure have all been described as stress phenomena. Thus physical stress is certainly a non-pecific reaction. It seemed to me that the non-specific manifestation of the adaptation syndrome are the biologic equivalents of what had been called stress in inanimate matter. Perhaps one could best describe them as "biologic stress."

The term had the additional advantage that it was not strictly a neologism even in medicine. The expressions nervous "stress and strain" had often been used by psychiatrists to describe mental tension. Although it had not been applied previously to any non-specific somatic changes, such as a histologic lesion

or a derangement in the chemical constitution of the body, I saw no reason why it should not be used in this sense, and during the subsequent years — despite the initial opposition — I again began to speak of somatic stress, first quite informally in lectures and later even in publications.

None of these terms, "alarm reaction," "G-A-S," "stress" etc., was immediately well received, but since they have now become part of the medical vocabulary in every language, we need not go into lengthy semantic discussions in their defense.

. . . but creates more semantic trouble.

It is of psychologic interest, however, to recall the particularly great resistance against my use of the word "stress," because here rejection of the name was largely dependent upon a failure to grasp the concept itself. Again and again, in the discussion periods that followed my lectures on the G-A-S, someone would get up and ask why I have to speak of "stress" when I actually used formalin, cold or x-ray. Would it not be more straight-forward to say that the adrenals are stimulated by cold, when it was to cold that the animals were exposed? I tried to point out that it could not be cold itself that is necessary for adrenal stimulation, since heat or any number of other agents exert the same effect. By way of a simile, I mentioned that a pharmacologist interested, say, in the effects of ether, should not look upon adreno-cortical enlargement, or thymico-lymphatic involution, as being the effects of ether in the same sense as anaesthesia is. Indeed, I emphasized that now, in my opinion, one would have to re-examine the whole of pharmacology to distinguish the changes due to stress from those caused by specific drug actions.

Stress is an abstraction

This same kind of objection was formulated by others in a slightly more articulate manner, by pointing out that actually stress is an abstraction and does not occur as such in the pure state. In other words, it is just a purely hypothetical entity which possesses no actual reality or independent existence.

Hence, my opponents said, it is impossible to isolate stress for the objective, direct, scientific observation of its own characteristics, which would be a prerequisite for any scientific approach to this problem. You cannot study stress; you can merely explore the effects of real and tangible factors, such as exposure to cold, injections of formalin, infections, etc. . . . For these reasons, I was told, even if we admitted the existence of stress, it would not lend itself to a really scientific study.

Of course, it must be admitted that "stress" is an abstraction; but "life" is also an abstraction, and yet, it could hardly be rejected as a worthless concept in biology. No one has studied life in a pure uncontaminated form. It is always inseparably attached to something else which is more tangible and seemingly more real, such as the body of a cat, a dog or a man; still, the whole science of physiology is built upon this abstraction.

However, I must admit that during the first few years such arguments convinced but a very few people. It was only gradually, through habit rather than logic, that the term slipped into common usage, as the concept itself became a popular subject for research.

The "stressor."

Even after that, when everyone began to speak of stress, I was again exposed to severe criticism because of a new terminologic difficulty. It was pointed out that the word stress is indiscriminately applied both to the agent which produces the general adaptation syndrome (some people speak of cold-stress,

adrenaline-stress, etc.) and to the condition of the organism that is thus exposed. This impressed me as a justified criticism and I therefore proposed to substitute the word "stressor" for the agent and stress for the condition. In this sense, cold, adrenaline, etc. may be designated as stressor agents, although, of course, it was always tacitly understood that by cold-stress, one meant stress caused by cold.

Lectures at the Collège de France.

More recently, yet another unforeseen complication arose, namely, that stress cannot be translated accurately into foreign languages. I became acutely aware of this in 1946, when the Collège de France honored me by an invitation to give a series of lectures on the adaptation syndrome in Paris.

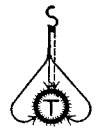
Now, I was to speak in this famous Research Institute in which, a hundred years ago, Claude Bernard himself delivered his classic lectures on adaptation, or at least on the importance of maintaining the constancy of the "milieu intérieur." Since I was to speak there as a representative of a French-Canadian university, I took great pains to deliver my lectures in good French. This appeared all the more important since it is the charming tradition of this venerable Institution of learning to honor visiting foreign lecturers — at least at the occasion of their inaugural address — by the presence of all the professors of the Collège de France, irrespective of their personal fields of interest. This meant that right in the first row, in front of me, sat several of the most famous litterati of France. You may well imagine that my linguistic responsibilities weighed heavily upon my shoulders! Yet, I had to use at least one anglicism, the word "stress," as I could not think of a proper French substitute for it.

The need of a French term for stress.

After my lecture, there ensued a rather spirited debate between the men of letters as to the correct translation of "stress." I feel quite incompetent to give you an adequate account of the erudite, scholarly discussions which followed, but you may be interested to learn their end-result. After eliminating as unsuitable, one by one, such terms as "aggression," "tension," "détresse," and many others, the unanimous conclusion was that there is no exact equivalent, but that one must necessarily be coined. Upon weighing the matter carefully, it was decided first that the gender of stress would have to be masculine. Then it was agreed that the best French term for it would be: "le stress."

Thus, a new French word was born and this experience did much to encourage me during subsequent lectures in Germany, Italy, Spain and Portugal, to speak without the slightest hesitation of "der Stress," "lo stress," "el stress" and "o stress," thus giving me the satisfaction of having enriched all these (and subsequently many other) languages by at least one word.

So much for the painful delivery which gave birth to the stress concept and the complex problem of properly naming the child and its various parts. Next time I shall describe our first experiments concerning the nature of "adaptation energy" and the dynamics of the adaptation syndrome.



SECOND LECTURE

Dynamics of the Adaptation Syndrome. Rôle of the Adrenal Cortex and of the Anterior Pituitary.

Ladies and Gentlemen!

IN THE FIRST LECTURE OF THIS SERIES, we surveyed the fundamental observations and thoughts which gradually led to the formulation of the stress concept. We have seen how, by the end of 1936, it became quite clear that the most diverse agents provoke an entirely non-specific and rather stereotyped pattern of reaction, in which the whole body participates. This response of alertness, the general adaptation syndrome or G-A-S, is to some extent superimposed upon every reaction of the body in health and disease. Evidently all the earlier observations concerning the specific characteristics of maladies or drugs, must have been vitiated — one might say "contaminated" — by this superimposed mantle of non-specific stress.

The descriptive approach.

One could compare this situation with that of a man who looks at a landscape through blue glasses and is never certain whether the apparently blue color of an object is real or merely simulated by his spectacles.

After realizing that we were forever condemned to look at medicine through "stress-colored" glasses,

it was obviously of importance to study the characteristics of the glasses themselves.

The great question was how to go about this. In other words how could we best dissect and analyze the G-A-S?

You can study and appraise an animal the way a naturalist does, descriptively, by examining its appearance and habits; or you can investigate it from the anatomist's and physiologist's point of view, by taking it apart to explore its internal structure and the mechanism through which its individual components work. Usually, in the natural sciences, the former approach precedes the latter, and this was also the case with our inquiry into the nature of the adaptation syndrome. At first, we just produced a G-A-S by exposing animals to a variety of stressors, and studied the syndrome as a whole without making any effort to break it up into its components.

Similarities between the G-A-S and inflammation.

This kind of investigation led us to realize that the G-A-S develops in three distinct stages and that it is non-specific inasmuch as almost any agent can produce it. Both the obligatory development through distinct phases and the non-specificity of the syndrome immediately reminded us of another biologic response, equally as important and as common as the G-A-S, but one which was known to man for many centuries: inflammation.

Like the G-A-S, the acute inflammatory tetrade of swelling, redness, heat and pain necessarily progresses through definite stages; it eventually ends in abscess formation, with a breakdown of tissue or replacement of the inflamed area by a solid scar. Just as systemic stress cannot keep the whole body indefinitely in the acute alarm reaction stage of the G-A-S, so is it

impossible to maintain any part of the body continuously in the acute initial stage of inflammation.

Indeed, the resemblance goes even further, because of the great non-specificity of the two responses. It seemed rather significant that *any* stimulus — if sufficiently severe and prolonged — can put the whole organism through the three stages of the G-A-S, while *any* local irritant (e.g., mechanical trauma, micro-organisms, cold, heat, ultraviolet or ionizing radiations) can evoke an inflammation at the site of application.

Yet another striking similarity between the G-A-S and inflammation is that both appear to be definitely "useful" reactions, the former being a systemic adaptive response of the whole body, the latter a topical defensive reaction limited to the directly injured area itself.

To summarize: both the G-A-S and inflammation are non-specific reactions which go through a series of distinct stages; both can be elicited by and can increase resistance to a variety of stressors.

Effect of G-A-S on inflammation.

There were other facts which led us to suspect some close correlation between the G-A-S and inflammation. For instance, during the alarm reaction, rats in which some tissue irritation was produced, e.g. by trauma or injection of egg-white (to which the rat is congenitally hypersensitive), did not show the usual inflammatory response to these agents. Apparently, the alarm reaction decreased the "inflammatory potential" of tissues throughout the body, so that various irritants (including allergens) were less than normally capable of causing inflammation. We concluded that in the face of stress-situations, which endanger the life of the whole body, local irritants are neglected "in favor of" systemic defense measures. But this was not

an explanation and we made no progress in our efforts to clarify the cause of this antiphlogistic effect until — as we shall see — other observations focused our attention upon the rôle of the adrenal cortex in the G-A-S. Then it was observed that adrenalectomy increases the sensitivity of the rat to the hyperergic inflammation caused by egg-white injections, while adreno-cortical extracts restore resistance to or above normal and exhibit a definite antiphlogistic effect.[1, 2] Evidently the alarm reaction exerts its antiphlogistic actions through the discharge of corticoids.

Crossed resistance.

This stress-induced increase in resistance was by no means limited to foreign protein reactions. During stress, animals tended to become more than normally resistant to a number of other agents as well. The production of inflammatory changes in the gastro-intestinal tract with histamine and the ability of adrenaline overdosage to cause hemorrhagic lung edema, were also diminished or abolished during the alarm reaction. In most of these and many other instances, the inhibition was primarily due to the suppression of inflammation and of capillary leakage, essentially antiphlogistic effects. In other cases, however, the mechanism of protection was not clear. Here we merely spoke of "crossed resistance" to denote that exposure to one stressor increased resistance to another kind of damaging agent, presumably due to the non-specific defensive value of the alarm reaction evoked by the former.

This purely descriptive period of research, during which we studied the G-A-S as a whole, without

---

(1) Selye, H.: "Studies on adaptation," Endocrinology, *21*, 169 (1937).
(2) Léger, J.: "Contribution à l'étude des phénomènes d'hypersensibilité," Ph.D. thesis, University of Montreal (1948).

attempting to dissect it into its constituent parts, yielded one other, rather fundamental, piece of information. It was observed that, depending upon the circumstances, stress can not only increase, but also decrease non-specific resistance; in fact, the latter is the more common result. This is what led to the concept of "adaptation energy" — to my mind the most important outcome of stress research to date.

Adaptation energy.

In the course of the first lecture, we have already had occasion to point out that, during long-continued exposure to the same stressor agent, the body first becomes adapted (stage of resistance); then, sooner or later, this acquired adaptation is exhausted (stage of exhaustion) and hence death ensues. Why is it that, even after the body has learned how to perform the necessary adjustments required by a change, the stage of resistance cannot be maintained indefinitely?

Let us illustrate this point by an example. A rat is placed into a very cold room of, let us say, 2°C. It gradually learns how to conserve heat, by constriction of the peripheral vessels in the skin, an increase in basal metabolism and so forth. A priori I would have thought that the animal should now be able to live just as long in this cold chamber as at room temperature, assuming that we furnish the necessary calories to produce adequate amounts of heat. Yet, experience showed that continued exposure to cold or, as far as that goes, to any other stressor, sooner or later inexorably leads to a breakdown of the adaptive powers; that is, exhaustion of what has been called the "adaptation energy".

Crossed sensitization.

Furthermore, an animal highly adapted to one stressor agent (e.g., cold) loses much of its resistance and adaptability to other stressors (e.g., drugs). We called this "crossed sensitization" and ascribed it to a

consumption of adaptation energy, necessitated by exposure to the first stressor agent. Adaptation energy (whatever this may be) proved to be a finite quantity of which each organism has only a given amount. Presumably, genetic factors determine just how much of it is apportioned to each new-born individual. Yet, whatever the total quantity, it may be used up very slowly during a long, monotonously restful existence protected against every kind of exposure, or it may be consumed rapidly to maintain life under ever-changing conditions, which require extreme efforts of adaptation. It appeared to be something like an inherited fortune which could be spent sparingly over a long, quiet lifetime, or rapidly in generous, large sums to cover the exigencies of a vigorous and eventful existence.

Can adaptation energy be regenerated?

Still, there is some evidence to suggest that adaptability or adaptation energy can be regenerated, at least temporarily, so that its total available amount may not be entirely fixed. For instance, the acute exhaustion induced by exposure of experimental animals to intense stressor agents (such as cold, muscular effort or infection) leads to death if the stress situation is long maintained. Yet, a complete and prolonged rest period can again restore considerable resistance and adaptability to subsequent exposure. It is highly probable that the total life span is nevertheless shortened by such intermittent periods of stress, but at least temporary rehabilitation of adaptability is undoubtedly possible.

This is nothing new. It has always been known that a long period of rest can restore strength, even to a man who had been on the verge of a breakdown. The great challenge was to translate the word "rest" into precise scientific terms by analyzing its intimate

mechanism. To what extent could it help us, for instance, to impart adaptation energy and, so to speak, recharge the run-down battery of life, if we learned more about the physico-chemical basis of exhaustion?

The problems posed by the concept of adaptation energy impress me as the most fruitful leads for further research that the G-A-S has given us. If someone in this audience could think of a fresh approach which would permit us to measure, isolate, regenerate or transmit this adaptation factor, I am sure he would do much more for medicine than we could ever hope to accomplish through adaptive hormones. Hence, even at the risk of becoming reiterative, I shall use yet another metaphor to clarify my meaning.

We might compare the utilization of adaptation energy to the wear and tear on an automobile, and the ingested food calories to its gasoline supply. An automobile has to refuel at frequent intervals to keep going, yet, even so, it cannot run forever. Sooner or later, it will get "tired" and will have to "rest" for minor repairs. These, however, can restore its efficiency to the original level. Depending upon "congenital factors" (the materials the car is made of and the type of its design) this kind of restoration will be possible for a shorter or longer period, but not indefinitely. As time goes on, repairs will, of necessity, become more and more frequent and time-taking. Then eventually, the wear and tear will be beyond repair.

Relationship between the exhaustion stage and aging.

Curiously, the structural changes observed in the organs of our animals, which died during the exhaustion stage of the G-A-S, greatly resembled the degenerative changes characteristic of old age. In view of the variable speed at which the exhaustion of adaptation energy can proceed, should one suspect

some relationship between normal senility and the "precocious aging" induced by life under stressful circumstances?

These were the great biologic problems suggested by the stress concept, and now we decided to proceed with the second stage of our investigations, which may be designated as the analytic period. But before we go on to speak about that, let us put down concretely, in the form of a diagram, the gains made up to the beginning of 1936, in the knowledge of the objective and measurable changes characteristic of the G-A-S. By that time, the fundamental constituents of our syndrome could be put down on paper as shown by the following synoptic drawing. (See pp. 52, 53.)

The analytic period. Dynamics of the G-A-S.

Now, our next problem was to elucidate the dynamics of the adaptation syndrome. To put it into more precise terms, we had to find out how a stressor — for instance, a trauma applied to one extremity — could find its way to the adrenals or the thymus and induce characteristic alarm-reaction changes in them. We felt that if we could elucidate such points, we would be in a much better position to influence the course of the G-A-S and to improve resistance by artificially complementing this syndrome wherever necessary.

Adreno-cortical stimulation is the clue.

For this whole second analytic period, the lead observation was the adreno-cortical stimulation. It was very striking, and quite unexpected to me, that exposure to a severe stressor should cause this change. During stress we found catabolism with tissue disintegration, cellular atrophy or even necrosis (that is, loss of living substance throughout the organism) resulting in a loss of body weight in all tissues, with the notable exception of the adrenal cortex. Only the

THE ADAPTATION SYNDROME

Among the characteristic changes of the alarm reaction, those which happen to have been observed first are:

(1) Acute *gastro-intestinal ulcers,* usually accompanied by signs of *damage* or shock (represented by a cross), such as a high mortality rate, catabolism, hypotension, hypothermia, hemoconcentration, etc.

(2) *Adreno-cortical stimulation,* evidenced by hyperemia and discharge of secretory granules from the adrenal cortex.

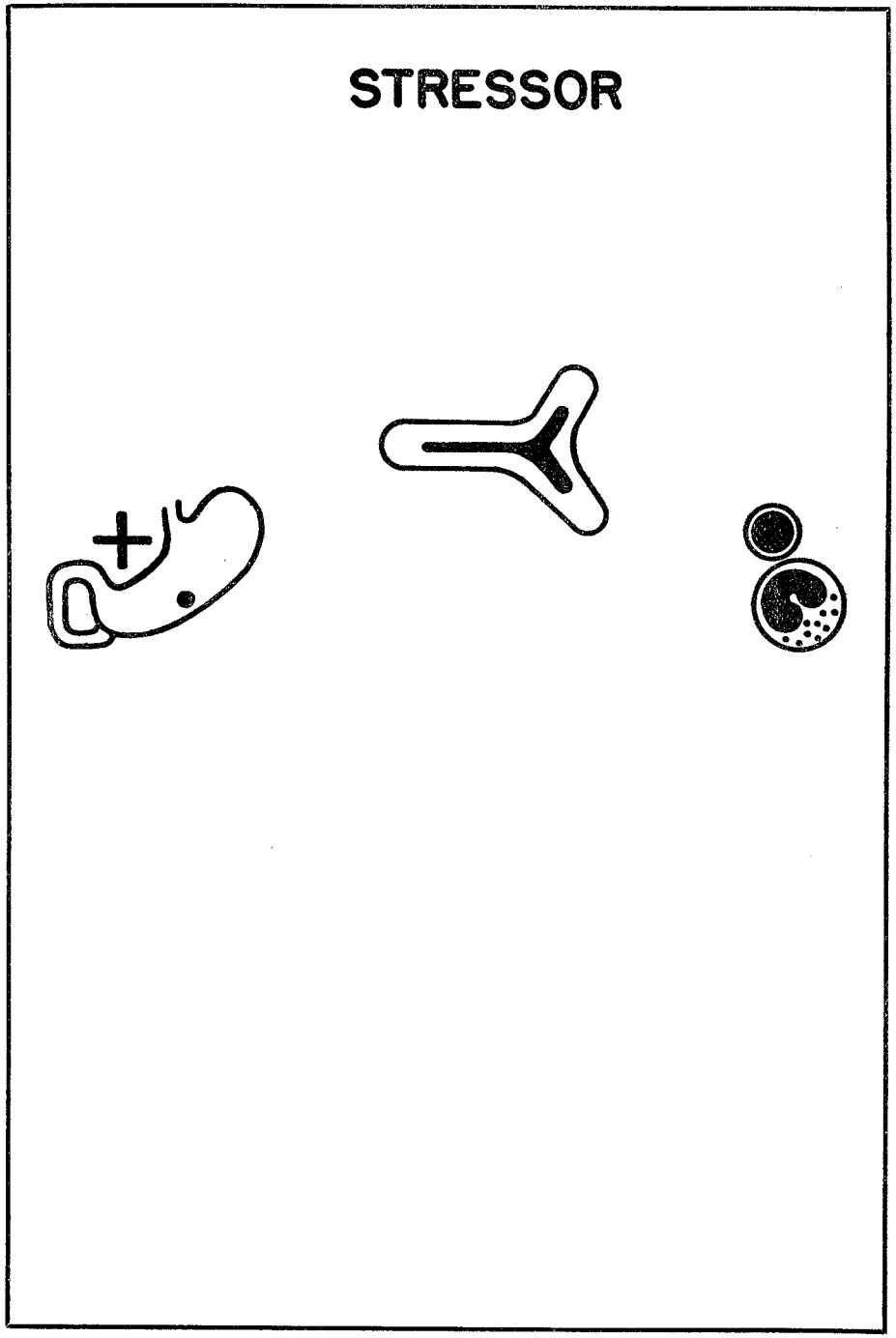
(3) *Thymico-lymphatic involution,* accompanied by characteristic *hematologic changes,* such as: lymphopenia, eosinopenia and polymorphonuclear leucocytosis.

As indicated in this diagram, it was also known by this time that the whole syndrome thus characterized is not produced by the specific actions of one agent or another, but by their non-specific *stressor* effects.

As we shall see later, it was a rather fortunate coincidence that the first observed manifestations of the adaptation syndrome happened to give us an example of each among the three different types of lesions characteristic of stress responses, namely: (1) signs of pure damage which have no manifest defensive value, (2) signs of increased activity in one of the endocrine glands (in this case the adrenal) concerned with the elaboration of adaptive hormones and (3) somatic changes caused secondarily through this stress-induced excess of adaptive hormones.

The great weakness of our schema at this stage was that it revealed nothing concerning the dynamics or mechanism of the stress response, a weakness which is graphically expressed here by the absence of arrows connecting the individual symbols. It was known that the stressor causes all these changes, but we could not indicate this pictorially since it was not known which among the three types of changes illustrated is caused directly by the stressor, and which is the indirect result of such a primary direct effect.

EARLY IN 1936



cortical cells of the adrenals were found actually "to thrive on stress."

The more we damaged an animal by heat, cold, infections, or even by complete starvation, the more the adrenal cortex grew.

This increase in size was not due to any degenerative swelling of its cells, but to enlargement of their active cytoplasm. It was usually associated with the appearance of many mitotic figures — that is, multiplication of cells.

Furthermore, the cortical lipid granules — presumably stored secretory products — which normally accumulate in the resting cells of the adrenal cortex, were rapidly discharged into the blood as if to aid in the fight against the damage caused by the stressor. These considerations suggested that a good way to commence the process of unravelling the adaptation syndrome would be: to adrenalectomize animals and then expose them to stressor agents. This, we felt, should help us to determine precisely how the absence of adreno-cortical secretion would influence the stress response.

Stress in the absence of the adrenals.

The ensuing animal experiments immediately taught us two important lessons:

(1) *Some manifestations of the adaptation syndrome depend upon the activity of the adrenals, since they are prevented by adrenalectomy.* — Among these changes, the most conspicuous were the involution of the thymico-lymphatic apparatus and the disappearance, from the circulating blood, of lymphocytes and eosinophils. In intact animals, such lesions were readily produced by any stressor agent, while after adrenalectomy they were absent, even in the face of fatal stress. This was particularly striking in starved animals, which normally exhibit an especially marked involution of most of their organs and particularly of their thymico-lymphatic apparatus, but after adrenalectomy fail to respond in this manner.

(2) *Other manifestations of the G-A-S were equally, or even more, pronounced after adrenalectomy; hence, they could be regarded with certainty as NOT being dependent upon an excess of adrenocortical hormones.* — Among these, one might mention the various signs of damage, such as: the general tissue wastage (except in thymico-lymphatic tissues), the gastro-intestinal ulcers, the drop in blood-chlorides, body temperature and blood-pressure, as well as other manifestations of "shock." This does not mean, of course, that the corticoids have nothing to do with this latter type of change, but merely that the stress-effects listed in this second category are not necessarily the direct results of increased cortical hormone production.

Proof by deficiency and by substitution or overdosage.

It is a general rule in endocrinology that two types of experiments must be carried out before one can conclude that a given organic change is normally due to the secretion of a certain hormone. First, one must show that extirpation of the endocrine gland, which produces this hormone, prevents the change. Then one must prove that, even after removal of this endocrine gland, the change can be artificially reproduced by suitably prepared extracts which contain the hormone of this gland. The first type of experiment is called the "proof by deficiency," the latter the "proof by hormone substitution or overdosage."

Let us illustrate this point by a generally known instance of a clear-cut endocrine relationship.

When it was not yet known that sex hormones are responsible for the development of the so-called secondary sex characteristics, for instance of the rooster's comb, the first experiments performed were of the deficiency type. It could be shown that after "caponization," the removal of the gonad, the rooster's comb involutes and becomes a pale, inconspicuous, protuberance on the head. This suggested that some gonadal principle is responsible for the normal development of the comb, but it did not prove it. Indeed, it is a historic fact that these first observations were combatted by scientists who thought that removal of the gonads might have caused some incidental damage to nerves and acted upon the comb through interference with neurogenic, rather than hormonal, stimuli. The final proof came only many years later, when it was shown that extracts of the male gonad can stimulate the capon's comb and restore it to the large size and bright red color characteristic of the intact rooster.

This same problem came up again in connection with the discovery of insulin. Removal of the pancreas was long known to cause diabetes in the dog, but most of the early physiologists ascribed this either to interference with the nerves in the vicinity of the pancreas or to the resultant absence of pancreatic secretions from the intestinal tract. Not until it was shown that pancreatic diabetes can be abolished by suitable extracts of the pancreas, has it been generally accepted that this disease is due to hormonal deficiency.

Many other examples of this type could be quoted, but these will suffice to show that it was imperative for us to demonstrate the possibility of inducing thymico-lymphatic involution, even in the absence of an adrenal gland, by means of some adrenal extract.

Substitution with adrenaline.

At that time, it was generally assumed that the principal hormone of the adrenal is adrenaline, a product of the medullary cells. Furthermore, the classic work of Walter Cannon had already demonstrated that excessive amounts of adrenaline are actually discharged from the medulla during fear, hunger and other nervous commotions, which, in our sense, could be described as stressors. It is natural, therefore, that we thought first of this hormone as being the crucial factor in the alarm reaction. Yet, we did not succeed in producing thymico-lymphatic involution in adrenalectomized animals, by adrenaline injections.

Substitution with adreno-cortical extract.

It was suggestive, furthermore, that signs of intense hyperactivity were also noted in the cortical cells of the adrenals, during stress. Hence, we directed our attention to the adreno-cortical hormones. At that time, these were not yet generally available in pure form for experimentation, so that we could not use cortisone, desoxycorticosterone or other steroids of this group. However, thanks to the investigations of W. W. Swingle, J. J. Pfiffner, F. A. Hartman and others, it had become possible to prepare a relatively impure, yet highly active adrenal extract which contained *the* "cortical principle," then known under the name of "cortine." We therefore proceeded to inject adrenalectomized rats with such crude cortical extracts and found that these, unlike adrenaline, were highly effective in causing thymico-lymphatic involution and changes in the blood-count, similar to those elicited by stressors in the intact animal. On the other hand, such extracts did not produce gastro-intestinal ulcers or manifestations of shock [3].

[3] Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." Brit. J. Exper. Path. *17*: 234 (1936).

At this point, I must make another small digression into semantics in order to avoid the possibility of misunderstanding the technical terms we use.

Corticoids.

When these experiments were performed, we had no reason to believe that the adrenal secretes more than one cortical hormone, namely "cortine." During the intervening years, it has become obvious, however, that there are several qualitatively different cortical hormones, hence the term cortine was no longer adequate. At that time, I suggested the use of the designation "corticoids" as a generic term for all those hormones which in some way imitate the physiologic function of the adrenal cortex.

Distinction between gluco- or antiphlogistic and mineralo- or prophlogistic corticoids.

Some of these hormones are especially effective in causing gluco-neogenesis, that is to say, sugar formation from non-sugars; these I called gluco-corticoids (G-C). Others proved to be especially active regulators of mineral metabolism in that they caused marked sodium chloride and water retention with simultaneous loss of potassium; for these, I suggested the term mineralo-corticoids (M-C).

It should be kept in mind, however, that the terms gluco- and mineralo-corticoids are based merely on certain biochemical effects of hormones which exert many other actions as well. From a general medical point of view, it is more important to emphasize that the glucogenic hormones are antiphlogistic-corticoids (A-C), in that they inhibit inflammatory reactions; while the mineral active cortical hormones are prophlogistic corticoids (P-C), in that they facilitate and exaggerate inflammatory responses.

We must, of course, foresee the possibility that future developments may reveal the existence of corticoids in which the gluco- and antiphlogistic activity,

on the one hand, or the mineralo- and prophlogistic activity, on the other hand, do not run strictly parallel. However, such instances have not yet been discovered; hence, for practical purposes we may now take the terms gluco- and antiphlogistic corticoids, as well as mineralo- and prophlogistic corticoids, as synonymous pairs of designations. They merely describe the same types of hormones from different viewpoints.

From a third point of view, it has been customary to speak of 11-oxy (or 11, 17-oxy) compounds on the one hand and 11-desoxy (or 11, 17-desoxy) compounds on the other, meaning anti- and prophlogistic corticoids respectively. This is grossly inaccurate for many 11-oxy and even 11, 17-oxy compounds have no antiphlogistic or gluco-corticoid activity whatever (e.g., all etiocholane, androstane or pregnane derivatives).

As we shall see, the identification of corticoids with qualitatively different types of pharmacologic activity had not been accomplished until a few years later than where we are with our story now. Yet, it should be mentioned right here that adreno-cortical extract, cortisone and hydrocortisone, are examples of substances with predominantly gluco- or antiphlogistic corticoid activity, while desoxycorticosterone and desoxocortisone are steroids whose predominant effect is of the mineralo- or prophlogistic corticoid type.

I will not bother to give you the chemical formulae of all these compounds; those of you who are chemically minded know them anyway, and those who are not, will find it quite simple to follow my story without burdening your memory with pictures which would have little real meaning for you in any case.

Although here we have deviated slightly from the chronologic order of presentation, with these parenthetic remarks about the terminology of the corticoids, I feel that this digression was necessary in order to eliminate an important source of possible misunderstandings. But now let us get back to the story where we left off.

We had just succeeded in blotting out part of the alarm-reaction picture by adrenalectomy, and in restoring this eliminated section (thymico-lymphatic and hematologic changes) by treatment with crude cortical extracts. Thus we had accomplished the first objective in our effort to elucidate the complex dynamics of the stress response.

The situation as we now saw it, at the end of 1936, is illustrated by the next synoptic drawing. (See pp. 62, 63.)

Now that the immediate cause of the thymico-lymphatic involution had been recognized to be "corticoids," our next task was to identify the other two arrows which, so far, had to be labelled merely with question marks. To use an example: by what messengers and through what pathways does a stressor, applied to the surface of the body (e.g., a skin burn), stimulate the adrenals or damage the organs which undergo purely degenerative changes?

The "first mediator of damage."

We need not spend much time discussing the mediation of damage ("shock," gastro-intestinal ulcers), since this problem still remains unsolved. Many possibilities have been considered; for instance, that histamine, or some histamine-like toxic tissue metabolite, may be produced during stress. Alternatively, it has been suggested that perhaps some vitally important metabolite (an enzyme? a vitamin?) is consumed during the fight against the stressor. It is also possible that there is no single common pathway, in that the impulse for the formation of gastro-intestinal ulcers and other purely degenerative lesions may be transmitted through a variety of mediators. I do not believe that the evidence in support of any of these theories is sufficiently conclusive to deserve a detailed discussion here.

On the other hand, we succeeded in learning much more about the identity of the second arrow, that leading from the stressor to the adrenal cortex.

Stress in the absence of the hypophysis.

Everyone knows today that stressors act upon the adrenal cortex through the discharge of the adrenocorticotrophic hormone (ACTH). This is certainly one of the most conclusively established and most generally accepted links in the chain of events which occur during stress. Indeed, this fact now appears to be so evident that any discussion of it may impress you as superfluous. Yet, for the sake of historic correctness, I must make an embarrassing confession. When I was first faced with this problem, in 1936, the possibility of a pituitary mediator never occurred to me. In fact, I thought of almost every organ, except the hypophysis, as a possible relay in the transmission of the stress response to the adrenal.

It must be recalled again that, at that time, we were strongly influenced by the investigations of Cannon who had found that, during emergencies, the secretion of the adrenal medulla is regulated by its secretory nerves. Naturally, my first thought was that, during stress, the corticoids are also manufactured under the impulse of nervous stimuli. Yet, denerva-

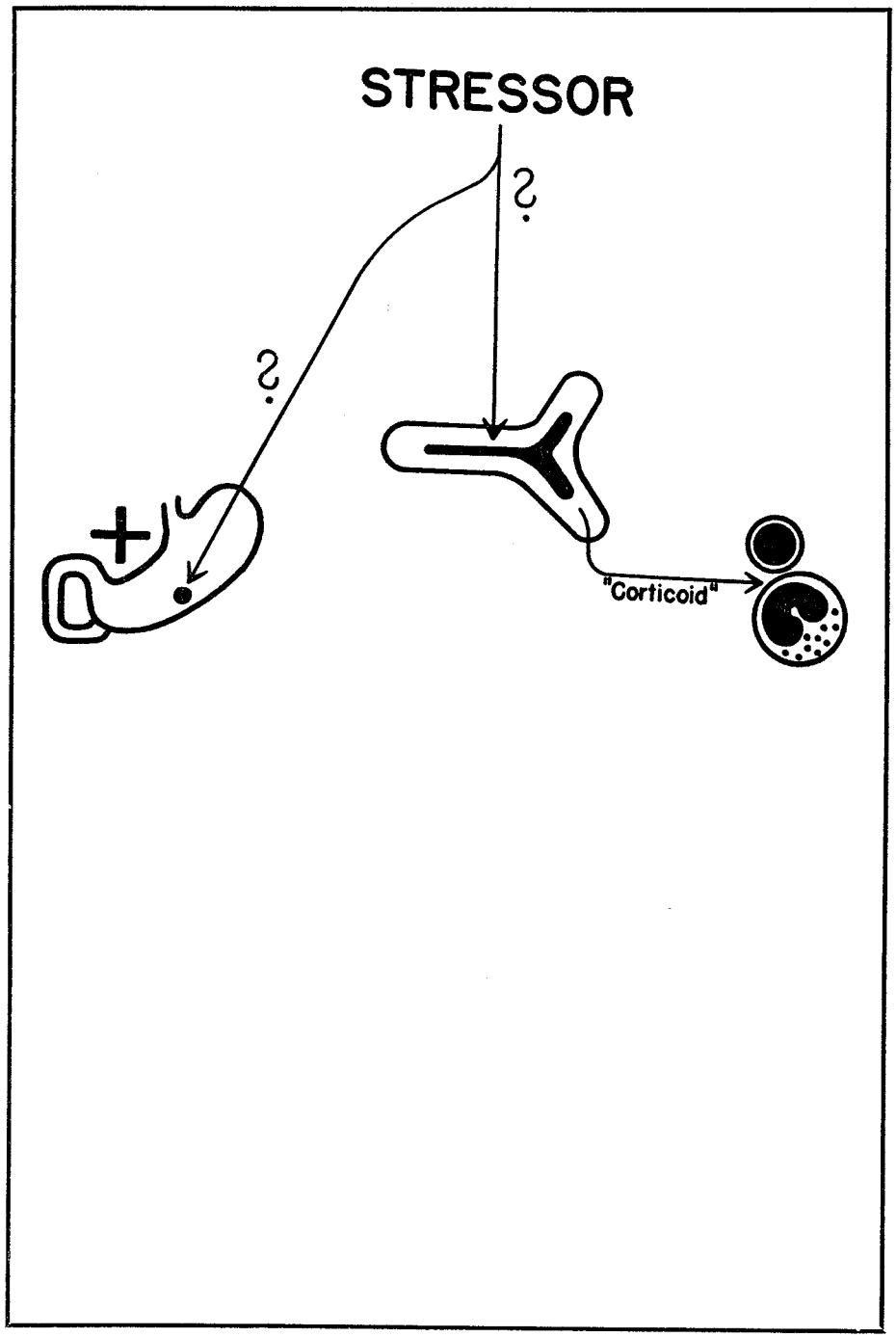
THE ADAPTATION SYNDROME

The drawing illustrates that a variety of agents, capable of producing an adaptation syndrome, act by virtue of their non-specific stressor effects. The stressor stimulates the adrenal cortex, through hitherto unidentified pathways, to cellular proliferation and increased corticoid production. It is not yet known whether the adrenal cortex can exert qualitatively different effects, hence "the cortical principle" is designated as "corticoid." It is definitely established, however, that stressors can cause thymico-lymphatic involution and characteristic hematologic changes, simultaneously with adreno-cortical stimulation, but fail to do so after ablation of the adrenal. It is also proven that corticoid-containing extracts imitate these extra-adrenal effects, this even in the absence of the adrenals. Hence, we concluded that stressors cause such lymphatic and hematologic changes through the intermediary of cortical stimulation.

The stressor also produces changes which are merely indicative of damage and have no defensive value (represented by the cross). Among these are: gastro-intestinal ulcers, hypotension, hypochloremia and shock, or even death. These effects are not mediated through the adrenal cortex since they also develop after adrenalectomy; indeed, many of them (e.g. hypochloremia, hypotension, shock and a high mortality rate) are even more manifest in the absence than in the presence of corticoids. Presumably, part of the defensive value of the adrenal stimulation during stress is to prevent such purely detrimental changes. Apart from the fact that corticoids are not indispensable for the production of these lesions, nothing definite is known about the mechanism of their mediation.

Parenthetically, it should be mentioned that, under certain circumstances, heavy overdosage with corticoids can also produce catabolism with degenerative changes in tissues, or even gastro-intestinal ulcers. We shall come back to this later. The main lesson learned from these first experiments was that the changes in this "damage" category differ essentially from the "defensive" responses of the G-A-S in that they do not necessarily presuppose an increased corticoid production.

LATE IN 1936



tion of the adrenals did not modify the cortical response during a subsequently elicited adaptation syndrome.

Needless to waste time with a detailed description of the numerous frantic experimental efforts that followed this negative finding. The important thing is that all our initial attempts to find out how the stress-reaction reaches the adrenal cortex had failed. Let us merely point out that we destroyed portions of the vegetative centers in the brain, denervated the directly injured tissues, removed a number of endocrine glands, all to no avail.

Then we thought that products liberated from the disintegrating thymus might be the mediators, but in thymectomized animals the adrenal cortex still continued to respond normally during stress.

Eventually, we argued that perhaps the liver — an organ known to be a sort of central chemical laboratory in the economy of the body — might elaborate some principle which has corticotrophic properties. Yet, complete removal of the liver, far from blocking the adrenal response, actually caused a most intense adreno-cortical stimulation, because this operation itself acted as a severe stressor.

It did not occur to me until a year later, in the spring of 1937, that the anterior pituitary might be involved. This suspicion was stimulated by the recollection that the ovarian and placental extracts, which we had used in the prodromal stage of stress research (when we thought we were on the track of a new sex hormone), never caused any adrenal stimulation in hypophysectomized rats. Furthermore, Herbert McLean Evans and Philip Smith had shown, much earlier, that removal of the hypophysis causes an involution of the adrenal cortex, and that the latter

can be restored by injections of hypophyseal material. Indeed, in our own department, J. B. Collip and E. Anderson had succeeded in preparing pituitary extracts containing an "adreno-corticotrophic hormone" in a fairly pure form as judged by bio-assays on hypophysectomized rats. You will remember that we have already mentioned most of these experiments in the first lecture. Yet, curiously, prior to 1937, I did not think of the adreno-corticotrophic hormone as being involved in the adaptation syndrome.

Of course, most tissues which receive impulses from one organ do not necessarily respond to all stimuli through this organ. For instance, an arteriole receives pressor impulses through its vasomotor nerves; it becomes dilated after transection, constricted after stimulation of these fibers. Yet, this does not mean that a stressor could not affect it (even after denervation) through secretion of adaptive hormones (adrenaline, nor-adrenaline) by the adrenal medulla.

Thus, the fact that the anterior pituitary is largely responsible for the structural maintenance of the adrenal cortex under conditions of rest, did not imply to me that stressors would act upon it through this channel. Even if they did, nothing suggested, prior to 1937, any participation of the pituitary in the *function* of adreno-cortical cells. Nevertheless, this seemed to be a good lead and, in the face of all our earlier failures, we immediately decided to follow it up.

At that time, my previous experience with hypophysectomy came in very handy. The technique I had developed necessitated a minimum amount of trauma and made it possible to remove the pituitary rapidly, without much damage; hence, rats, thus hypophysectomized, could be exposed to stressor agents and still survive. Our first experiment along

these lines immediately brought striking results. Hypophysectomized rats exposed to cold, trauma, toxic drugs, etc. completely failed to show any adrenocortical stimulation. The medullary cells, which are controlled by the sympathetic nervous system, discharged their adrenaline granules normally, even in the absence of the hypophysis. Yet, the cortex remained quite uninfluenced. Not only did it fail to show structural evidence of stimulation (discharge of secretory granules, mitoses, increase in weight), but it was also inactivated functionally, since the thymico-lymphatic atrophy of the alarm reaction was prevented after removal of the pituitary. Hence, we concluded that hypophysectomy blocks the pathway of the stress response to the adrenal cortex [4].

Substitution with anterior-pituitary extracts.

However, just as with the work designed to establish the rôle of the adrenal, a deficiency experiment in itself could not be considered entirely conclusive. We still needed the substitution, or overdosage, type of proof. Pure ACTH preparations were not yet available and even the partial purification of this principle was far beyond my competence in the field of extract chemistry. I therefore merely used implants of rat pituitaries or crude beef-pituitary extracts, which I introduced daily under the skin of hypophysectomized animals. But even with these, it was readily demonstrated that if sufficiently large amounts of anterior pituitary are given, one can accurately copy those morphologic changes in the adrenal cortex which normally occur during the alarm reaction. In other words, not only restitution to normal, but stimulation far beyond the norm, is possible by corticotrophic pituitary preparations.

[4] Selye, H.: "Studies on adaptation," Endocrinology, *21*, 169 (1937).

Now, on the basis of these deficiency and substitution experiments, it became possible to insert another link into what we thought was the chain of events which regulates adaptive responses during stress. We concluded that all stressors act on the adrenal cortex through the intermediary of the hypophysis by inducing the latter to discharge ACTH.

We can now complete our synoptic drawing so as to illustrate the theory as far as it had developed by 1937. (See pp. 68, 69.)

The "first mediator of hormonal defense."

It should be noted that, even today, we still do not know the identity of the "first mediator of hormonal defense" through which stressors act upon the pituitary. It is clear, however, that the anterior hypophysis responds to this mediator by an increased ACTH production, which in its turn transmits the impulse of stress to the adrenal cortex. It is quite possible that the "first mediator of damage" (of which I have spoken before) is identical with the "first mediator of hormonal defense." In this event, the pituitary would discharge ACTH in response to the same stimuli, which cause damage (catabolism, hypotension, gastro-intestinal ulcers, etc.) at a distance from the direct impact of the stressor upon the body.

To summarize the subject matter of this second lecture, one might say this:

By the end of 1937, it had become evident that the stress-response consists of two parts: damage and defense.

We had not learned much about the mechanism through which damage is produced in tissues situated at a distance from the actual impact of the stressor agent upon the body. We could not explain, for instance, how a circumscribed injury to the body-

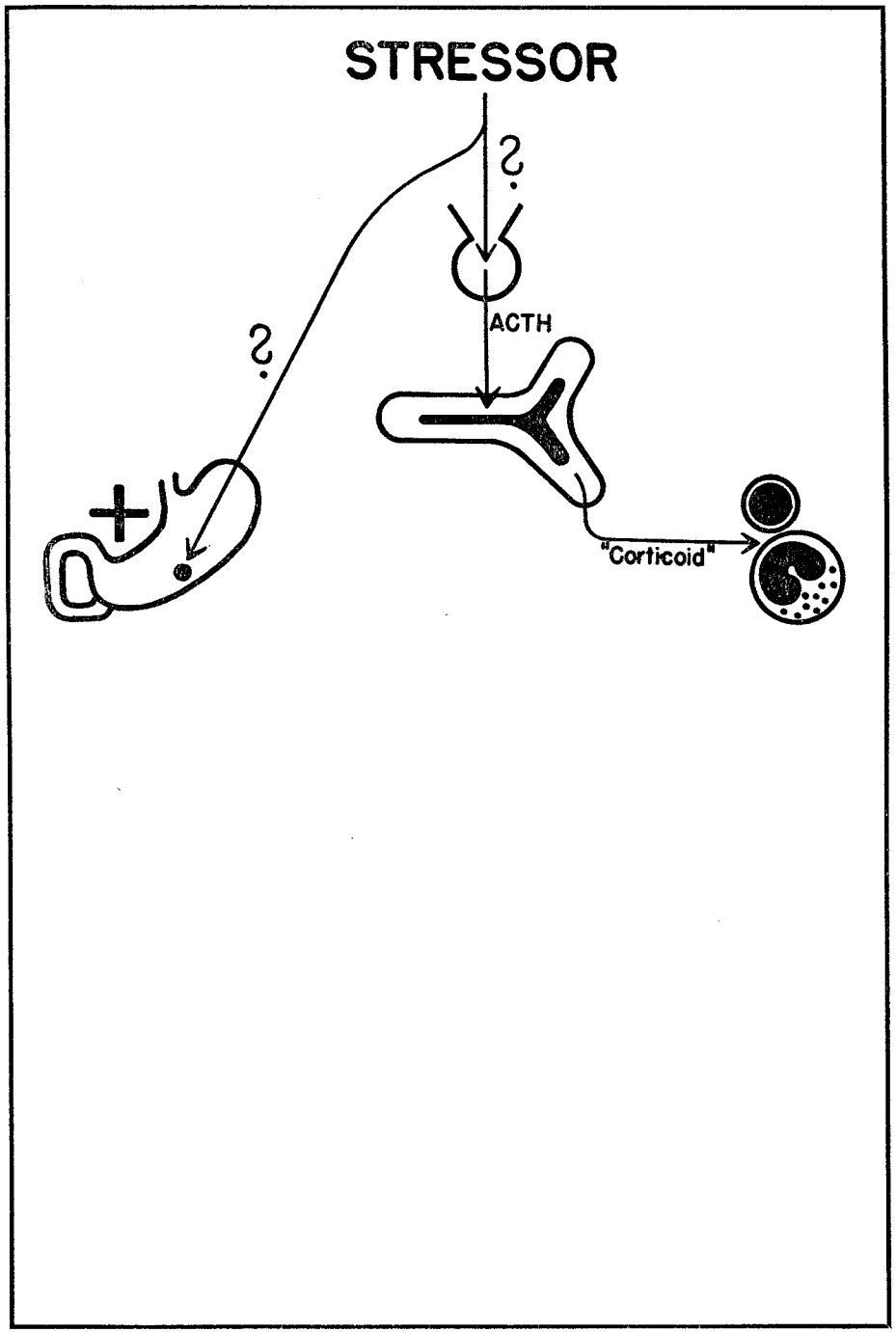
THE ADAPTATION SYNDROME

IN 1937

In addition to the data illustrated by the previous drawings, this figure depicts the position of the anterior pituitary in the adaptation-syndrome mechanism.

It remains to be shown how the stressor reaches the anterior lobe, but it has now become clear that the latter responds with an increased ACTH discharge which in turn stimulates corticoid production by the adrenals. This has been proven by experiments which showed that after hypophysectomy, stressors no longer stimulate the adrenal cortex or cause lympholysis. Conversely, even without exposure to stressors, hypophysectomized animals respond with adrenal stimulation and lympholysis if they are treated with suitable anterior-pituitary extracts (which contain ACTH).

Thus, it became clear that both the morphologic and the functional stimulation of the adrenal cortex during stress is mediated through the anterior pituitary.



surface (e.g., a burn) might produce gastro-intestinal ulcers, shock or death.

On the other hand, we had learned that an important part of the non-specific defense against damage as such (undoubtedly the most useful aspect of the "syndrome of just being sick"), is mediated through the pituitary—adreno-cortical system.

It had also become clear that endogenous corticoids can actually cause pathologic lesions, as exemplified by the thymus involution. Under the name of "accidental thymus involution," pediatricians had known this change long ago. It is an acute thymic disintegration which occurs in children (whose thymus, unlike that of adults, is normally well developed), under the influence of exposure to such stressors as: a severe infection, a burn or an intoxication. Now, we had not only learned that any stressor can produce such a sudden accidental thymus involution, but that it does so through the intermediary of the pituitary and the adrenal cortex, as a "by-product of defense," so to speak.

We concluded that hormones secreted for the purpose of adaptation and resistance, "adaptive hormones," such as ACTH and corticoids, can be the cause of naturally occurring pathologic organ changes.

This was the first observation which led us to the formulation of the concept of the "diseases of adaptation," which will be the major topic of our next lecture.

THIRD LECTURE

The Diseases of Adaptation. Effects of Overdosage with DCA and LAP(STH).

Ladies and Gentlemen!

YOU WILL RECALL that last time we spoke about the experiments which proved that an activation of the pituitary—adreno-cortical system represents an integral part of the adaptation syndrome and is elicited by all stressors. We concluded that this response is useful, since after removal of either the pituitary or the adrenal cortex, many characteristic manifestations of the adaptation syndrome are blocked and resistance to any kind of stressor becomes extremely low.

Accidental thymus involution is a "disease of adaptation".

Yet, a great excess in the production of such pituitary or adrenal "adaptive hormones" may have its drawbacks. We have seen that excessive amounts of corticoids (endogenously produced during stress, or injected into the body in the form of extracts) imitate certain naturally occurring pathologic organ changes; for instance, the "accidental thymus involution." This finding was very intriguing because it first raised the possibility that some spontaneously occurring diseases of hitherto unknown origin may be due to the excessive, or abnormal, production of adaptive hormones. In a sense, these would then be

"diseases of adaptation," that is, derangements of the adaptive response more than maladies due to organ lesions caused directly by any particular pathogen.

In order to test this hypothesis, it would have been necessary to produce heavy overdosage with cortical hormones and to determine whether — in addition to the already verified thymus involution — this induces experimental similes of spontaneous diseases. For technical reasons, this plan could not be carried out for many years after it was formulated. Even if we had given huge doses of our crude adreno-cortical extract, it would not have been possible to evaluate the results, since the changes produced could have been due just as well to the impurities as to the corticoids contained in our preparations. Clearly, what we had to do was to overdose animals with pure corticoids. However, at that time, such were not yet available in the quantities required for this type of work. It was not until much later, thanks to progress in chemistry, that we managed to proceed with this aspect of our program.

DCA becomes available.

In 1938, the Swiss chemists T. Reichstein and J. von Euw [1] demonstrated the presence in the adrenal of a corticoid "desoxycorticosterone" which could be synthesized from comparatively simple compounds in the laboratory. The pharmaceutical industry immediately developed methods for the large-scale production of this steroid and in 1941, through the courtesy of the Schering Corporation, we were able to obtain generous amounts of it for our work. It was furnished in the form of desoxycorticosterone acetate, usually

(1) Reichstein, T. and J. von Euw: "Über Bestandteile der Nebennierenrinde. XX. Mitt. Isolierung der Substanzen Q (Desoxy-corticosteron) und R, sowie weiterer Stoffe." Helvet. chim. acta *21*: 1197 (1938).

referred to in the literature as "DCA" or "DOCA."

I must admit that when we embarked upon experiments concerning DCA overdosage, I fully expected to reproduce with it those same changes that can be obtained with active adreno-cortical extracts, that is: thymico-lymphatic atrophy, lymphopenia and eosinopenia. However, in addition to these, I thought probably many other changes would also appear, because one could administer much larger doses of this pure steroid than of the dilute and impure extracts.

Actually, this was not the case. Animals treated with large doses of DCA showed no thymico-lymphatic atrophy, lymphopenia or eosinopenia; instead, they exhibited a peculiar syndrome that looked like a combination of nephrosclerotic hypertension and rheumatic disease.

In animals DCA overdosage causes nephrosclerosis . . .

Thus, in chicks and rats heavily overdosed with DCA, we observed the development of a particularly malignant nephrosclerosis with hyalinization of the renal glomeruli and of the afferent glomerular arterioles. The larger arteries of the kidney gradually also underwent hyalinization and sclerosis, but only at a later stage [2].

. . . hypertension . . .

This nephrosclerosis progressed eventually to the stage of a greatly shrunken, "secondary contracted" kidney, which — as its counterpart in human pathology — was associated with severe hypertension. Yet, curiously, the rise in blood-pressure tended to precede the development of any marked glomerular or vascular change in the renal parenchyma; hence, the former could not be merely a consequence of the latter.

During the first two weeks of DCA overdosage, the morphologic changes in the kidney were limited

(2) Selye, H.: "Production of nephrosclerosis by overdosage with desoxycorticosterone acetate." Canad. M. A. J. *47*: 515 (1942).

to some hypertrophy of the epithelial cells, especially those of the "spiral segments" in the proximal convoluted tubules. It was therefore suspected that this part of the nephron is particularly concerned with the regulation of blood-pressure. Subsequently, this view received considerable support from our observations on the "endocrine kidney" about which I shall speak in my next lecture.

Now, even though the hypertension may be initiated by changes in the renal epithelia, the subsequent restriction of the vascular bed by sclerosis should further augment the blood-pressure. It would presumably act like the "Goldblatt clamp," by diminishing the blood-supply of the kidney. There could hardly be any fundamental difference between the surgical application of a single metallic clamp upon the main renal artery and the thousands of microscopic "arterial clamps" placed upon the minute renal vessels, by us, in the form of hormonally-produced hyalin deposits and sclerotic granuloma tissue.

To summarize, we felt that DCA probably initiates hypertension through some effect upon the renal epithelia, but later this rise in blood-pressure is further aggravated by the purely mechanical effect of the vascular and glomerular sclerosis in the kidney.

. . . arteritis . . .

In our DCA-overdosed animals, simultaneously with these renal changes, there developed characteristic inflammatory lesions throughout the vascular tree; particularly in the arteries and arterioles of the mesentery, the heart, brain and adrenals. In all these locations, the arterial wall tended to become infiltrated with homogenous hyalin deposits and a proliferating granuloma tissue. Such inflammatory changes were usually visible, even by mere naked eye inspection,

in the form of bead-like swellings along the course of the arteries. In the acute stages, these foci often contained many eosinophils and polynuclear giant cells. Thus both macroscopically and microscopically, they resembled periarteritis nodosa. In the later stages, however, after prolonged treatment or after interruption of DCA administration, these acute inflammatory changes frequently gave way to the more chronic pictures of obliterating arteritis and arteriosclerosis.

. . . encephalitis . .

This polyarteritis frequently affected the vessels of the brain and led to a rather characteristic encephalopathy. The histologic features of the brain lesions varied, depending upon the dosage, length of treatment, etc., but tended to resemble the so-called rheumatic encephalitis, allergic encephalitis, hypertensive encephalopathy or periarteritis nodosa of the brain, depending upon the circumstances. Frequently, it was accompanied by an extensive edema of the brain and meninges, and sometimes by meningitis.

Incidentally, let me point out here that pronounced changes in the function of the central nervous system may be produced by steroids, even if they do not elicit any morphologic changes. Thus, in the rat, acute overdosage with DCA may cause a state of acute excitation, followed by deep anesthesia, but this effect is not specific in that it is shared by a great variety of other corticoids, and indeed even by steroids of gonadal origin.

The electric excitability of the rat brain is reduced by DCA and this action appears to be more specific since other corticoids (e.g., cortisone) actually counteract it (Woodbury and Sayers). We recently found that rats chronically treated with STH tend to become sluggish and sleep a great deal.

The relationship between these morphologic or functional changes in the central nervous system of animals overdosed with adaptive hormones and the mental disturbances frequently observed in patients receiving ACTH or cortical hormone therapy, remains to be elucidated.

. . . myocarditis . . .

In addition to the aforementioned polyarteritis, we often observed roundish or spindle-shaped granulomas in the heart. These usually contain a large number of polynuclear giant cells and much homogenous, hyalin, eosinophilic material, as well as many Anitschkow myocytes with their characteristic "caterpillar" nuclei. Such structures strikingly resemble the Aschoff nodules of acute rheumatic fever. The similarity to rheumatic carditis was further underlined by the concurrent development of an endocarditis with the deposition of fibrinous material on the endocardial surface, especially on the valves. These deposits gradually became organized by a granuloma tissue. Serous or serofibrinous pericarditis occurred rarely in the rat, but subsequent experiments showed that in dogs this change is more frequent [3].

. . . polyarthritis . . .

The resemblance of our experimental syndrome with clinical rheumatism became even more striking when we observed, a few months later, that young rats heavily overdosed with DCA frequently exhibit an acute polyarthritis. This is characterized by swelling, hyperemia and edema of the paws, which become extremely painful. The rat rarely uses a foot thus afflicted and shrieks with pain if such an arthritic joint is touched.

This polyarthritis tended to develop especially in the metacarpal or metatarsal region of one or the other leg, but, curiously, despite continuous treatment with the same daily amount of DCA, it frequently healed in one paw only to reappear in another. As a rule, the polyarthritis lasted only between the second and third weeks of DCA treatment, flitting about from one

(3) Selye, H. and E. I. Pentz: "Pathogenetic correlations between periarteritis nodosa, renal hypertension and rheumatic lesions." Canad. M.A.J. *49*: 264 (1943).

joint to another, and subsequently disappearing even though hormonal injections were continued. Only rarely did this type of arthritis become chronic.

Histologic observations of the joints revealed that the inflammation elicited by DCA begins as a periarthritis although it also affects the stroma of the synovial membrane. In the acute stages, it exhibits the structural characteristics typical of acute rheumatic fever, but in the occasional chronic case this gradually develops towards a picture more reminiscent of rheumatoid arthritis.

. . . and an increased "inflammatory potential".

In short, with DCA, we had produced a state of hyperreactivity, an increased "inflammatory potential" in the connective tissue, which resulted in an arteritis of the periarteritis nodosa type, a myocarditis with Aschoff-nodule-like granulomas, an endo- and pericarditis as well as a polyarthritis.

Surely, here we were faced with so many elements of the rheumatic syndrome that their concurrent production by a single agent, DCA, could not be merely ascribed to coincidence.

Stress may cause "diseases of adaptation".

We were not yet entitled to conclude, however, that the adrenal cortex plays a decisive rôle in the pathogenesis of nephrosclerosis or of the rheumatic-allergic diseases in the course of some derailment of the G-A-S. One of the most important pieces of information was still missing. We had no proof that, through stimulation of endogenous corticoid secretion, stressors can produce experimental replicas of such maladies. Usually, during the G-A-S, such disease manifestations did not occur, even if exposure was continued to the stage of exhaustion and death. Perhaps, the physiologic and useful adaptation syndrome had to be "derailed" before it would become pathogenic.

Sensitization by partial nephrectomy and sodium chloride.

In the course of our earliest experiments on DCA overdosage, we had already noticed that partial nephrectomy and diets rich in sodium chloride greatly sensitize animals to the production of nephrosclerosis or inflammatory changes by this steroid. We shall have more to say about such selective sensitization a little later, in our discussion of the so-called "conditioning factors." Apparently, enforced hyperactivity of the kidney, as caused by unilateral nephrectomy, and an excess of sodium, tend to sensitize tissues to the toxic effects of overdosage with the prophlogistic- or mineralo-corticoids of which DCA is but one example.

Of course rats thus specifically sensitized would be most likely to respond, with nephrosclerosis and inflammatory lesions, to endogenous corticoids produced during stress. Hence, we exposed unilaterally nephrectomized rats, given 1% sodium chloride as a drinking fluid, to a variety of stressor agents for several weeks. These experiments left no doubt that at least exposure to certain types of stressors (such as cold, foreign-protein injections, etc.) do produce organ changes similar to those which we had previously obtained by DCA overdosage [4].

It is not quite clear, even today, why certain stressors are much more effective in this respect than others. Be this as it may, under our experimental conditions it was possible to cause a "derailment of the adaptation syndrome" so that it became pathogenic. It remains to be seen whether this "derailment" is due to excessive production or deficient detoxification of prophlogistic corticoids. To some extent it is probably

[4] Selye, H.: "On the production of malignant hypertension by chronic exposure to various damaging agents." Rev. canad. de biol. *2*: 501 (1943).

also due to sensitization of certain peripheral target organs for such hormone overdosage effects. In any event, we had now experimentally reproduced certain "diseases of adaptation" by stress, without any parenteral hormone administration.

Adrenocortical participation in rheumatic-allergic diseases.

On the basis of all these observations, we published a paper in 1944 on the "Hormonal production of arthritis" [5], in which we arrived at the conclusion that there must be some pathogenic relationship between the adreno-cortical hormones and the rheumatic diseases.

We argued that if overdosage with an exogenous corticoid (DCA) results in a rheumatic syndrome, the same may be true if an excess amount of corticoid is endogenously produced. Our earliest work had clearly shown that corticoid secretion increases during exposure to stress. Furthermore, under certain conditions, stressors caused lesions which simulated overdosage with cortical hormones. Indeed, depending upon the experimental circumstances, it was possible to reproduce by stress, the manifestations characteristic of overdosage with antiphlogistic (diminution of hyperergic inflammation, thymolysis) or prophlogistic corticoids (nephrosclerosis, hypertension, arteritis, arthritis, myocarditis).

From here, it was only one step to postulate that when, during the G-A-S, the adrenal discharges an excessive amount of corticoids, these could, under certain conditions, sensitize the tissues to rheumatic-allergic diseases.

Let us now complete my diagram so as to depict our ideas on the dynamics of the stress-response as they were in 1944.

[5] Selye, H., O. Sylvester, C. E. Hall and C. P. Leblond: "Hormonal production of arthritis." J.A.M.A. *124*: 201 (1944).

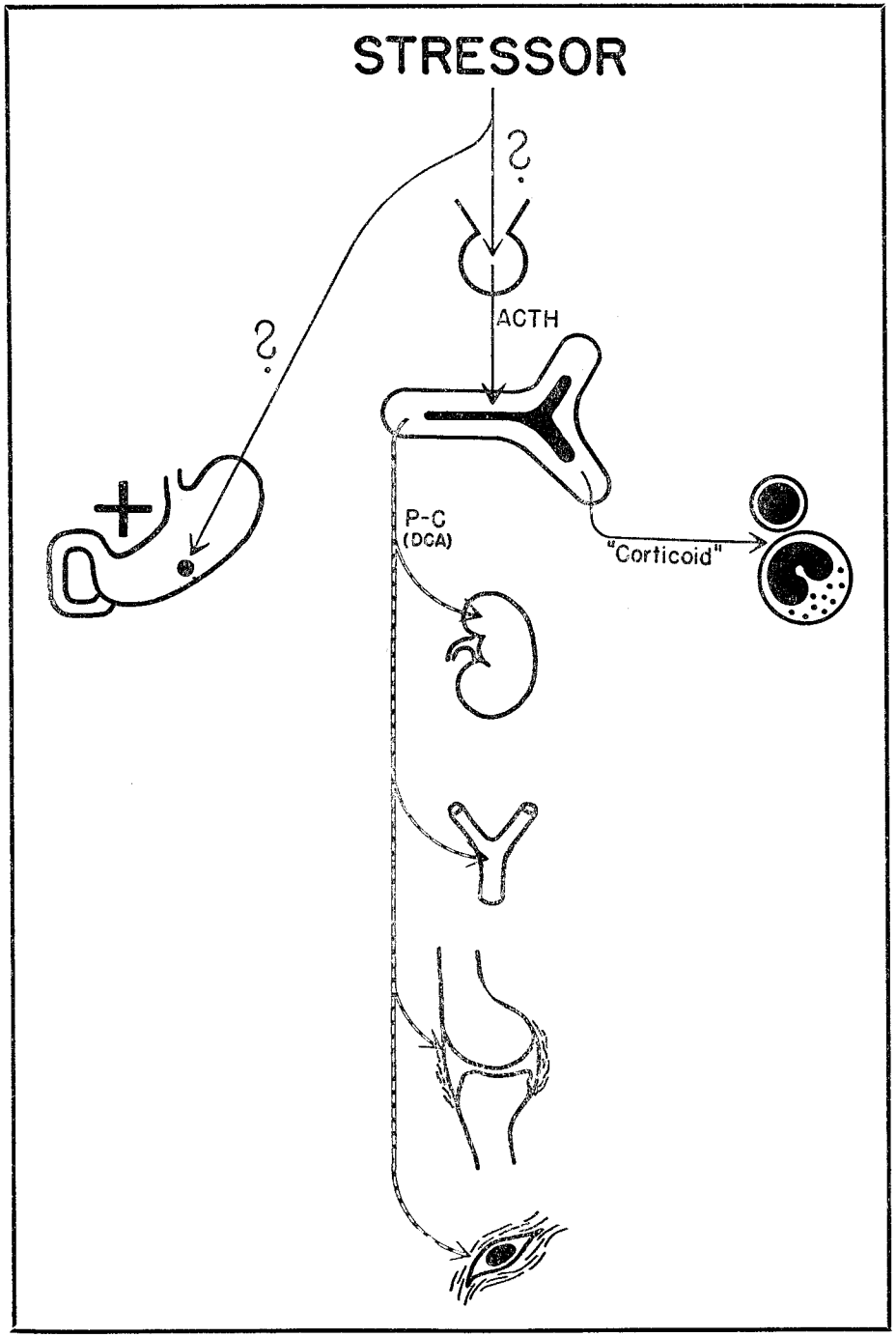
At this stage, we still represent adrenal extracts by the generic term "corticoid," since it is not yet known which individual corticoids are responsible for their characteristic lympholytic, eosinopenic and anti-inflammatory properties. However, as the first representatives of a prophlogistic corticoid (P-C) became available in the form of desoxycorticosterone acetate (DCA), it was found that the actions of such substances are qualitatively quite different from those of our crude adreno-cortical extracts.

DCA causes renal lesions (reminiscent of malignant nephrosclerosis), arteritis (reminiscent of periarteritis nodosa or rheumatic arteritis), joint lesions (reminiscent of acute rheumatic fever or rheumatoid arthritis), and manifold other inflammatory changes in various organs (myocarditis, endocarditis, polyserositis, with a great increase in the "inflammatory potential" of the connective tissue everywhere). These organs are represented here by schematized symbols for the kidney, the cardio-vascular system, the joints and the connective tissue respectively.

It is not yet clear how stress can selectively influence the production of the adreno-cortical-extract-like or the DCA-like compounds through a single type of adreno-corticotrophic stimulus, ACTH.

By this time it had already been shown, however, that certain "conditioning factors," such as partial nephrectomy or sodium chloride can selectively sensitize organs to the toxic actions of pro-inflammatory corticoids. The presence or absence of such selective sensitization suffices in itself to alter the response of the tissues qualitatively, even if the various corticoids were always secreted in the same proportion.

At this stage, it was not yet definitely proven that, during stress, DCA or any other P-C compound is normally secreted by the adrenals; yet, we had rather convincing indirect evidence in support of this view. For instance, exposure to certain stressors (e.g., cold, foreign proteins, etc.) duplicated the effects of P-C overdosage, at least in animals specifically sensitized to such actions by partial nephrectomy and sodium chloride overdosage.



In 1944, these seemed to be very daring conclusions (which did not remain uncriticized!), but to us the facts that were established by then appeared to justify the assumption of some pathogenic relationship between the adrenal cortex and the rheumatic-allergic diseases. At least we considered this to be a profitable basis for a working hypothesis. It was impossible, however, to go any further than this and to specify the nature of this relationship. Many of our observations were difficult to understand and appeared to be quite contradictory.

Inexplicable "paradoxes" which stimulate further research.

Why was it that DCA predisposed to a variety of inflammatory lesions when adreno-cortical stimulation (during an alarm reaction) actually exerted antiphlogistic effects: for instance, upon the "hyperergic inflammation" normally caused by egg-white in the rat? In one instance, corticoids appeared to have prophlogistic, and in other, antiphlogistic properties.

Why was it that only some animals, and even in these only some joints, responded with inflammatory lesions to DCA overdosage?

Why was it that even in a manifestly responsive joint, inflammation occurred only at a certain stage of DCA overdosage, although the hormone was administered continuously over several weeks?

Can the adrenal "neutralize" DCA?

There were many other incongruous observations in this first communication on the "hormonal production of arthritis." For instance, in adrenalectomized rats, arthritic changes were much more constant and of greater intensity, than in intact animals. This was so, although all animals received the same amount of DCA under identical conditions. Unexpectedly, here, in the adrenalectomized and DCA-overdosed animal, an adrenal insufficiency coexisted with hyperadrenalism, since removal of the suprarenals had predisposed the animals to certain manifestations of DCA-intoxication.

Was there something in the adrenal gland which could actually antagonize the actions of DCA?

Does DCA cause inflammation or merely raise the "inflammatory potential"?

We observed, furthermore, that the incidence and severity of arthritis among DCA-overdosed animals can also be greatly augmented if their joints are exposed to the direct action of some irritant, such as cold or humidity. Does DCA not actually cause inflammation, but merely augment the reactivity of the periarticular connective tissue to local irritation? If this were so, we would have a perfect explanation of our inability to produce arthritis regularly and in all joints, no matter how much DCA we gave. Perhaps, under the influence of DCA, only those joints became inflamed which happened to be exposed to some incidental irritant, such as a minor trauma or an otherwise latent infection.

It was only much later that most of these problems could be clarified by experimental analysis and, indeed, some of them remain unsolved even today.

You can see that we actually knew very little about the relationship between the adrenal cortex and the rheumatic-allergic diseases in 1944.

We did not yet realize clearly that the adrenal cortex can produce both pro- and antiphlogistic corticoids.

We did not know that a prophlogistic corticoid does not necessarily produce inflammation of itself, but may merely sensitize the tissues so that minor irritants will cause pronounced inflammation.

We did not know why our DCA-produced rheumatic-allergic syndrome was invariably accom-

panied by hypertension with renal changes; nor did we clearly realize the possibility of selectively exaggerating or eliminating any one manifestation of DCA overdosage by "conditioning factors."

But all these points impressed me as mere details of the fundamental problem with which we were faced. They were important details, no doubt worthy of subsequent careful analysis, but details just the same. To me, the principal fact that emerged from all these observations was that there exists some kind of a relationship between the adrenal cortex and the pathogenesis of nephrosclerosis and rheumatic-allergic diseases. Objective animal experiments had shown, in an unequivocal manner, that an excess of one of the "adaptive hormones," the corticoids, can facilitate the development of such maladies; hence, the latter were, at least in part, "diseases of adaptation."

Certain anterior-pituitary extracts imitate the effects of DCA overdosage . . .

Almost simultaneously with this work on corticoid overdosage, we initiated some studies on the effect of intoxication with anterior-pituitary preparations. We performed these experiments mainly because, at that time, the two main objections to our whole concept were that:

(1) DCA is not a normal product of the adrenal, but an artifical synthetic corticoid which plays no rôle — and probably does not even occur — in nature.

(2) Even if DCA or some similar corticoid were produced by the adrenal, it is unlikely that the gland could ever manufacture anything like the amounts required to produce our experimental similes of nephrosclerosis or of the rheumatic-allergic diseases.

Now, if only with some corticotrophic pituitary extract, we could elicit organ changes similar to those

caused by DCA, both these objections would be simultaneously refuted. We would have proof that the proper kind of adrenal stimulation produces adequate amounts of (or conditions for the actions of) endogenous prophlogistic corticoids.

Much to our satisfaction, right in our first experiment with the crudest anterior-pituitary preparations, we had produced renal, cardio-vascular and even joint lesions similar to those typical of DCA overdosage.[6] The one striking difference between the syndrome caused by DCA and that elicited by anterior-pituitary extracts was that only DCA produced the well known "compensatory atrophy" of the adrenal cortex. This is elicited by an excess of any corticoid substance and is presumably due to an inhibition of endogenous ACTH formation. Conversely, our anterior-pituitary extracts induced a marked hypertrophy and hyperplasia of the adrenal cortex, as a result of their strong corticotrophic activity.

. . . but cause nephrosclerosis only in the presence of adrenal tissue.

This adreno-cortical stimulation was undoubtedly related to the development of nephrosclerosis. In adrenalectomized animals given similar treatment with anterior-pituitary extracts, nephrosclerosis could never be obtained; not even if the rats were maintained in a perfect condition by adequate substitution therapy with adreno-cortical extracts. Consequently we concluded that the pituitary preparations were nephrotoxic only in the presence of functional adrenal cells.[7]

---

(6) Selye, H.: "Rôle of the hypophysis in the pathogenesis of the diseases of adaptation." Canad. M.A.J. *50*: 426 (1944).

(7) Hall, C. E., P. Dontigny, E. Beland and H. Selye: "The rôle of the adrenals in the production of nephrosclerosis by anterior pituitary preparations." Endocrinology *38*: 296 (1946).

I intentionally speak here of nephrosclerosis only, since the extra-renal inflammatory lesions caused by pituitary extracts were not so dependent upon the presence of the adrenals. Later we shall come back to this singular difference in the responsiveness to adaptive hormones of the kidney and of most other tissues.

Let us point out right now, however, that it is not fully understood, even today, just how the adrenals participate in the causation of renal changes by pituitary preparations.

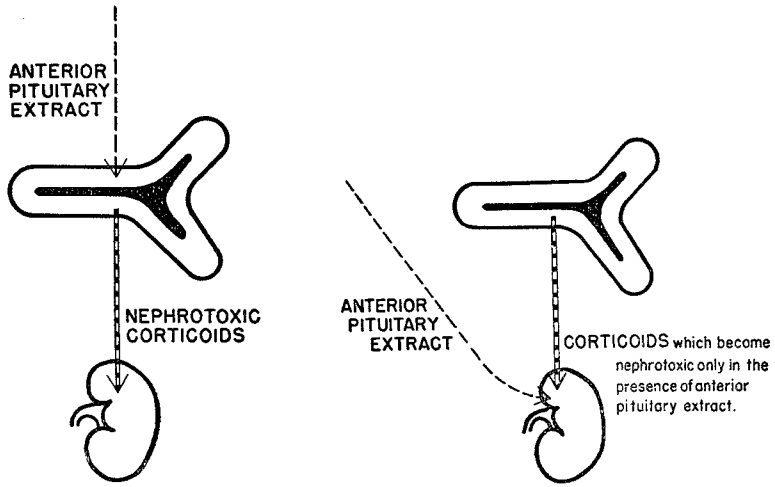
Several possibilities have to be considered:

(1) The anterior-pituitary extract could induce the adrenals to produce excessive amounts of DCA or of some similarly nephrotoxic corticoid.

(2) The anterior-pituitary extract itself could cause a nephrosclerosis similar to that elicited by DCA. In this event it would act directly upon the renal tissue and not by stimulating the secretion of DCA-like compounds. Yet, as shown by our adrenal extirpation experiments, even in this case the activity of the pituitary extract would be dependent upon the simultaneous presence of potentially nephrotoxic corticoids — compounds of a quality or quantity not supplied by maintenance doses of our adreno-cortical extract.

These two possibilities are illustrated by the adjacent schemas.

Either mechanism of action is compatible with the observed fact that, in the adrenalectomized animal, pituitary extracts fail to cause nephrosclerosis, even if maintenance doses of adreno-cortical extract are supplied.



What is the prophlogistic principle in the anterior-pituitary extracts?

It should also be stated that these first experiments furnished no clue concerning the kind of anterior-pituitary hormone involved in this phlogistic response. In view of the close association between the induction of nephrosclerosis and the stimulation of the adrenal cortex, it was considered likely that some "adreno-corticotrophic principle" is involved. On the other hand, it did not seem probable that this could be ACTH; at least, not ACTH alone. As we said in the second lecture of this series, an alarm reaction, which we knew to be accompanied by a pronounced ACTH discharge, actually exhibits antiphlogistic properties. It inhibits inflammation caused by foreign proteins and other irritants.

Furthermore, whenever ACTH was given in doses capable of causing adrenal enlargement, this was accompanied by thymico-lymphatic atrophy; conversely, the rats treated with our prophlogistic anterior-pituitary extracts had exhibited thymico-lymphatic hypertrophy simultaneously with adrenal enlargement.

Could it be that the anterior pituitary produces several kinds of corticotrophins: one which stimulates the production of antiphlogistic corticoids, another which induces the adrenal to secrete prophlogistic, nephrotoxic substances?

Or does one of the other anterior-pituitary hormones exert a direct nephrotoxic effect which depends, however, upon the simultaneous presence of an adreno-cortical hyperactivity? An increased corticoid secretion may well have been induced here by the ACTH content of our impure extracts or by their ability to stimulate endogenous ACTH production, by the animal's own pituitary.

None of these problems lent itself to accurate analysis with the extracts we had at our disposal.

Again the choice between simplicity and refinement in medical research

I cannot resist the temptation of interjecting another parenthetic remark here. It is concerned with that constant struggle which goes on in the mind of an investigator who must always choose between the possibility of attaining an immediate but limited objective or waiting until real perfection is possible.

Naturally, at this point the ideal procedure for the solution of our problem would have been to assay all the various pure anterior-pituitary hormones, individually and in combination, for possible nephrosclerotic and prophlogistic potency. However, such pure hormones were unavailable and, as we shall see, what we actually did is a far cry from this ideal type of experimentation.

We went out to the slaughter-house in Montreal and collected a refrigerated thermos bottle full of cattle anterior pituitaries. The glands were thus kept at a very cold temperature to prevent post-mortem decomposition on the way to the laboratory. Then, using a simple knife, I carefully removed the posterior lobe, which is notoriously toxic because of its high vasopressin content. The anterior lobes were merely ground up with sand in a mortar and then physiologic saline was added to the resulting brei. After letting this stand for a few hours, we decanted the supernatent fluid, to free it from sand and from gross

particles of residual tissue. This was our first potent prophlogistic and nephrotoxic pituitary "extract."

Lyophilized anterior-pituitary extracts are highly nephrotoxic and prophlogistic.

Later, we also used various kinds of simple alkaline extracts, but soon it became obvious that even these primitive manipulations are not essential and we proceeded to inject the anterior-pituitary substance as such. In order to help its preservation, and to break it up adequately for suspension in saline and subsequent injection, we lyophilized the whole anterior lobes. The process of lyophilization is a very simple one, frequently used by chemists because it permits dessication of proteins without denaturing them. It consists of drying frozen material under low pressure, a so-called "freezing-drying" procedure. The resulting lyophilized anterior pituitary (LAP) proved to be a highly potent and convenient source of all the anterior lobe hormones; it has subsequently been used by many investigators.

Advantages of "total pituitary extracts".

Of course, this material is very impure. It contains not only all the anterior-pituitary hormones, but also a great deal of hormonally inert, proteinaceous cell debris. However, in experiments on rats, the latter is no great disadvantage, because this species is singularly resistant to the toxic effects of foreign proteins. On the other hand, the possibility of thus giving all the pituitary hormones at the same time may even be an advantage in trying to solve problems such as the one with which we were faced. Since at first we did not know which, if any, anterior-pituitary hormone is responsible for the nephrosclerotic and prophlogistic effects, experimentation with a "total pituitary preparation" appeared to offer the greatest chance of success. And in fact, as we have seen above, we did succeed in reproducing the expected syndrome of nephrosclerosis, hypertension and rheumatic-allergic inflammatory changes with these "total anterior-pituitary preparations."

Our objective was limited as these experiments could not be expected to reveal which hormone is involved. But Nature promptly answered our simple question with a simple and, in this case, affirmative answer: the pituitary does possess inflammation-stimulating properties.

Had we waited until this investigation could be performed to the liking of a perfectionist, we would not be even that far today. According to prevalent contemporary opinion, there are at least six anterior-pituitary hormones. Although highly purified prepara-

tions of all these are now available, none of them has actually been isolated in completely pure form. Thus, even today, we could not assay any one pituitary hormone for nephrosclerotic and prophlogistic effects under ideal conditions. Let us keep in mind, furthermore, that these effects may not be due to any one hormone, but to a combination of two or more substances. The complexities of solving this kind of problem "perfectly" require no comment.

In the meantime, highly purified, though still not entirely pure, preparations of anterior-pituitary hormones have become quite easily available; and yet, even now, a total pituitary preparation such as LAP is our preferred starting material when we wish to examine some hitherto unexplored hypophyseal action, which we have no reason to associate, a priori, with any one hypophyseal principle.

I mention all this to you because I am very partial to simple experimentation and rather impatient with investigators who justify constant dallying by superciliously setting their standards of research far above what can be attained in the particular time and place in which they have to work.

Those who would like to do research and have a real gift for it, but are limited by the very modest facilities at their disposal, may find some encouragement in these considerations. I believe that any medical student who is really interested in research and formulates a good and simple plan, has a reasonable chance of success, even without much training and without special facilities. He can certainly keep a few laboratory rats in an attic or cellar and study their reactions under uncomplicated, but informative, conditions of experimentation. To use the above experiments as an example, the effect of hyperpituitarism upon the most varied reactions to malnutrition, trauma, heat, etc., could readily be investigated by any one of you, using nothing but an anterior-pituitary brei made by grinding the glands with a little sand in a mortar.

But let us get on with our story again.

The "X-factor" in LAP is probably STH

Despite the inherent technical difficulties of solving this point, one could make reasonable guesses about the identity of the anterior-pituitary hormone, the "X-factor" in the LAP, which is responsible for the prophlogistic effect.

Our crude extracts, and particularly LAP, were especially rich in the so-called somatotrophic hormone (STH), also known as "growth hormone." This was quite obvious because of the extraordinary growth-stimulating properties of these crude extracts. There was no reason to suspect any of the gonadotrophic anterior-pituitary hormones — such as the follicle-stimulating (FSH), the luteinizing (LH) or the luteotrophic hormone (LTH) — of having any inflammation-stimulating properties. All the known actions of these substances are quite specifically concerned with reproduction. ACTH, as we have seen, is actually a strongly antiphlogistic substance. This left us with only two anterior-pituitary hormones, namely: somatotrophin (STH) and thyrotrophin (TTH). We did not have any pure preparation of thyrotrophin, but thyroxin overdosage failed to reproduce the great increase in inflammatory potential or the nephrosclerosis that we had obtained with LAP. Since thyrotrophin acts mainly through the production of thyroxin, this observation strongly suggested that the "X-factor" is not thyrotrophin. By elimination, this left us only with STH as a possibly prophlogistic compound among the authenticated anterior-pituitary hormones. Of course, the prophlogistic "X-factor" could also have been a new, hitherto unidentified hormone.

This problem has still not been solved entirely to my satisfaction, but for the sake of clarity I shall again deviate slightly from the chronologic order of presentation and tell you right now what we learned about it so far.

It was not until 1951 that I was able to obtain an adequate amount of a highly purified STH for this

type of study. At that time, professor C. H. Li supplied me with an STH preparation which was pure, as judged by electrophoresis, ultra-centrifugation and its tendency to form crystals. This material reproduced the nephrosclerotic and inflammatory changes which we had previously obtained with LAP. We therefore concluded that, most probably, the activity of the latter was in fact due to its extraordinarily high STH content.[8] Yet, it must be admitted that this is still not definitely proven. All the characteristics which I have mentioned do not suffice to establish with certainty that a protein such as STH is absolutely devoid of impurities. It is still conceivable that the nephrosclerotic and prophlogistic activities of our purest STH preparations are due to some traces of contaminating substances.

However, for the sake of simplicity, we shall henceforth merely speak of "STH effects" whenever we refer to changes produced by our STH preparations. It will be silently understood that such effects may also be due to principles which cannot be dissociated from STH by our present day methods of purification.

As I said, the first observations concerning the production of nephrosclerosis and rheumatic-allergic inflammatory changes, with crude anterior-pituitary extracts or LAP, had only implied that the responsible factor is STH. The fact that seven years later we were able to reproduce these effects with highly purified STH preparations gave strong support to this suspicion. In the following drawing we shall indicate the status of our knowledge as it was in 1945,

[8] Selye, H.: "Rôle of somatotrophic hormone in the production of malignant nephrosclerosis, periarteritis nodosa and hypertensive disease." Brit. M. J., Feb. 10, p. 263 (1951).

by inserting the participation of nephrosclerotic and prophlogistic pituitary effects. For the sake of historic correctness, we shall label this as the "X-factor" of LAP, but you will keep in mind that this is presumably STH. (See pp. 94, 95.)

Conditioning of adaptive hormones by dietary factors.

Another very important fact which came to light in the course of our work on DCA and LAP was the observation that overdosage with these adaptive hormones is so extraordinarily dependent upon "conditioning factors." As I have told you before, the production of nephrosclerosis and inflammatory changes by DCA is greatly facilitated if the experimental animals are kept on a high-sodium diet. These toxic manifestations are not particularly influenced, however, by the protein content of the food. On the other hand, the production of the same lesions, or even of adrenocortical hypertrophy by LAP, is facilitated by high-protein diets. Excessive sodium intake likewise augments the nephrotoxic and hypertensive action of LAP, but it does not affect the stimulation of the adrenal cortex by this pituitary preparation. As we found later, the effects of STH are similarly affected by dietary factors as those of LAP, presumably because STH is the active factor in LAP.

Rations rich in sodium and protein do not cause manifest pathologic changes in themselves, but merely sensitize the tissues for the toxic effects of these hormone preparations. I used the designation "conditioning factors" for such agents which do not produce very evident changes by themselves, but are highly potent in exaggerating or suppressing the effects of hormones.

THE ADAPTATION SYNDROME

Experiments performed during the period 1943-45 had shown that various impure anterior-pituitary extracts, particularly lyophilized anterior pituitary (LAP), contain some substance (at that time referred to as the "X-factor") which closely simulates the toxic effects of DCA overdosage in the kidney, the cardio-vascular system, the joints and the connective tissue in general. It produces nephrosclerosis, hypertension, rheumatic-allergic manifestations and a rise in the inflammatory potential.

The ability of LAP to produce nephrosclerosis and hypertension is abolished by adrenalectomy. Yet even after ablation of the suprarenals, LAP raises the inflammatory potential of connective tissue, particularly in the joint regions. Apparently not all the actions of the "X-factor" depend upon the integrity of the suprarenals.

LAP is especially rich in somatotrophic hormone (STH). There is some reason to believe that STH is the "X-factor." In any event, the most characteristic effect of STH, the stimulation of growth, is likewise not prevented by adrenalectomy.

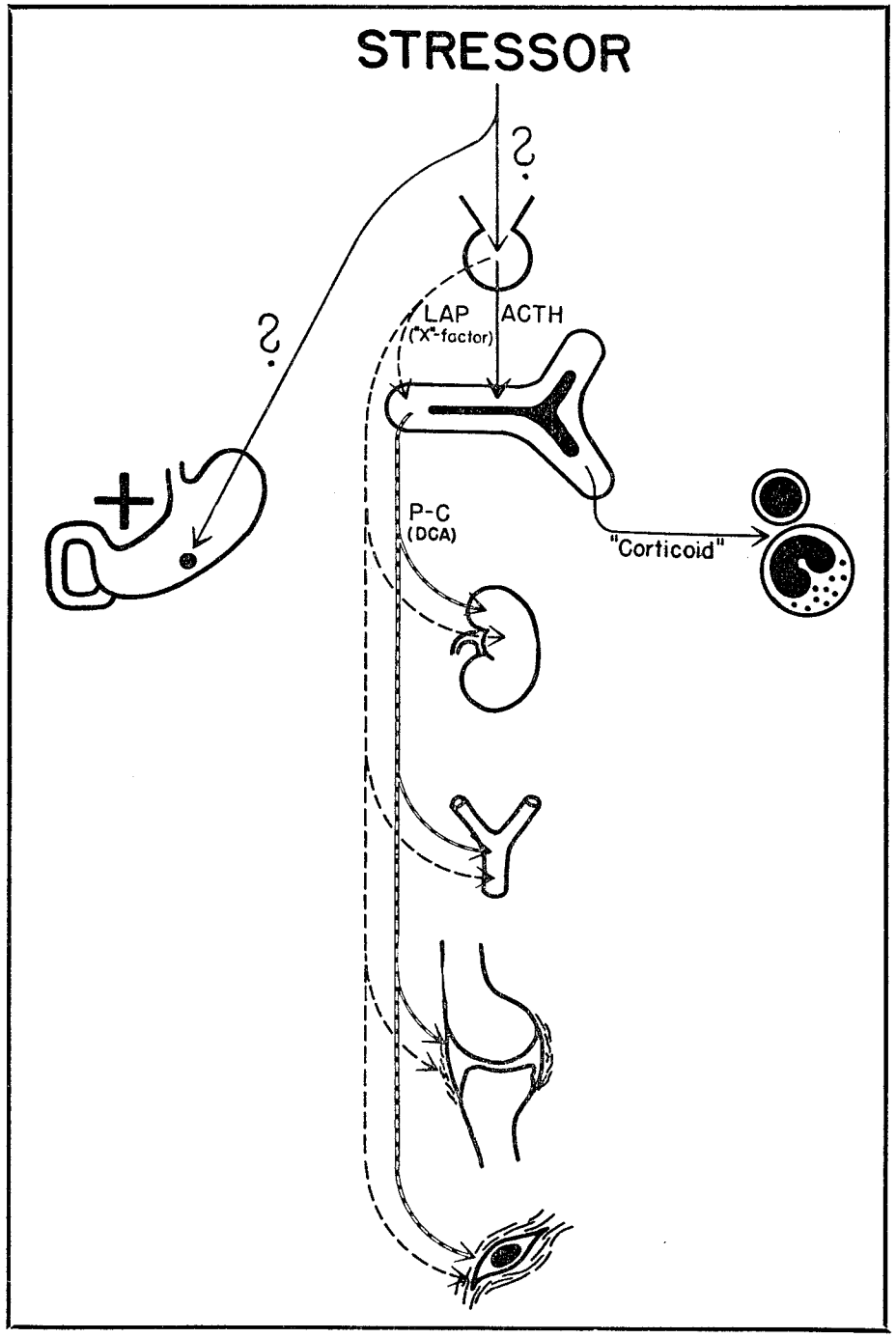
These observations were difficult to interpret at this stage of our inquiry and several alternative possibilities had to be considered:

(1) The "X-factor" in LAP may act as a second corticotrophic hormone which, unlike ACTH, stimulates the adrenals to secrete predominantly nephrosclerosis-producing and prophlogistic corticoids; yet the "X-factor" must also exert direct prophlogistic effects, since it raises the "inflammatory potential" even after adrenalectomy.

(2) The "X-factor" in LAP is not in itself corticotrophic at all, but exerts some of its effects (e.g. nephrosclerotic hypertension) only if the adrenal is simultaneously stimulated by ACTH.

In any event, most of the extra-renal actions of this "X-factor" are relatively independent of the adrenals and presumably direct.

IN 1945



Indeed, the effect of LAP (or STH) upon the blood-pressure and the cardio-vascular system is so highly subject to "conditioning factors" that, under certain circumstances (e.g., in the absence of sensitization by sodium, after thyroidectomy or partial nephrectomy) these pituitary preparations may actually decrease the blood-pressure and even protect against the production of hypertension by DCA. The mechanism of this inversion of effect is now under study, since it could be of therapeutic importance.

You may find it difficult to visualize these complex interrelations between dietary factors and the actions of adaptive hormones. It will simplify matters to summarize by saying that all available data are in agreement with the assumption that:

(1) STH increases the ACTH production of the pituitary, since the former hormone markedly augments the weight of the adrenals in intact, but not in hypophysectomized, animals.

(2) This ACTH-secretion stimulating effect of STH is facilitated by high-protein diets.

(3) The corticotrophic action of ACTH itself is not augmented by rations rich in protein.

(4) Sodium appears to sensitize the kidney directly to the nephrotoxic actions of DCA and similar prophlogistic corticoids, whether they are endogenously produced under the influence of corticotrophic hormones, or exogenously administered by injection.

As we shall see, the actions of adaptive hormones can thus be "conditioned" not only by dietary factors, but also by other hormones, local or systemic nonspecific damage and many other agents.

Conditioning of DCA-overdosage effects by the pituitary.

One striking example of such a "conditioning" by one adaptive hormone to the actions of another, has come to light when we first treated hypophysectomized rats with heavy doses of DCA. If pituitary hormones did produce nephrosclerosis exclusively by stimulating the adrenals to secrete DCA-like hormones, then DCA overdosage should produce nephrosclerosis in adrenalectomized or hypophysectomized rats, just as easily as in normals. Actual experimentation showed that this is not the case.

In adrenalectomized rats, it is quite easy to produce nephrosclerosis and a rise in the inflammatory potential with DCA, especially if the animals are sensitized by sodium chloride and unilateral nephrectomy. However, after hypophysectomy, contrary to expectations, even rats thus sensitized fail to develop nephrosclerosis under the influence of heavy DCA overdosage.

These findings led us to consider that perhaps DCA acts through the intermediary of the pituitary, rather than vice versa. But we immediately rejected this interpretation because of our earlier experiments, which had shown us that hypophyseal preparations on the other hand fail to produce nephrosclerosis in the absence of the adrenals. We therefore had to conclude that some pituitary principle (STH?) sensitizes or conditions the organism to certain actions of DCA-like prophlogistic corticoids.

In various respects the responsiveness of the kidney differs from that of most other organs.

Now, you will remember that only the production of nephrosclerosis was really completely abolished by adrenalectomy in anterior-pituitary-extract-treated rats and by hypophysectomy in DCA-overdosed animals. Certain other changes are not absolutely dependent upon the presence of both hormones. For instance, even in the hypophysectomized animal, DCA stimulates diuresis and raises the blood-pressure. Conversely, in adrenalectomized animals,

the ability of the connective tissue to respond with a marked inflammation to topical irritants can still be stimulated either by DCA or by STH.

Thus, here again the production of nephrosclerosis obeys somewhat different rules from those governing other manifestations of overdosage with adaptive hormones. Nevertheless, simultaneous treatment with STH and DCA tends to produce the most pronounced overdosage effects in all these respects.

The special number of the "Journal of Clinical Endocrinology" issued in February 1946.

Observations concerning these complex interactions between the prophlogistic pituitary and corticoid hormones represented only a small section in the first extensive monograph on "The General Adaptation Syndrome and the Diseases of Adaptation," [9] which appeared, in February 1946, as a special number of "The Journal of Clinical Endocrinology." This review was published almost exactly ten years after the one-page note, in which the discovery of the adaptation syndrome had been reported. At this stage, it already took me more than a hundred pages of text to describe what had been learned about the syndrome, and seven hundred references to cover the pertinent literature. While the manuscript was in press, requests had been received for simultaneous publication by the editors of the "Journal of Allergy" (St. Louis, Mo.), "Annales d'Endocrinologie" (Paris, France), "Manpower" (Johannesburg, South Africa), "Piersol's Cyclopedia of Medicine, Surgery and Specialties" (Philadelphia) and the "Bulletin de Biologie et de Médecine expérimentales de l'URSS" (Moscow, USSR). The appearance of this progress report in so many widely different publications stimulated pertinent research on a large scale. It is really only from then on that serious attention began to be given, throughout the world, to our work on the pituitary-adrenal system as a major factor in the development of disease as such.

[9] Selye, H.: "The general adaptation syndrome and the diseases of adaptation." J. Clin. Endocrinol. *6*: 117 (1946).

First edition of my "Textbook of Endocrinology" — 1947.

To my way of thinking, the whole direction of endocrinology appeared to change so much that during this same year I decided to write a new "Textbook of Endocrinology." In it, I tried to present all our knowledge about the endocrine glands in accordance with the new views derived from research on the G-A-S. These new principles were outlined in the introductory section of this book.

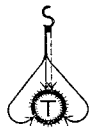
I shall close this lecture by a direct quotation of these relevant passages, since I think they illustrate rather poignantly the crystallization of that new point of view in hormone research which is also the "Leitmotiv" of the present lecture series:

"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 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 cardio-vascular, renal, "rheumatic" and old

age diseases) may belong to this latter group; they are probably by-products of faulty hormonal adaptive 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".[10]

Little could I suspect that it would be only a few years now before these conclusions, derived solely from animal experiments, were to receive such striking clinical confirmation. As we shall see, the remarkable observations of P. S. Hench and his co-workers showed us, in 1949, that ACTH and the antiphlogistic corticoids can dramatically ameliorate the condition of patients suffering from rheumatic-allergic and other inflammatory diseases, including periarteritis nodosa. Almost simultaneously, P. Wertheimer, D. M. Green and G. Thorn demonstrated that severe hypertensive disease in man is beneficially influenced by subtotal or even complete adrenalectomy. All these measures are still fraught with considerable danger, but their effectiveness increases our confidence in the practical applicability of this approach to problems of clinical medicine.



[10] Selye, H.: Textbook of Endocrinology. Acta Med. Publ., First Edition, Montreal (1947).

FOURTH LECTURE

How, Depending upon "Conditioning" Circumstances, the Same Adaptation Syndrome Can Produce Various Diseases. The "Endocrine Kidney." Clinical Use of Adaptive Hormones.

Ladies and Gentlemen !

Two diametrically opposed responses to stress or adaptive hormones.

IN THE COURSE OF MY LAST LECTURE, I told you about animal experiments which showed that overdosage with various adrenal and pituitary preparations can imitate spontaneously occurring diseases of man. We have seen that adreno-cortical extracts, as well as the discharge of ACTH and corticoids, which normally occurs during exposure to stress, produce an accidental thymus involution. On the other hand, overdosage with DCA or with certain pituitary extracts (which, like LAP, are rich in somatotrophin) causes nephrosclerosis, hypertension and an increase in the inflammatory potential, with systemic manifestations reminiscent of rheumatic-allergic diseases. Unlike the first, this second type of response is rarely obvious during stress, unless the experimental animals are sensitized by certain "conditioning factors," such as partial nephrectomy or diets rich in sodium or protein.

From all these observations there gradually emerged the concept that stress invariably stimulates

the pituitary—adreno-cortical system. However, depending upon the circumstances, the same stimulation may result in diametrically opposite types of response:

(1) A reaction which appears to be mediated through a discharge of ACTH and the kind of corticoid which is plentiful in ordinary adreno-cortical extracts. This response is primarily characterized by thymico-lymphatic involution and by an inhibition of inflammatory processes.

(2) A reaction which presumably depends upon pituitary principles other than ACTH, something like the "X-factor" in LAP, and upon prophlogistic corticoids, such as DCA. This response is characterized by nephrosclerosis, hypertension and rheumatic-allergic manifestations, with a marked increase in the inflammatory potential throughout the body.

Apparently, both kinds of reactions can occur during stress, but only if the pituitary-adrenal system is intact, and it depends largely upon incidental "conditioning factors" which type of response will predominate.

Some diseases may not have any specific cause!

These manifestations of stress resemble certain common spontaneously occurring maladies of man. Hence we concluded that presumably the development of the latter may largely depend upon such adaptive responses to the non-specific stressor effects of potential pathogens. In other words, a well characterized disease, for instance, rheumatic fever with its typical cardio-vascular and arthritic manifestations, may not have any specific cause in the sense of being invariably elicited by the same microbe or allergen. It could equally well be produced by the common effect of various pathogens: that of eliciting non-specific stress. In this case, it would be futile to search

for *the* cause of, say, rheumatic fever, rheumatoid arthritis or nephrosclerosis. Perhaps it was precisely because they have no specific cause that it proved impossible, despite centuries of research, to find *the* agents which elicit these particular diseases.

How a single G-A-S can lead to manifold diseases of adaptation.

Of course, if we contemplate such an unorthodox view, objections come to mind immediately. One can hardly conceive of any mechanism through which a single reaction, the G-A-S, could cause such a multiplicity of essentially different diseases.

After all, tuberculosis bacilli do not cause typhoid fever and lead-poisoning is unlikely to produce leprosy! But are we really justified in accepting as self-evident that each specific disease is due to a specific pathogen? I do not think so.

A priori we would be also inclined to think that if all our "diseases of adaptation" would have a single cause in the G-A-S, they should necessarily always occur simultaneously in the same patient; everybody who is exposed to any stressor of sufficient intensity should develop them all. This is obviously not the case. The patient who has nephrosclerosis does not necessarily suffer from rheumatic fever and accidental thymus involution is not usually accompanied by rheumatoid arthritis.

In reality, all these are only apparent paradoxes. We could cite any number of simple examples, taken from everyday experience, which show that a single agent can cause vastly different results and that any combination of — often mutually antagonistic — effects can be elicited by a single cause, depending upon "conditioning circumstances." The same electricity can create motion, light, sound, heat, cold and innumerable combinations of these effects, depend-

ing upon whether it is conducted, selectively or in combination, to an electric motor, a light bulb, a bell, a stove or a refrigerator. For a savage who never heard of electricity, it would be quite incredible that all these gadgets can be operated, singly or in any desired combination, by regulating one force from a single switch-board. To him this would seem just as incredible as it seemed to me, at first, that diverse derailments of a single adaptation syndrome could call forth such vastly different manifestations of disease as those which I have enumerated in my previous lecture.

After we had overcome the mental block which opposed itself to the very principles of this kind of thinking, our next task was to find specific proof in support of the concept that stress may be the principal pathogen of diverse maladies.

I have already told you how, through certain "conditioning factors," we can selectively exaggerate or suppress the response of certain target-organs, both to stress and to overdosage with adaptive hormones. To take some specific examples: unilateral nephrectomy and a high-sodium diet specifically sensitize the kidney for nephrosclerosis; yet, these factors have no effect whatever upon, say, the thymico-lymphatic involution caused by stress. Adrenalectomy, which exaggerates the fatal, damaging effects of stressors, actually blocks their power to cause thymico-lymphatic involution.

A brief glance at our last drawing shows that by interrupting the complex and branching biologic chain reaction of the G-A-S, certain parts of it can be selectively eliminated. Conversely, specific sensitization to the effects of any one adaptive hormone can exaggerate a certain aspect of the stress-response. Undoubtedly, there are innumerable combinations and

permutations of disease manifestations which can thus result from a single biologic reaction, the G-A-S.

There is considerable evidence in support of the view that dietary factors, hereditary predisposition, previous exposure to various pathogens, etc., may specifically sensitize or desensitize certain organs to such an extent that the actual manifestations of the resulting syndrome will be quite different, despite the fundamental sameness of the stress response.

Many physicians still find it difficult to believe that the same disease may be produced by a variety of pathogens — through the common pathway of stress — and that, on the other hand, the same stressor may cause a variety of diseases by selectively conditioning or deconditioning some parts of the stress response. Actually, this situation is not without precedent in medicine. We all know that the same, well identified pathogen, the tuberculosis bacillus, may produce: pulmonary phthisis, meningitis, peritonitis, Pott's disease, miliary tuberculosis or tuberculous lupus of the skin. Before it had been shown that all these conditions can be reproduced by infection with tuberculosis bacilli, it would have seemed quite unreasonable to think of them as being in any way related to each other. One could hardly make up a list of more dissimilar maladies. Yet we are certain now that all these are diseases produced by the same micro-organism. Their polymorph nature must be ascribed to conditioning circumstances, such as: differences in hereditary, traumatic, nutritional, serologic factors, the portal of infection and many other agents which selectively render certain tissues "loci minoris resistentiae."

Indeed, by now I find it somewhat difficult to decide which is more important in determining whether

an organ will be afflicted by disease or not, the pathogen (in my simile the tuberculosis bacillus) or the conditioning factors. After all, most human beings are infected with tuberculosis bacilli at some time during their lives; yet only a minority develops tuberculosis and among these again only a fraction develops it in any one organ.

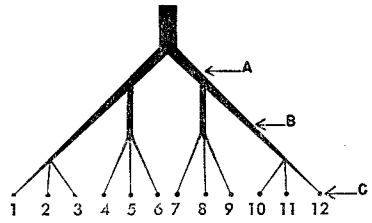
A few simple sketches may help to make this rather complex subject easily understandable.

In the adjacent schema, the three pairs of arrows represent potentially pathogenic agents. All of them possess a non-specific stressor effect which, being non-specific, *ipso facto* is always of the same quality (solid arrows). Yet everyone of these three agents also possesses specific effects which are qualitatively different in each case (other arrows). Obviously, the end-result of exposure to the three agents represented here could not be the same.

I have just compared the manifold effects of the adaptation syndrome to those one can obtain with the same electric current. This metaphor will also help to explain the point under discussion. 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-existing main channels. Yet, depending upon the kind of emergency and the special needs of each district, both its quality and quantity have to be regulated locally in the periphery. Thus, the same current can be used to produce the most varied effects or may be shut out completely, say 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 cable, and secondly because interventions anywhere along the line, above such a peripheral point, would affect the latter.

Essentially the same is true of the adaptation syndrome. The more we approach the periphery, the more often do we note deviations from the standard stress-pattern. All stressors cause an ACTH discharge, but this may or may not be accompanied by signs of excessive prophlogistic hormone activity. Interference at a lower level can cause even more selective deviations from the typical stress-response. Thus, transection of the splanchnics may impede adrenaline discharge during the alarm reaction, 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 manifestations of the adaptation syndrome.

It is an inherent characteristic of ramifying systems that side-branches are more readily influenced than main lines. The adjacent schematic drawing will help to illustrate this. 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 target organ marked 12.



In view of all these considerations, it is understandable that during the subsequent years we attached much importance to the study of the mechanisms through which conditioning factors can thus selectively alter the response of certain organs to stress. To do this well, we had to learn more about the dynamics of the G-A-S.

Basic techniques in studying the G-A-S.

You will have noticed that up to now, in all our efforts to elucidate the rather complex biologic chain reaction of the G-A-S, we utilized but two techniques: gland extirpations and substitution or overdosage with the hormones normally produced by these glands. Any complex, long and ramifying sequence of biologic events lends itself well to this type of analysis,

which, incidentally, is by no means limited to endocrinology or even to medicine. The network of an electric circuit, consisting of many interconnecting branches and relay stations, can similarly be clarified by systematically interrupting or initiating its activity at many points until the course of all its pathways is established.

This procedure proved useful in the elucidation of the G-A-S as regards the first three levels examined. We met no major obstacles when we undertook to study the behavior of the organism: (1) in the presence or absence of stressors, (2) after hypophysectomy or overdosage with pituitary hormones, and (3) following extirpation of the adrenals or intoxication with corticoids.

Rôle of the kidney in the G-A-S.

At the renal level, however, this procedure was no longer practicable. It was obvious from the classic investigations of Goldblatt and his co-workers [1] that direct interventions on the main artery of the kidney can produce hypertension and certain morphologic cardio-vascular changes, presumably as a result of increased renal pressor substance (RPS) production. However, neither extirpation of the kidney nor substitution therapy with its hormones is practical.

Nephrectomy is impractical.

Removal of both kidneys is incompatible with the maintenance of life. It is true that even completely nephrectomized animals can be maintained, for many weeks, with suitable artificial kidney or peritoneal lavage procedures. However, these life-maintaining techniques, in themselves, cause grave alterations in

(1) Goldblatt, H., J. Lynch, R. F. Hanzal and W. W. Summerville: "Studies on experimental hypertension; production of persistent elevation of systolic blood pressure by means of renal ischemia." J. Exper. Med. 59: 347 (1934).

the homeostasis of the body. They seriously affect the volume and constitution of the intercellular fluid, which in turn may alter peripheral resistance and blood-pressure, quite apart from any renal pressor mechanism. At the same time, such artificial lavage procedures may wash out insufficient or excessive amounts of metabolites which can affect the blood-pressure. All these derangements represent especially serious sources of errors in the completely nephrectomized animal, which has no means of correcting them adequately.

Overdosage with renal pressor substances is impractical.

The production of a chronic "hyperrenalism," by the injection of purified renal pressor substances, is equally impractical for a variety of reasons:

Firstly, specialists in this field still do not agree that the hypertension induced by compression of the main renal artery is necessarily always due to the secretion of pressor substances by the kidney.

Secondly, even if we admit that renin and hypertensin are formed, at least at a certain stage of renal hypertension, there is no proof that these are the pressor substances principally responsible for renal hypertensive syndromes (such as Bright's disease) in man.

Finally, there is no agreement as to the relative part played by renal deficiency and renal hyperactivity in the genesis of hypertension; depending upon circumstances, the blood-pressure can rise, both under the influence of complete nephrectomy and under that of overdosage with renal pressor substances.

In these circumstances, it was obviously of the utmost importance to devise some technique which could help us to clarify the part played by the kidney in the pathogenesis of the hypertension produced by stress, anterior-pituitary extracts or corticoids.

The Goldblatt technique had already yielded a great deal of information about the syndrome of primarily renal hypertensive disease. However, this method had the major disadvantage that it did not make it possible to study the results of interfering selectively with the incretory or the excretory function of the kidney. Compression of the main renal artery raises renal-pressor-hormone secretion, but simultaneously it causes a variable, though never complete, interference with urine formation.

Could one separate incretion from excretion by the kidney?

Of course, under such conditions it is impossible to determine whether any accompanying change in the kidney, the blood-pressure or the structure of the cardio-vascular system, is due to interference with the endocrine or excretory functions of renal tissue. What we wanted was a technique which would permit us to abolish, selectively, one of the two main renal functions.

Our problem is not without precedent in other fields of medical research . . .

A similar problem arises in experimental medicine every time one attempts to study the physiology of a complex gland, which has both endocrine and exocrine functions. To take an example from the pages of Canadian medical history, let me remind you that the same difficulty had been encountered, and successfully overcome, by Banting in connection with the pancreas. As you know, he obtained a complete atrophy of the acinar tissue, without interference with Langerhans' islands, by ligating the main duct of this gland. Under these circumstances, no diabetes developed. However, subsequent removal of the residual pancreatic tissue, which contained no parenchyma other than the Langerhans' islands, immediately induced diabetes.

. . . but earlier experience is not applicable to the questions of renal physiology.

Unfortunately, in the case of the kidney, this type of intervention is impractical. Ligation of the excretory duct — in this case the ureter — causes complete destruction of the renal parenchyma; the unusually high pressure under which this gland produces its secretion, the urine, transforms the whole kidney into a fibrous, hydronephrotic cyst. Such an intervention is evidently equivalent to complete extirpation of the kidney, since no parenchymatous elements remain.

At first we considered it futile even to think of means by which we could "dissect" the incretory and excretory elements in the kidney. In fact, we did not know which structural elements are responsible for the secretion of renal pressor substances. Indeed, even if we had accepted indirect evidence pointing to the glomerulus or the tubule as the source of pressor hormones, it was difficult to see how one could ever eliminate any section of all nephrons, without destroying the kidney as a whole.

Actually, this apparently insoluble task was largely solved, without great difficulty, through what is now known as "the endocrine kidney operation." The technique of this intervention is admittedly not essential for the understanding of the adaptation syndrome, but I want to tell you about it anyway. The manner in which we came to develop it makes a rather amusing, simple story, which will take but a few minutes to tell and will give us a welcome rest amidst the complexities of the diseases of adaptation.

The "endocrine kidney."

In view of the manifest impossibility of physically separating the excretory from the (hypothetical and unidentified) incretory elements in the kidney, only interventions which might functionally block one or the other type of renal activity were even considered.

Since much more was known about the mechanism of urine formation than about the secretion of vasopressor hormones, we felt that attempts to block the former function, selectively, would hold the greater promise. Could one eliminate urine formation without interfering with the hormone producing capacity of renal tissue?

To suppress the entire complex mechanism of urine formation, one would have to interfere with its very first phase. That, as you remember, is the process of filtering fluid and solutes through the semipermeable membrane of the glomerular tuft. This filtration is now considered to be essentially a physical process. It depends upon the fact that the hydrostatic blood-pressure in the glomerular capillaries tends to push fluid and solutes out into the free space of Bowman's capsule, despite the much weaker colloid-osmotic pressure of the blood which tends to keep the fluid in the vascular bed.

I shall illustrate this interaction between the two opposing forces by this little drawing. The large arrow represents hydrostatic, the small one osmotic, pressure.

It occurred to us that if by some means, for instance, by a modification of the Goldblatt clamp, one could diminish the hydrostatic pressure in all the glomerular capillaries exactly to the level of the colloid-osmotic pressure, then filtration would have to stop. Yet, there is no reason to fear that the endocrine and other metabolic functions of renal tissue would be seriously impaired under these conditions. After all, it is only

due to the special vascular arrangement of the kidney that the hydrostatic pressure in the glomerular capillaries so greatly exceeds the colloid-osmotic pressure that a filtrate is produced. No such great excess in hydrostatic pressure is seen in other organs, for instance, in the endocrine glands. In these, the hydrostatic and the colloid-osmotic pressures are approximately equal, so that no more is filtered than can be reabsorbed into the circulation.

Of course, the great practical question was how to accomplish such a reduction in the hydrostatic pressure of the renal glomeruli. Theoretically this could be achieved by constricting every glomerular arteriole exactly to the desired degree. Since operations on each individual glomerulus are out of the question, one might attempt to find a way by which the main renal artery could be so compressed that the desired reduction in hydrostatic pressure would automatically ensue in all the glomeruli. Experience had shown that this cannot be accomplished by the Goldblatt clamp in the dog. Firstly, we found it impossible to adjust the clamp as accurately as would be required; secondly, the renal circulation of the dog is so complex that even an optimal degree of constriction at the level of the main renal artery fails to produce the desired result. It tends to cause ischemic necrosis in certain parts of the kidney without reducing the hydrostatic pressure sufficiently elsewhere to prevent continued filtration in other regions of the same organ. The rat with its much simpler renal circulation, arranged within the territory of a single small pyramid, would appear to offer much more promise of success. However, in this species the renal artery is so minute

that an accurately gaged degree of constriction is hardly possible.

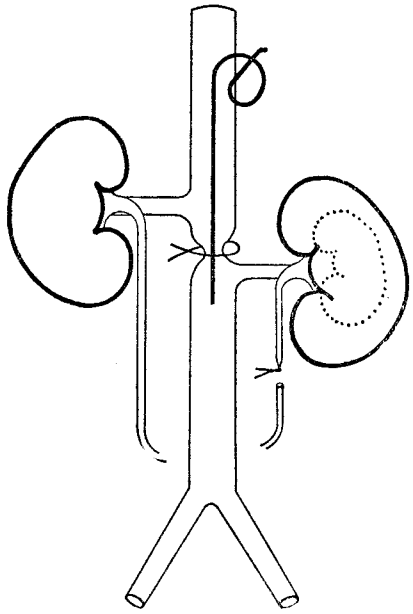
While we were considering these various technical points during the dissection of the renal region in a rat, we noted that in this species the two renal arteries arise from the aorta at some distance from each other. Between the two, there is a sufficiently long piece of aorta on which to perform a well gaged degree of constriction. A clamp placed here would diminish the hydrostatic pressure within the tissue of the left kidney (whose artery arises at a relatively low level), while the right kidney would continue to secrete urine and prevent uremia.

How to constrict the aorta consistently to the same degree . . .

The next problem was to find some surgical technique which would permit us to constrict the aorta consistently to the same degree. In the rat even this vessel is rather narrow for such fine manipulations. The difficulty was circumvented with the aid of a simple piece of wire (the stile of a hypodermic injection needle). One end of this wire was curved back, so that one could easily hold it between two fingers; then it was placed on the anterior surface of the aorta, parallel to its main axis, between the two renal arteries. After this, a nylon thread, which does not shrink or swell, was passed around aorta and wire, embracing both. This loop was tied solidly, so that it completely obliterated the circulation from the cranial to the caudal part of the ligature. Now, we only had to remove the wire to establish a lumen corresponding accurately to the caliber of our stile. This solved the problem of obtaining an exactly reproducible degree of constriction, but of course, it was by no means necessarily the desired degree.

. . . and at that to any previously defined degree.

You will remember that our operation could be successful only if we managed to find a way to constrict the aorta precisely so that the hydrostatic pressure in the glomeruli would equal the colloid-osmotic pressure of the blood. Hence, the next task really



consisted of two parts: firstly, of developing a technique which would permit us not only to produce always the same degree of constriction, but the desired degree; secondly, to verify that whatever constriction we have produced does in fact equalize the hydrostatic and colloid-osmotic pressures in the glomerular capilllaries. Again, it was difficult to visualize how we could possibly accomplish this. At first, we thought that we would have to adjust the aorta ligature on each rat, while taking measurements of the hydrostatic glomerular pressure, and then stabilize the constriction at the point which gives the desired result. Neither such an accurately adjustable application of the con-

striction, nor the actual measurement of the glomerular pressure seemed to be technically feasible. Fortunately it turned out that this dual task could be solved by a trick which obviated the necessity for all this. We arranged things so that we did not even have to measure the glomerular pressure and still could be sure of obtaining an optimal degree of constriction.

We argued that for a rat of any given size, there must be a caliber of wire to the size of which the aorta should be constricted in order to produce the desired result. So, actually the problem limited itself to finding the thickness of wire which would be suitable for any one rat.

Now, what we actually did is this. By that time, I had done a good deal of work with the piece of wire used in the initial experiments and became rather fond of it; so, instead of laboriously trying to find a wire whose caliber would suit a given rat, I did the opposite. Taking a number of rats of varying ages, I determined the size of rat which happened to fit my wire.

How to tell that the operation was successful.

It was a priori obvious that if I take rats of various weights (ranging between, say, 40 and 200 gm.) and constrict their aortae in all cases to the caliber of my particular wire, there would have to be one size of rat in which the resulting degree of constriction would happen to be the right one. The success of the operation should then be readily detectable if, between two ligatures, we also sectioned the ureter of the kidney in the low pressure territory. There should be no accumulation of fluid in the renal pelvis itself, if the glomerular hydrostatic pressure fell to or below the colloid-osmotic pressure. This would mean the constriction is not too lax. If, on the other hand, the constriction were too severe, resulting in glomerular hydrostatic pressures below the level of the colloid-osmotic pressure, then necrosis of renal parenchyma should reveal this.

All these predictions were confirmed by actual observation, and I am happy to report that rats of about 100-120 gm. body weight just fitted my favorite wire. In larger animals, the constriction was too intense and there were more or less extensive white patches of necrosis in the kidney, which were perfectly obvious by naked eye inspection. In rats smaller than 100 gm., a variable degree of hydronephrosis occurred, because the constriction was not great enough and some degree of filtration continued after the operation.

Actually, the occlusion of the ureter on the left side proved to have more than just this diagnostic value. It turned out that if the constriction is not quite, although almost, severe enough, some urine will be secreted, but in the presence of the ureter obstruction, this will build up sufficient hydrostatic pressure in the renal pelvis itself to counterbalance the slight excess of glomerular pressure. Thus, this ureter ligature saved many border-line cases, in which the operation would otherwise have failed because of slightly insufficient constriction.

Macroscopic aspect of "endocrine kidney."

In successful cases, the kidney in the low pressure territory rapidly undergoes a considerable reduction in size, but maintains the color of healthy parenchymatous tissue. About a week after the operation, a section through the organ shows the medulla to be extremely hyperemic, while the cortex is comparatively pale. Perhaps this is due to some "renal shunt" mechanism, which brings blood preferentially to the medullary and juxta-medullary areas. On the border-line between the cortex and the medulla, there is a fairly

wide layer of greyish tissue, whose color delimits it distinctly from both cortex and medulla. This layer corresponds to the spiral segments of the nephrons.

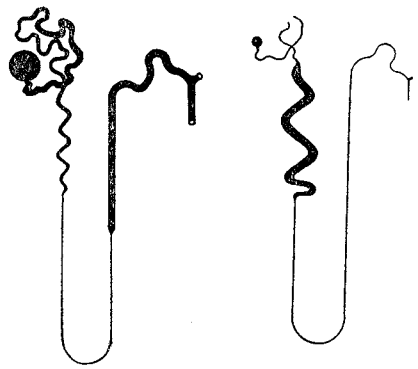
Microscopic aspect of "endocrine kidney."

Detailed histologic and particularly microdissection studies of the nephrons have subsequently revealed that within the first two weeks after the operation, the entire renal tissue transforms itself into a parenchyma exhibiting the typical morphologic features of pure endocrine tissue. It loses all the characteristics of a secretory or excretory gland. That is why we called this artificially produced organ — which has no exact physiologic equivalent in nature — the "endocrine kidney."

All of the glomeruli undergo considerable involution and transform themselves into comparatively anemic scar-like foci in which adhesions tend to develop between the parietal and visceral lamina of Bowman's capsule; if the animals live long enough, most of these glomerular remnants eventually disappear. In any event, even immediately after the operation, they do not filter, as shown by the fact that no fluid accumulates in Bowman's capsule. Correspondingly, the tubular parts of the nephron collapse and become solid cords.

Serial sections and microdissections show that all parts of the nephron undergo severe involution immediately after the "endocrine kidney" operation, with the sole exception of the spiral segments. I could illustrate the result of this operation by the adjacent two sketches.

The drawing on the left shows schematically the approximate appearance and relative proportions of the various segments in a normal nephron. Compare this with the drawing on the right, depicting conditions after the operation. You will note that the glomerulus has become atrophic and most of the tubular structure has disappeared. Only the spiral segment detaches itself by the fact that it not only fails to involute, but actually undergoes hypertrophy. Since in the single-pyramid kidney of the rat, all the spiral



segments are arranged in one roughly semicircular layer, their hypertrophy becomes macroscopically visible; they are represented by that grey line on the cross-section, about which I spoke a few minutes ago. In this layer, there are many mitotic figures, signs of active cell proliferation. As a result of such growth, the lumen of each tubule is gradually filled out and distended by living and apparently highly functional cells. This particular region is well supplied with blood; its wide sinusoids surround solid cords of typical glandular cells, this simulating the histologic characteristics of a functional endocrine gland.[2]

Is the "endocrine kidney" really endocrine?

Yet, such purely morphologic criteria would not allow us to conclude with certainty that this organ is actively producing hormones. The following pertinent facts strongly imply, however, that this is the case:

[2] Selye, H. and H. Stone: "Pathogenesis of the cardiovascular and renal changes which usually accompany malignant hypertension." J. Urol. *56*: 399 (1946).

(1) After the "endocrine kidney" operation, the blood-pressure rises rapidly, the heart hypertrophies and there develops a myocarditis (often with "Aschoff nodules") as well as diffuse periarteritis nodosa, with nephrosclerosis in the contralateral (right) kidney. All these changes occur only if the left kidney has actually transformed itself into such an organ of endocrine aspect. They are absent if it undergoes necrosis, because the aorta ligature is too severe, or if marked hydronephrosis occurs, as a result of insufficient aortic constriction. Of course, if the caliber of the aorta is suddenly much reduced, there will be a transitory rise of pressure — presumably due to a purely mechanical increase in the peripheral resistance — but this vanishes as soon as collateral pathways of circulation have adjusted themselves.

(2) In rats in which the endocrine kidney operation was successful and did cause a persistent and progressively increasing hypertension, the blood-pressure returns to normal if the endocrine kidney is removed within the first few days. Such animals do not develop nephrosclerosis in the contralateral kidney, nor do they subsequently show any signs of periarteritis nodosa or myocarditis.

Extirpation of the "endocrine kidney" two or more weeks after the operation, rarely succeeds in curing the hypertensive syndrome or even in preventing its progression towards death. This is probably due to the fact that, secondarily, the contralateral (right) kidney becomes nephrosclerotic under the influence of its "endocrine" partner.

(3) Denervation of the endocrine kidney does not interfere with its ability to raise the blood-pressure or to cause cardio-vascular damage. Since the organ no

longer excretes anything and, after denervation, is connected with the body exclusively through its vascular system, it could act only in two ways: either by secreting some pressor hormone into the blood, or by destroying some antipressor principle brought to it by the blood. The last-mentioned mechanism is less probable, but its possibility must be conceded. In any case, the "endocrine kidney" would have to act through humoral means.

It would thus appear that with the aid of a comparatively simple surgical technique, we have been able to destroy selectively the excretory function of the kidney. This left the organ with cellular elements which are no longer in contact with the outside and affect the body exclusively through their influence upon the blood which circulates through them.

Evaluation of "endocrine kidney" —

Now, what did this endocrine kidney preparation teach us ?

Urine formation is not necessary for RPS production.

(1) *The filtration of urine is not essential for the production of renal hypertension.* It will be recalled Goldblatt and his co-workers, who produced renal hypertension with the metallic clamp technique, had found that by ligating the ureter of the clamped kidney, the blood-pressure can be restored to normal. They concluded that the production of pressor substances depends upon simultaneous urine formation. However, in their experiments, obstruction of the ureter, after the blood-pressure had risen, probably cured the hypertension merely by destroying the kidney through hydronephrotic changes. The "endocrine kidney" which (unlike that of the Goldblatt clamp bearing animal) does not secrete urine, raises the blood-pressure even after ligature of the ureter.

Site of RPS production.

(2) *The site of renal pressor hormone production (or of antipressor substance detoxification) appears to be in the spiral segment of the convoluted tubule,* not in the glomerulus as had previously been thought. This is made highly probable since, in our "endocrine kidney," the glomeruli disappear or become anemic and atrophic, just as all other parts of the renal parenchyma, with the sole exception of the spiral segment.

(3) *The hypertrophy of the spiral segment induced by the purely mechanical "endocrine kidney" operation, bears a striking similarity with the renal changes seen during the hypertension which is produced by DCA, STH or LAP,* under suitable experimental conditions. This implies that the hypophyseal and corticoid adaptive hormones could raise the blood-pressure, in part, through this effect upon the kidney.

Renal hypertension not dependent upon renal deficiency.

(4) *Renal hypertension is not necessarily due to incipient uremia or any other type of pure deficiency in renal function.* The "endocrine kidney" operation causes only partial involution of one kidney, yet it produces severe hypertension, while complete removal of this organ leaves the blood-pressure uninfluenced. Some investigators, especially Grollman and his school,[3] are still emphatically defending the pure deficiency theory of renal hypertension because their completely nephrectomized (indeed, even bilaterally nephrectomized and adrenalectomized) dogs, maintained by peritoneal lavage, develop hypertension. As I have stated earlier, peritoneal lavage and even the more refined artificial kidney techniques, can seriously alter the volume and constitution of the intercellular

[3] Turner, L. B. and A. Grollman: "Role of adrenal in pathogenesis of experimental renal hypertension as determined by a study of the bilaterally adrenalectomized dog." Am. J. Physiol. *167*: 462 (1951).

fluid compartment and thus raise the blood-pressure by increasing peripheral resistance or augmenting the blood-volume. Of course, there is no question about the fact that the blood-presure is affected by many factors apart from renal hormones, and hence it is not unexpected that hypertension can appear even in the absence of kidneys.

On the other hand, it has also been definitely shown that completely nephrectomized dogs can be maintained for months by an artificial kidney, without developing hypertension.[4] Hence, renal deficiency in itself is not necessarily conducive to hypertension.

Pressor effect of corticoids and RPS largely interdependent.

(5) *The pressor actions of corticoids and of renal pressor substances are largely interdependent.* To what extent the corticoids act upon the blood-pressure through the kidney remains to be determined. It is undoubtedly possible, indeed probable, that they also influence the blood-pressure homeostasis directly through their effect upon vessels and upon the volume and the constitution of intercellular fluid, just as the artificial kidney and lavage procedures do. In the light of what we have just said, there can be little doubt, however, that the corticoids can also cause hypertension through the kidney. They do so firstly by inducing "endocrine-kidney-like" changes, and subsequently through nephrosclerosis with a constriction of the renal vascular bed, that is, changes similar to those obtained by the surgical techniques.

The importance of this latter pathway in determining the effect of corticoids upon the blood-pressure was also demonstrated by recent investigations of M.

[4] Leonards, J. R. and C. R. Heisler: "Artificial kidney — IV. Maintenance of life in bilaterally nephrectomized dogs and its relation to malignant hypertension." Am. J. Physiol. *167*: 553 (1951).

Van den Bossche and Roger Guillemin in our Institute. Both these authors showed that in completely nephrectomized rats maintained by peritoneal lavage — unlike in intact animals — DCA fails to produce hypertension and cardio-vascular lesions. Of course, this observation does not preclude the possibility of peripheral synergisms between corticoids and renal pressor substances, say in the blood-vessels themselves. In fact, there is convincing experimental evidence to demonstrate such a synergism with various pressor hormones, including nor-adrenaline.

Incidentally, we have now learned through the particularly instructive clinical observations of Thorn [5] that, in patients with severe hypertension, the blood-pressure can be restored to near-normal levels by complete bilateral adrenalectomy. Threshold doses of cortisone plus DCA maintain them in reasonably good health without restoring any severe degree of hypertension. In my opinion, this is strong evidence in favor of our theory according to which the adrenals play an important rôle in the pathogenesis of clinical hypertensive disease.

Relation between RPS formation and electrolyte changes caused by corticoids.

(6) *The endocrine kidney has helped to clarify the correlations which exist between changes in electrolyte metabolism and the hypertension caused by hormones.* DCA overdosage regularly elicits hypokalemia and some degree of hypochloremic alkalosis, when it is administered in doses capable of producing nephrosclerosis and hypertension. Besides, high-sodium intakes aggravate the hypertensive and nephrosclerotic effect of DCA. All this strongly suggested that much

[5] Thorn, G. W.: "Further clinical studies with ACTH and adrenal cortical hormones." In: Adrenal Cortex. Transactions of the Second Conference, Josiah Macy Jr. Foundation, Publ., New York (1951).

of the toxicity of this steroid depends upon changes in electrolyte metabolism. The "endocrine kidney," on the other hand, produces nephrosclerosis in the contralateral kidney, hypertension, periarteritis nodosa and myocarditis, without causing hypokalemia. This showed that a fall in blood-potassium is not essential for the pathogenesis of such changes.

Furthermore, the damage caused by the "endocrine kidney," unlike that of DCA overdosage, is not aggravated by a high-sodium intake. Perhaps an excess of sodium helps only in the process of transforming nephrons into "endocrine nephrons," under the influence of DCA, but exerts no further damaging effect once this transformation is maximal, as after the surgical intervention.

These are quite fundamental differences between the hypertensive disease produced on the one hand by DCA, on the other by the "endocrine kidney;" yet, hypochloremic alkalosis was elicited by both procedures. This does not prove any fundamental interrelationship between the two types of experimental hypertensive disease, but it is consonant with the view that DCA could cause hypochloremic alkalosis through the intermediary of its effect upon the endocrine function of the kidney.

Chemistry of "endocrine kidney tissue."

(7) *The "endocrine kidney" technique supplied us with virtually pure specimens of endocrine kidney tissue for chemical analysis.* This proved useful in determining which chemical characteristics (e.g., enzymes) are dispensable for the pressor effect of renal tissue because it was found that, after urine secretion is abolished, the kidney undergoes just as severe "regressive" changes in its chemical constitution as in its morphologic structure. Obviously, a

normal chemical constituent of the kidney which disappears during the process of "endocrine transformation" could not be indispensable for the renal pressor effect.

It would be far beyond the scope of my lecture series to enumerate the many other uses to which the "endocrine kidney" technique has been put, or to discuss in greater detail the complex problem of renal hypertension. As a general conclusion, we may say, however, that the adaptive hormones, and particularly the prophlogistic ones such as STH and DCA, can raise the blood-pressure: (1) through their effect upon the kidney and the consequent activation of the renal pressor system, and (2) through their effect upon the blood-volume, the intercellular fluid volume, and the peripheral circulation itself.

Now, after this digression into the field of renal hypertension and its possible connection with the major pathways of the G-A-S, let us return to the pituitary-adrenal system itself.

Ever since the beginning of this lecture series, we have hardly said a word about the antiphlogistic hormones. This had to be so because, at first, our only means of studying them was to increase their endogenous production by stress, or to inject them in the form of very impure extracts. The disadvantages of working with endogenous hormones or impure extracts require no comment. It will be clear to all of you that important progress along these lines could not be made until chemists furnished us with adequate methods for the purification and large-scale production of antiphlogistic hormones. Most important among these principles are: ACTH, which induces the adrenal to

produce predominantly antiphlogistic corticoids (A-Cs), and the pure antiphlogistic corticoids themselves, for instance, cortisone and hydrocortisone.

First therapeutic results with ACTH and cortisone.

It was in 1949 that P. S. Hench and his co-workers at the Mayo Clinic announced their important findings concerning the clinical use of ACTH and cortisone.[6] A little later, it was shown that hydrocortisone (Kendall's compound F) exerts effects essentially similar to those of cortisone. Given at high dose levels, all these antiphlogistic hormones proved to be eminently effective in inhibiting manifestations of inflammation in such diseases as rheumatoid arthritis or acute rheumatic fever and, less constantly, in certain types of periarteritis nodosa, gout, ulcerative colitis, allergic inflammations, lupus erythematosus, and a great variety of inflammatory diseases of the skin and eyes.

To me, the essential feature of all these maladies, which respond so favorably to ACTH or A-Cs, is that the eliciting pathogen (microbe, drug or allergen) does not in itself cause any severe and widespread tissue injury. It stimulates a disproportionately excessive inflammatory defense, and, to the patient, this excessive inflammation is actually the most disturbing manifestation of disease.

In many of the maladies which I have just enumerated, we do not know the exact nature of the eliciting pathogen. It is evident, however, that even after the inflammatory response is suppressed by antiphlogistic compounds, the provocative factor is still

---

(6) Hench, P. S., E. C. Kendall, C. H. Slocomb and H. F. Polley: "The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis: preliminary report." Proc. Staff Meet. Mayo Clin. *24*: 181 (1949).

there; only now, it causes little, if any, "disease manifestation" in the usual sense of the word. I say it is still there because, in almost every instance, when treatment with the antiphlogistic hormones is discontinued, the disease manifestations reappear again. One might say that these antiphlogistic hormones suppress the manifestations of the disease but not its cause. This is very reminiscent of the results we had obtained with antiphlogistic adreno-cortical extracts in animals, for instance, as regards the hyperergic inflammation normally produced in rats by parenteral injections of egg-white. The egg-white is not destroyed by the extract, but the manifestations of hyperergic inflammation in the connective tissue are suppressed.

Antiphlogistic hormones may also cause temporary remissions in the course of lymphatic leukemias, lymphomatoses and thymus tumors (presumably due to their lympholytic effect), as well as in certain anemias and nephroses (perhaps due to their antiallergic effect). However, in these latter diseases the mechanism of their action is admittedly still obscure.

These clinical observations had a considerable influence upon the development of medical thought, because they objectively demonstrated the possibility of influencing comparatively common diseases of the connective tissue by means of hormones. They corroborated the tenet that hormones — and particularly pituitary and cortical hormones — can play a decisive rôle in maladies which are not commonly considered to be "endocrine diseases," because they are not due to a clear-cut primary hyper- or hypofunction of an endocrine gland. These maladies are not actually due to hormonal defects; they are caused by microbes, poisons or allergens, yet their course is largely determined by hormones.

Now, suddenly, ACTH and cortisone became quite generally available to practising physicians and an enormous amount of information came to light concerning the effects of adaptive hormones in man. Those who had considered them as primarily concerned with adaptation itself were not unprepared to learn that they influence so many conditions, since adaptation notoriously plays a prominent part in most vital processes, including disease. It was extremely valuable, however, to accumulate data concerning their pharmacologic actions in man, the complications one may encounter and, especially, the degree of their therapeutic efficacy in various spontaneous maladies.

It would not be within the frame of these lectures to discuss purely clinical aspects of this kind in any detail. Besides, I have already done so in my series of monographs on stress and many pharmaceutical companies furnish pamphlets giving the principal indications and counter-indications of these substances for the use of the practising physician.

Let me merely mention a few highlights.

Principal effects of ACTH and A-Cs in normal man.

Both ACTH and the A-Cs (cortisone and hydrocortisone), in high doses, cause an increase in may encounter and, especially, the degree of their metabolites, for instance the 17-ketosteroids. They tend to produce euphoria and insomnia. They raise the blood-sugar and the urinary elimination of nitrogen and uric acid. They cause lymphopenia and eosinopenia in man, just as they do in experimental animals. The principal difference between ACTH and the A-Cs is that the former stimulates, the latter inhibit, adrenocortical function.

Principal drawbacks of ACTH and A-Cs in clinical practice.

If given for several weeks at high dose levels, especially in constitutionally predisposed individuals, they may produce a syndrome of Cushing's disease with hypertension, osteoporosis, loss of nitrogen, diabetes, hyperpigmentation, purple striae of the skin, a typical "buffalo neck" and "moon face."

Although the antiphlogistic corticoids are predominantly "gluco-corticoids," that is, substances which promote gluconeogenesis from protein, they do also have varying degrees of "mineralo-corticoid" effects. Hence, ACTH, cortisone and hydrocortisone are all capable of producing sodium chloride and water retention, with increased elimination of potassium, in man. Simultaneously, the blood-potassium values may fall to dangerously low levels. In order to counteract these electrolyte disturbances, it is advisable to keep patients, who are receiving therapy with these hormones, on a low-sodium-chloride, high-potassium intake. If this precaution is not observed, dangerous retentions of water, with an increase in blood-volume and interstitial-fluid volume, may result in cardiac decompensation, while the hypopotassemia may induce serious neuromuscular disturbances.

Perhaps as a side effect of their inhibitory action upon inflammation (diminution of encapsulation, normalization of sedimentation rate and blood-protein pattern, decrease in fever, etc.), the antiphlogistic hormones diminish resistance to a variety of microbial pathogens. Thus, a latent focus of tuberculosis may be activated by ACTH or cortisone.

Among the contraindications, one might also mention that antiphlogistic hormones occasionally tend to delay wound healing or produce a gastric ulcer, although these effects are rarely prominent in man.

Nephritis and nephrosclerosis may be aggravated and (with the exception of certain presumably allergic types of renal inflammation) are seldom, if ever, beneficially influenced by treatment with ACTH, cortisone or hydrocortisone. This is of special interest because, as we shall see later, the experimental nephritic and nephrosclerotic lesions produced by prophlogistic corticoids in animals are likewise aggravated by antiphlogistic hormones. On the other hand, as we have already stated, remissions in the clinical syndrome of nephrosis are frequently obtained during, or immediately following, a course of treatment with ACTH, cortisone or hydrocortisone.

Especially in hereditarily predisposed unstable individuals, intense treatment with antiphlogistic hormones can precipitate serious mental disturbances of a psychotic character. These may be severe enough to necessitate shock therapy, but almost invariably all of the detrimental changes which I mentioned, disappear upon cessation of hormone treatment. Unfortunately,

the favorable actions likewise tend to last only as long as treatment is continued.

Practical pharmacology of ACTH and A-Cs.

To complete this résumé concerning the clinical actions of antiphlogistic hormones, I should just like to add a few, perhaps less fundamental but practically important, data pertaining to their therapeutic use.

ACTH acts almost only through the adrenals.

For all practical purposes, the actions of ACTH are dependent upon the responsiveness of the patient's adrenals. After destruction of the adrenal cortex in Addison's disease, ACTH has no effect. Thus, topical administration of ACTH by injection into the inflamed area is not indicated, since it is not ACTH itself, but the corticoids manufactured under its influence by the adrenals, which are effective. We do have some data suggesting that certain actions of ACTH are not mediated through the adrenals, but none of these is of importance to the clinician.

Activity of ACTH is increased by delay in absorption rate.

It is highly recommendable to administer ACTH in a manner which permits a constant effect over a long period. Parenterally injected water-soluble preparations of the hormone are rapidly picked up into the blood-stream and detoxified or excreted. It is therefore recommended to use "slow acting" ACTH preparations whose therapeutic value is greatly enhanced by the admixture of substances which retard the absorption rate and thus permit protracted actions. To accomplish this same result, ACTH can be administered over a period of many hours or days by a constant intravenous drip; special techniques have been perfected to make this possible without too much inconvenience to the patient. Under these conditions, much less ACTH is required to obtain a certain effect than if single injections of the rapidly acting free hormone were administered.

A-Cs act also in the absence of the pituitary and adrenals.

Cortisone and hydrocortisone are both effective in the presence or absence of the adrenal and pituitary since they act upon the receptor cells directly. This has been shown, for instance, in patients with bilateral inflammatory diseases of the eyes. Here, application of cortisone, in the form of a subconjunctival injection or of an ointment introduced into the conjunctival sac, can inhibit inflammation on the treated side, without affecting the other eye. Such topical treatment is particularly advisable wherever the lesion is circumscribed and readily accessible from the outside, for instance in inflammatory diseases of the anterior part of the eye or in patients with rheumatoid arthritis when only one or two joints are seriously afflicted.

Advantages of hydrocortisone for topical use

For topical application, hydrocortisone is preferable to cortisone, presumably because of a more favorable absorption rate. In some instances of rheumatoid polyarthritis, systemic treatment with low doses of cortisone permits an easy control of almost all the lesions, but too much would have to be given

in order to improve the condition of one or two particularly resistant joints. Here, topical treatment with hydrocortisone may be used as an adjunct to systemic therapy with low doses of either cortisone or ACTH.

Routes of administration of A-Cs.

Cortisone and hydrocortisone are now commercially available for parenteral administration in the form of microcrystals suspended in an aqueous medium and, for oral use, in tablet form. Unlike ACTH, these steroids are not destroyed by digestive enzymes; they are well absorbed from the gut. For topical use, cortisone is also prepared in the form of eye-drops and ointments, for inhalation through nebulizers, etc. etc.

The antiphlogistic hormones have now been used in such a variety of clinical conditions that their major indications and contraindications are fairly well established. As regards such essentially pharmaceutical points as dosage, route of administration, vehicle for these hormones, etc., undoubtedly much progress is still to be expected, but this kind of advance is not really fundamental.

I believe that much valuable information will be obtained, however, as we progress in the analysis of the many other factors which tend to affect the course of the diseases of adaptation. First among these are the many "conditioning factors" such as diet, pre-existing impairment of certain organs, particularly the kidney (through which the vasopressor mechanism can be affected) and the liver (which participates in the metabolism of steroids), etc. Then, there are the actions of STH and of the prophlogistic corticoids, as well as the many intricate interactions, synergisms and antagonisms, between the various adaptive hormones themselves; none of these has yet received much attention from clinicians. As I said at the beginning of this lecture, it is probably as a result of the "conditioning factors" and of the manifold interactions between the adaptive hormones, that a comparatively small number of these humoral substances can produce such a variety of lesions in almost any combination.

It will be the subject of my next address to examine the changes produced in animals by overdosage with purified antiphlogistic hormones such as ACTH, cortisone and hydrocortisone. [Adequate amounts of these substances have become available for large-scale animal experimentation only after their industrial production had been fully developed in answer to clinical demands. Hence, in this chronologically presented account, we could not deal with these important aspects of our subject before.]

This will quite naturally lead us to the study of the manifold interactions between the various members of the adaptive hormone group.

Finally, I shall present some data concerning the therapeutic usefulness of prophlogistic hormones, a hitherto badly neglected and yet very promising aspect of this approach.

FIFTH LECTURE

Overdosage with Antiphlogistic Hormones. – Interactions between Various Adaptive Hormones. – "Conditioning" of Adaptive-Hormone Actions by (Systemic or Topical) Stress Itself. – The Therapeutic Value of Prophlogistic Hormones.

Ladies and Gentlemen !

ALTHOUGH THE EFFECTS of overdosage with prophlogistic hormones — notably DCA, desoxocortisone and even STH (the latter in the form of LAP) — had been the subject of intensive study ever since 1942, the consequences of severe intoxication with antiphlogistic hormones had remained almost completely unexplored. Until this point in our story, the main facts we did know about them were that: impure ACTH preparations and more or less crude adreno-cortical extracts exert predominantly glucocorticoid effects (in that they promote gluco-neogenesis from protein), they are strongly thymolytic and lympholytic, they cause catabolism, they play an important rôle in resistance against systemic stress and they tend to inhibit certain types of inflammation (e.g., the hyperergic reaction to egg-white in the rat).

Some of these data had already suggested that antiphlogistic hormones may play a rôle in the pathogenesis of certain "diseases of adaptation." For instance, when the organism is deprived of such substances (as that of a hypophysectomized or adrenalectomized animal) the major cause of shock after ex-

posure to stressors is presumably an insufficiency in these hormones. On the other hand, excess production of antiphlogistic substances was found to be the immediate cause of the so-called "accidental thymus involution," commonly seen in pediatric practice. It may be debated whether shock or the sudden disintegration of thymus tissue are really "diseases" in the usual sense of this word; yet, here we had objective proof that damage, or even a morphologically well-characterized pathologic change, could be due respectively to an absolute deficiency or excess in antiphlogistic hormones.

ACTH and cortisone overdosage.

As soon as purified ACTH and cortisone preparations became generally available, we were naturally interested to find out whether a massive overdosage (technically possible only with such purified substances) would bring to light additional manifestations of disease.

The most prominent features of the syndrome elicited by severe intoxication with ACTH or cortisone in the rat were these:

In addition to the already mentioned thymicolymphatic atrophy, the metabolic effects and the diminution of the "inflammatory potential," there was a considerable diminution in resistance to various infections. For instance, both in the rat [1] and mouse,[2] even normally saprophytic organisms begin to proliferate actively and tend to form large, macroscopically visible foci in the pleural cavity, the lung, liver, spleen, kidneys and many other organs. At the same time, there is osteoporosis, atrophy of the skin with loss of hair and particularly pronounced involu-

(1) Selye, H.: "Stress (The physiology and pathology of exposure to systemic stress)." Acta Med. Publ., Montreal (1950).

(2) Antopol, W.: "Anatomic changes produced in mice treated with excessive doses of cortisone." Proc. Soc. Exper. Biol. & Med., *73*: 262 (1950).

tion of connective tissue throughout the body; in young animals, this is associated with a marked inhibition of growth and a great diminution in the width of the epiphyseal cartilage plates.

Interactions between the various adaptive hormones: ACTH + A-Cs.

In rats simultaneously treated with ACTH and cortisone, or other A-Cs, there appears to be essentially a summation of the hormone effects as regards metabolic changes, inhibition of inflammation, diminution of resistance to infections, etc.

One notable exception is the effect of ACTH and A-Cs upon the adrenal cortex itself. Under normal conditions, the A-Cs, just as all other corticoids (as well as the androgens), tend to cause a "compensatory atrophy" of the adrenal cortex, presumably by diminishing ACTH production. After massive injections of ACTH, however, this atrophy fails to appear, since a decrease in the endogenous production of the hormone becomes relatively unimportant in the presence of great exogenous excesses.

STH + P-Cs.

Simultaneous treatment with STH and P-Cs, such as DCA, results in a pronounced potentiation of the prophlogistic, nephrosclerosis-producing and, to a lesser degree, of the anti-infectious and somatic growth-promoting effects of somatotrophin.

ACTH (or A-Cs) + P-Cs.

Conversely, simultaneous treatment with ACTH (or A-Cs) and P-Cs, for instance with ACTH (or cortisone) and DCA, results in a rather complex interaction which cannot be simply described either as a synergism or as an antagonism; in certain target organs the two hormones increase each other's effects while, in most respects, they are mutually antagonistic. We refer to this interaction as an "inter-hormonal tension;" as we shall see in a moment, it plays an important rôle in medicine.

Synergisms.

A simple synergism between A-Cs and P-Cs is noted as regards their ability to maintain life in the ab-

sence of adrenal tissue, to produce nephrosclerosis or nephritis, adreno-cortical atrophy, and anesthesia.

Antagonisms.

The two types of hormones antagonize each other in most other respects. The production by DCA of arthritis, periarteritis nodosa, an increase in the inflammatory potential of the connective tissue throughout the body, an increase in erythrocyte sedimentation rate and in the electroconvulsive threshold, are all powerfully counteracted by ACTH or cortisone.

Lack of interaction.

Finally, antiphlogistic hormones possess certain actions which remain uninfluenced by the P-Cs. For example, the thymico-lymphatic involution induced by ACTH or A-Cs is not significantly affected by simultaneous treatment with the P-Cs which, in themselves, do not exert any significant effect upon lymphatic cells. (I must admit that, offhand, I cannot think of any P-C action which is neither inhibited nor enhanced by A-Cs !)

ACTH (or A-Cs) + STH.

As regards some effects, for instance granuloma formation, essentially the same type of interaction which exists between ACTH or A-Cs and P-Cs, also exists between ACTH or A-Cs and STH. Yet, in other respects, there are important differences: STH, unlike the P-Cs so far examined, has a very pronounced anabolic growth-promoting effect and particularly enhances the development of the thymus, spleen, lymph nodes and liver; furthermore, it stimulates endogenous ACTH production and, most important of all, it exerts a marked anti-infectious effect, especially in animals whose resistance has been previously impaired by ACTH or A-Cs.

Conversely, the diabetogenic action of the STH preparations, now available, is considerably aggravated by simultaneous treatment with ACTH (Reid, Engel et al.). Thus, here again synergisms are intermixed with antagonisms.

It is not yet clear why only STH is powerfully anti-infectious, since both STH and DCA greatly stimulate phlogistic responses as judged by granuloma formation. A hint concerning the possible cause of this difference is given by the histologic aspect of the granuloma produced. This, in the case of STH-overdosed animals, resembles normal proliferating inflammatory tissue, while after excess DCA, the connective tissue cells and fibers, though numerous, are of abnormal appearance and usually separated by a hyalin matrix. Perhaps the effect of STH upon blood-protein formation in the liver and upon lymphatic organs in general also plays a rôle here; through these actions, STH might enhance antibody formation, but this has not yet been definitely demonstrated.

Mechanism of anterior-pituitary hormone secretion.

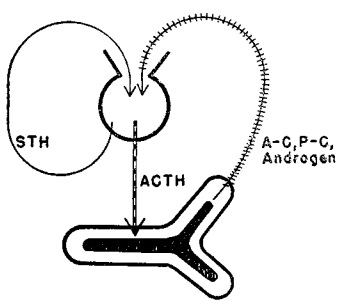
In connection with the interactions between the various adaptive hormones, we must give special attention to the mechanism regulating their discharge from the anterior lobe.

Some pertinent questions have already been discussed. Thus, we mentioned that the nature of the "first mediator of hormonal defense" is not yet known. Adrenaline, histamine-like tissue metabolites, nervous stimuli have all been considered as being potentially involved in causing ACTH discharge during stress, but it has not been possible to single out any one of these agents as the fundamental mediator involved in all stress responses.

We also mentioned the "compensatory atrophy" of the adrenal cortex which can be obtained by administration of excess A-C, P-C or testoid ("androgenic") compounds, presumably due to an inhibition of ACTH secretion. Conversely, lack of corticoids (e.g., after partial adrenalectomy) causes a "compensatory hypertrophy" of adreno-cortical cells due to an increased ACTH secretion.

Diets rich in protein also tend to augment the adrenal hypertrophy during the adaptation syndrome, presumably because they increase ACTH secretion.

Finally, exogenous STH administration augments adrenal development, but only in the presence of the pituitary. Hence, here again, the adrenal stimulation is apparently achieved through the intermediary of a hypophyseal ACTH discharge.



The adjacent drawing illustrates these interactions. You will note that the A-Cs, P-Cs and androgenic compounds of the adrenal cortex all possess in common the property of inhibiting ACTH secretion and thus causing adrenocortical atrophy (cross-hatched arrow). On the other hand, STH stimulates ACTH secretion and thus, in this respect, it antagonizes all the previously mentioned steroids. High-protein diets further augment the stimulation of ACTH secretion by STH, presumably due to an effect upon the pituitary itself.

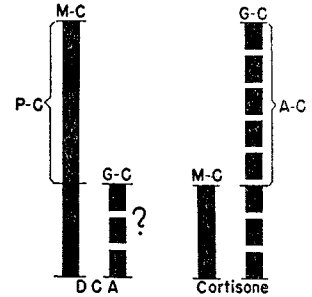
Manifest and masked hormone actions.

We already had occasion to speak about certain overlaps between the effects of A-Cs and P-Cs upon mineral metabolism. We said that all the adequately investigated A-Cs (such as cortisone, hydrocortisone, corticosterone, dehydrocorticosterone) are gluco-corticoid (G-C), since they promote gluco-neogenesis from protein. On the other hand, the P-Cs (for example, DCA, desoxocortisone) are predominantly mineralo-corticoid (M-C), in that they prove particularly effective in inducing sodium chloride and water retention, with potassium excretion. However, *there is some overlap in these activities.* All G-Cs so far examined exhibit varying degrees of M-C activity as well, although none of the M-Cs appears to be endowed with any significant degree of G-C activity.

On the other hand, if we examine these compounds from the viewpoint of their effect upon inflammation,

such an overlap of activity is not demonstrable. I say "not demonstrable" instead of "absent" because the possibility must be admitted that A-Cs also possess some P-C activity, but this point is purely academic. Since these two actions are antagonistic, only the one which quantitatively predominates can become manifest in any case. In typical antiphlogistic compounds, such as cortisone, the activity which is actually measurable is the excess of A-C over P-C, and in predominantly prophlogistic substances, such as DCA, the excess of P-C over A-C.

The following schematic drawing will illustrate what I have in mind.



This illustrates the actions of two corticoids: (1) *DCA,* whose predominant effect is M-C (and P-C) and which has little, if any, G-C (or A-C) actions; (2) *cortisone,* whose principal effect is G-C (and A-C), although it definitely also possesses some M-C activity. We have no means of detecting the possible prophlogistic actions of such steroids, since these would necessarily be "masked" by the preponderantly antiphlogistic effects of these same compounds.

The situation is entirely different as regards the M-C effect of predominantly G-C compounds. For instance, it is readily demonstrable that cortisone can cause sodium chloride retention and potassium excretion, because these actions are not abolished by the gluco-corticoid effect of the same substance.

Hence, the manifest P-C activity of DCA (bracketed part) would consist of the difference between its total P-C action minus any A-C effect which it might possess (?). On the other hand, the manifest M-C activity

of DCA (the whole black column) would correspond to its total M-C activity, since any possible G-C contamination would not detract from this.

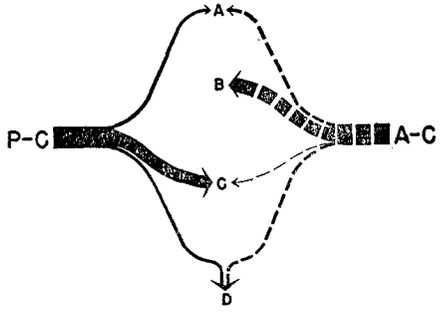
Similar considerations apply even more to a predominantly A-C (and G-C) compound such as cortisone, because here contamination with M-C activity has actually been proven, while the presence of G-C activity in DCA is merely a theoretic possibility, which we consider to be unlikely.

All this is merely one specific application of a general principle in steroid pharmacology, according to which the same compound may exert several, qualitatively different and even diametrically opposed actions. Some of these are "manifest" under all conditions, others may be "masked" under certain circumstances, but their existence can be revealed by appropriate bio-assay procedures.[3]

"Inter-hormonal tension."

You will understand that, in the face of so many intricate interactions between the various adaptive hormones, simultaneous overdosage with both types may lead to a great variety of changes. Their pattern will depend mainly upon relative dose levels and conditioning factors, which can selectively inhibit or augment the response of individual target organs.

A schematic drawing might again help to clarify my meaning.



(3) Selye, H.: "Section I. Classified index of steroid hormones and related compounds." Encyclopedia of Endocrinology, Acta Med. Publ. (1943).

On the left are indicated the effects of P-Cs, on the right of A-Cs, upon four target organs, respectively designated as A, B C and D. On "A" the effects of the two hormones mutually neutralize each other. "B" is markedly influenced by A-Cs, and this effect is unopposed by P-Cs. P-Cs exert a very marked effect upon "C," but this action is only slightly opposed by A-Cs. Finally, as regards the effect upon the target "D," the two hormones mutually synergize each other.

I have already mentioned examples of each type of interaction illustrated here; hence these considerations must not be regarded as purely theoretic; they are actually based upon objective observations. Keep in mind also, that such hormone effects upon almost any target can be selectively aggravated or inhibited by conditioning factors (such as diet, pre-existing disease of certain organs, heredity). Furthermore, the relative effect of the individual pro- and antiphlogistic hormones upon the various target organs varies. For instance, STH possesses many actions which DCA does not possess and so forth. In view of all this, you may well imagine that — depending upon conditions — such inter-hormonal tension can predispose to disease manifestations in a great variety of combinations.

Since it has been definitely demonstrated now that antiphlogistic hormones (ACTH and A-Cs) are produced in excess during various conditions of stress, the problem of inter-hormonal tension assumes considerable practical importance in the interpretation of the "diseases of adaptation." The quotient $\frac{\text{antiphlogistic hormones}}{\text{prophlogistic hormones}}$ would vary depending upon the magnitude of the numerator, even if it should turn out (contrary to my expectations) that the denominator never varies.

Experiments on animals simultaneously overdosed with various types of anti- and prophlogistic hormones are now underway in this laboratory and preliminary observations already indicate that the manifestations of such combined overdosage result in experimental syndromes, qualitatively different from, but equally interesting as those of simple overdosage with ACTH, A-Cs, STH or P-Cs.

If we now complete our much discussed main diagram, so as to include these most recent data, we arrive at the synoptic drawing shown on pp. 144, 145. Naturally, all these simplified sketches are quite incomplete, but I think they do help us to visualize the kind of objective observations upon which our concept rests. You will note that the kidney, the cardio-vascular system and the connective tissue (the main site of inflammation), are not equally affected by pro- and antiphlogistic hormones. Although in the connective tissue the antagonism is very obvious and constant, in the kidney there may be a synergism. It is not difficult to understand that — depending also upon conditioning factors — many patterns of disease may thus arise from variations in the production of a few adaptive hormones during exposure to stress.

Permanent effects of temporary overdosage with adaptive hormones.

It is also very important for the interpretation of the diseases of adaptation that, sometimes, lesions produced by excesses of adaptive hormones develop only long after such overdosage has ceased to exist. Thus, many of our rats treated with large amounts of STH or DCA during a period of about two weeks did not show any distinctly pathologic changes at the end of this period, yet all of them eventually succumbed from nephrosclerosis, periarteritis nodosa and hypertension.

Consider these experimental data from the viewpoint of their possible clinical implications. Perhaps a temporary endogenous overproduction of such substances (for instance, during a short period of nervous strain, exposure to cold or infection) may also lead to manifestations of disease at a time when neither blood nor urinary analyses could reveal any hormone excess.

"Conditioning" of adaptive-hormone actions by stress itself: ...

Perhaps the most debated and important problem in connection with the diseases of adaptation is just how the same adaptation syndrome can produce such a variety of diseases. Since, to my mind, the answer lies mainly in the conditioning factors, I shall have to take up this — already so often discussed — subject yet once more, but this time from a new viewpoint.

We have already seen how the sodium and protein content of the diet, or an experimentally produced partial renal insufficiency, can alter the course of the adaptation syndrome and render the adaptive hormones pathogenic. We have also discussed, at length, those manifold interactions between the individual adaptive hormones themselves, through which they can selectively increase or decrease each other's effects upon certain target organs. Now, I would like to call your attention to what is probably the most important conditioning factor for the actions of adaptive hormones, namely stress itself.

... by systemic stress...

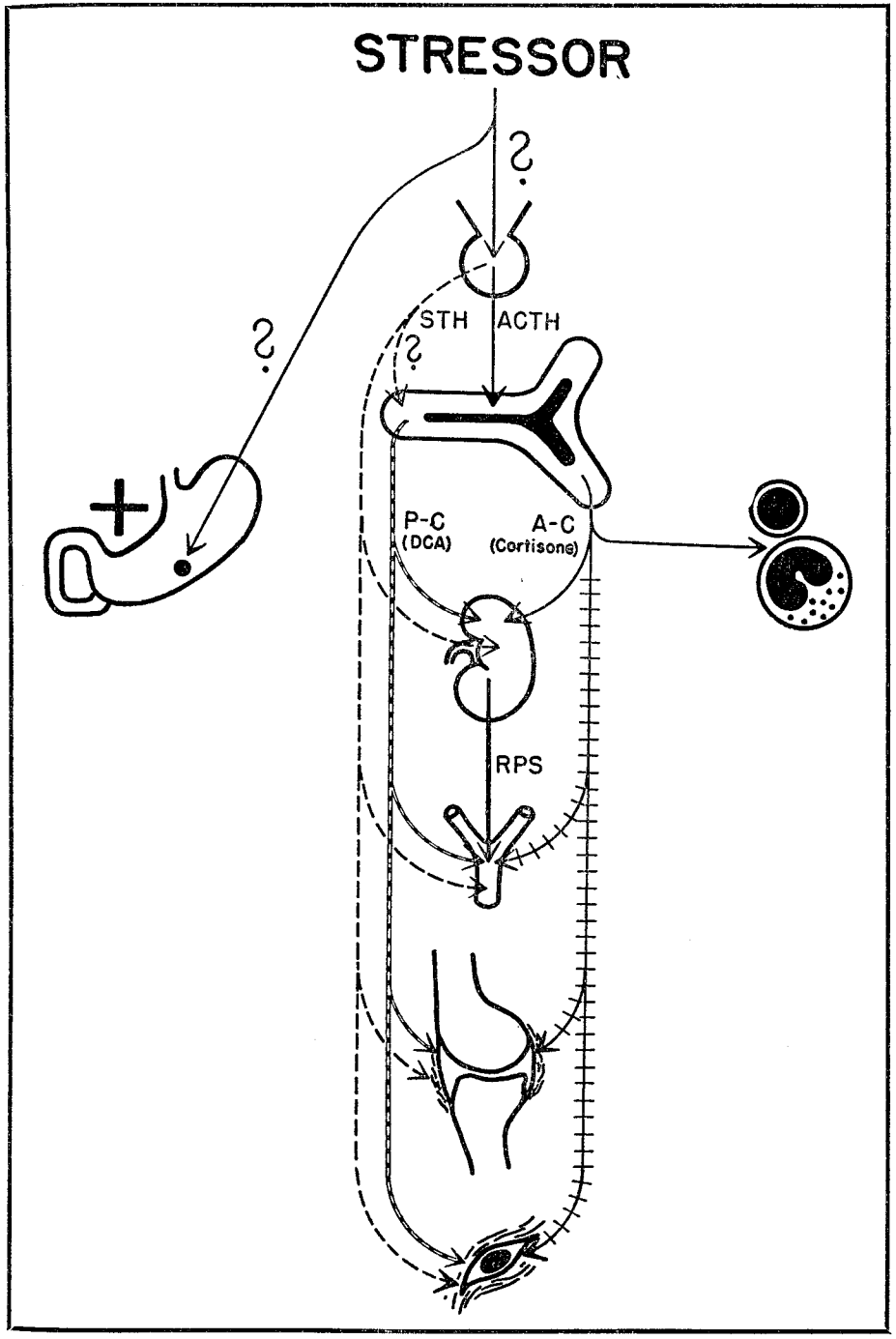
It is a very characteristic feature of the adaptive hormones that many of their actions are not obvious in the resting state, but become prominent only when an adaptive reaction to injury is required. Thus, we had seen that the usual hyperglycemia of the alarm reaction is abolished, indeed often reversed, following adrenalectomy. For instance, in the absence of the adrenals, a rat exposed to traumatic shock may develop a fatal hypoglycemia instead of the usual rise in blood-sugar. Yet, if such an adrenalectomized rat is treated with threshold doses of adreno-cortical extracts — doses which in themselves fail to affect the blood-sugar — it responds with a pronounced hyperglycemic

By now, the experiments performed with the "endocrine kidney" technique had helped to clarify, to some extent, the participation of the renal pressor mechanism in the adaptation syndrome. The changes elicited in all nephrons by this surgical procedure are reproduced in a certain number of individual nephrons, by suitable pituitary and corticoid hormones. It is assumed that the kidney, perhaps through the production of renal pressor substances (RPS), plays an important part in producing cardio-vascular lesions and hypertension during stress; this effect is further accentuated by the direct (not kidney mediated) actions of prophlogistic hormones. Any "conditioning factor," (e.g. a low-sodium diet), which selectively protects the kidney from the actions of such hormones, can qualitatively modify the stress response by diminishing the participation of the renal pressor mechanism.

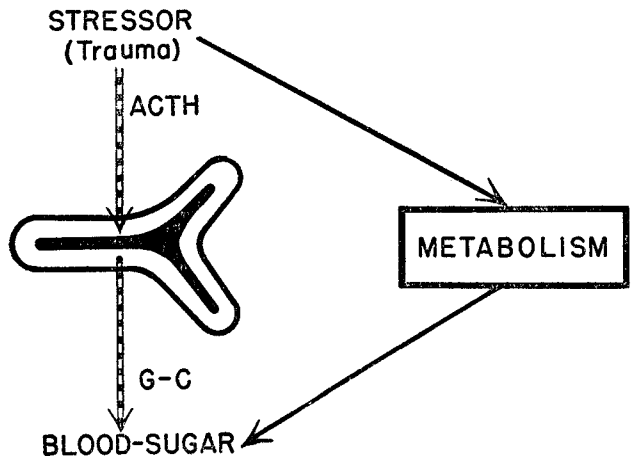
As soon as highly purified preparations of ACTH, STH and cortisone became more readily available, in 1949, it was found that the prophlogistic effects of LAP can be duplicated by STH; the latter is presumably identical with the "X-factor." It is not yet clear whether STH only sensitizes the tissues to P-Cs by a peripheral action, or whether it actually increases their production in the adrenal cortex.

Cortisone (and hydrocortisone) reproduced the characteristic effects of the "corticoids of the adreno-cortical extract." Hence, we can now substitute the designation "A-C (cortisone)" for the vague term "corticoid," which hitherto represented the antiphlogistic activity of the crude extracts in our schema. (Simple arrows for positive effects, cross-hatched arrows for inhibitory effects.)

The renal damage caused by P-Cs and STH is aggravated by A-Cs. The inflammatory potential in the cardio-vascular system, the joints and the connective tissue in general, is increased by the prophlogistic hormones, but depressed by A-Cs. Outside the cardio-vascular system, this inhibition is always very obvious; in the heart and vessels it is more variable. This variability presumably depends upon the degree of renal damage caused by the A-Cs. If they induce marked nephrosclerosis and nephritis, the ensuing increase in RPS production may cause such a severe cardio-vascular inflammation that it cannot be prevented by A-Cs, at least not in doses compatible with life.



reaction to trauma and other systemic stressor agents.[4] Here, the stressor does not act exclusively through the adrenal cortex, nor solely by means of extra-adrenal metabolic effects, but through both these pathways, as illustrated in the diagram below.



In a sense, one might say that here the corticoids do not produce changes of themselves, but exert a "permissive action," that is, a positive conditioning effect upon a non-adrenal mediated systemic stress response.

A similar interrelationship between systemic stress and corticoids exists as regards the thymico-lymphatic involution of the alarm reaction. This typical response is abolished by adrenalectomy. However, it can be elicited, even in adrenalectomized animals, with doses (in themselves inactive) of adreno-cortical extract or cortisone, providing that the animals are simultaneously exposed to a systemic stressor.

---

(4) Selye, H. and C. Dosne: "Influence of traumatic shock on blood sugar of adrenalectomized rats treated with adrenal cortical extract." Proc. Soc. Exper. Biol. & Med. *48*: 532 (1941).

This situation could be illustrated by merely inserting "thymus involution" instead of the word "blood sugar" in my last drawing. Thus, the stressor (e.g., trauma) causes thymus involution not only through the excess secretion of G-C (or A-C) corticoids, but simultaneously also through extra-adrenal channels, which sensitize the peripheral target (here the thymus) to the thymolytic effect of these corticoids.

Many apparently paradoxical manifestations of stress could be explained on a similar basis. For instance, we have seen that gastric ulcers are more readily produced by stressors in adrenalectomized than in intact animals. On the other hand, an excess of ACTH or cortisone may in itself produce gastric ulcers. In our synoptic diagrams, the gastric ulcers have always been pictured as being direct effects of stressors, not mediated through the pituitary-adrenal axis. It must be kept in mind, however, that, although they can be produced by stressors in hypophysectomized and adrenalectomized animals and hence are evidently not dependent upon the integrity of the pituitary-adrenal system, their production could, nevertheless, be enhanced under certain circumstances by antiphlogistic hormones, perhaps through some synergism between the latter and the non-hormonal actions of the systemic stress.

The highly instructive pertinent studies of Engel [5] and Ingle [6] have brought many additional instances of this type to light and greatly helped us to understand their significance.

---

(5) Engel, F. L.: "A consideration of the roles of the adrenal cortex and stress in the regulation of protein metabolism." In: Recent Progress in Hormone Research, Acad. Press Inc., Publ., New York, *6*: 277 (1951).

(6) Ingle, D. J.: "The biologic properties of cortisone: A review." J. Clin. Endocrinol. *10*: 1312 (1950).

... and by topical stress.

Perhaps even more striking is the conditioning of pro- and antiphlogistic hormone actions by circumscribed topical stress, since the standard response to it is inflammation. One need hardly emphasize that an antiphlogistic effect cannot manifest itself if there is no inflammation to inhibit, but it may be worth pointing out that even the prophlogistic hormones hardly ever cause inflammation of themselves.

Endogenous topical stress.

It is true that the phlogistic effect of these hormones was first noticed when they proved to elicit nephritis, myocarditis, periarteritis nodosa and arthritis. Yet, even here, it is debatable whether the observed inflammation was solely due to an excess of DCA or STH. It is hardly a coincidence that, in animals overdosed with these prophlogistic hormones, inflammatory changes tended to occur always in strained areas. The places of bifurcation in the arteries (where the blood-column hits strongly against a resistance), the afferent arterioles and capillaries of the renal glomeruli and the arterial vessels in the myocardium are most commonly affected. In all these locations, the blood-pressure itself may have been the local stressor. This pressure would not cause inflammation in itself, to be sure, but in animals whose inflammatory potential is maximally raised by prophlogistic hormones (particularly if combined with special systemic conditioning factors, such as unilateral nephrectomy and a high-sodium intake), even this slight injury may eventually cause inflammation.

It will also be recalled that DCA in itself produced arthritis only in exceptional cases; the incidence could be raised, however, by exposure of the joints to a topical stressor, such as extreme cold. Perhaps endogenous metabolic (e.g., gout) or microbial (e.g., infectious polyarthritis) factors can similarly cooperate with hormones in determining whether any one joint will respond with inflammation.

Hyperergic inflammation.

The conditioning, by adaptive hormones, of the phlogistic response to topical stress is also illustrated by the hyperergic inflammatory response of certain shock organs (the paws and the snout) to egg-white. This reaction, as I have already said, has been inhibited by adreno-cortical extract (rich in A-Cs) and aggravated by adrenalectomy (which removes the source of A-Cs) and by LAP (rich in prophlogistic STH). As soon as cortisone and ACTH became available in adequate amounts, we were able to confirm that this hyperergic type of inflammatory response is also effectively inhibited by the purified antiphlogistic hormones.[7]

"Topical irritation arthritis."

Pertinent investigations were also greatly aided by the development of a simple technique for the production of the so-called "topical irritation arthritis." It was found that if irritants are introduced into the connective tissue in various parts of the body, they do not produce the same degree of inflammation everywhere. The ability to respond with inflammation, the "inflammatory potential," is particularly high in the joint regions. Thus, in the rat, a few drops of dilute formalin introduced into the connective tissue around the small metatarsal joints of the hind paw, produce a pronounced granulomatous connective tissue response which eventually may lead to permanent ankylosis. This reaction is greatly aggravated by pretreatment with DCA or STH and can be almost completely inhibited by the administration of ACTH, cortisone or

[7] Selye, H.: "Effect of ACTH and cortisone upon an anaphylactoid reaction." Canad. M.A.J. *61*: 553 (1949).

hydrocortisone.[8] I will show you pictures, to illustrate all this, in my next lecture.

This topical-irritation-arthritis test, and its numerous variations, have helped a great deal in the screening of diverse hormones, drugs and stress conditions, which can affect the course of inflammation. Among the main modifications, one might mention the use of croton oil, scalding, freezing, hyaluronidase, mustard powder, kaolin, or egg-white, instead of formalin. These irritants produce different types of inflammation (with a predominance of suppuration, edema, connective tissue proliferation or hyperergic inflammation), so that we can select the one which suits our purpose best. Each of these techniques has certain advantages and disadvantages. Their common feature is to reproduce an experimental inflammation in joints. This is necessary if we wish to study problems concerned specifically with the pathology of arthritis or, more generally, with phlogistic reactions in a region whose inflammatory potential is notoriously high.

Other modifications of this test for anti- and prophlogistic hormones were devised with the special aim of producing a granulomatous response which lends itself better to accurate measurement. In a joint, the amount of granuloma tissue cannot be exactly assessed because of its very diffuse distribution. On the other hand, an irritant (for instance, a piece of cotton, wood, cork or glass) introduced under the skin of the rat soon becomes enveloped by a thick layer of granuloma tissue. The foreign body, with its artificially formed capsule, can readily be separated from the

[8] Selye, H.: "Further studies concerning the participation of the adrenal cortex in the pathogenesis of arthritis." Brit. M.J., Nov. 19, p. 1129 (1949).

surrounding loose connective tissue and (after removal of the foreign body) the capsule itself, which is pure granuloma tissue, can be weighed and chemically, or histologically, analyzed. In our laboratory, formalin-soaked pipe-cleaner brushes were found to be particularly useful for this type of experiment.

The "granuloma tube."

Upon implanting under the skin a piece of pipe-cleaner brush, about 2.5cm. in length and about 3mm. in diameter, a thick connective tissue granuloma capsule forms around it within about 9 days. If the foreign body is soaked in formalin, mustard, kaolin or some other irritant, the granuloma will not grow in between the bristles of the pipe-cleaner, being separated from the latter by some fluid or pus. Hence, at the end of the ninth day, the foreign body can be removed without difficulty. The remaining "granuloma tube" lends itself excellently as a test object for investigations concerning the functional efficacy of the granulation tissue. For instance, one can inject dies, bacteria, chemical irritants or hormones into its cavity. Since, under standard conditions, such a "granuloma tube" is always very evenly developed, one can accurately measure the effect of these substances upon the structure of the tube and, vice versa, the action of the granuloma upon the absorption and spreading of the enclosed materials.

Some authors [9] recommend the use of cotton pads. These are quite adequate if the granuloma is merely to be weighed, but, since they cannot readily be extracted from the tissue and produce capsules of irregular shape, they are unsuited for the production of a "granuloma tube."

[9] Meier, R., W. Schuler and P. Desaulles: "Zur Frage des Mechanismus der Hemmung des Bindegewebswachstums durch Cortisone," Experientia 6: 469 (1950).

In all these instances ACTH, cortisone and hydrocortisone inhibit, while STH, DCA or desoxocortisone increase granuloma formation. If both types of hormones are simultaneously administered, the pro- and antiphlogistic substances mutually antagonize each other's effects.

Beneficial effects of STH in:...

Chronologically, the last hormone to be recognized as having adaptive properties was STH. In the course of our early studies with the STH-containing LAP preparations, it had already been noted that — like DCA — this pituitary principle can cause nephrosclerosis, cardio-vascular lesions, hypertension, an aggravation of hyperergic inflammation, etc., but all these were detrimental effects. It was only quite recently that the beneficial actions of STH upon responses to non-specific stress, could be demonstrated.

..."spontaneous" infections, ...

The great sensitization to infection which follows overdosage by ACTH or A-Cs was found to be most effectively combatted by simultaneous treatment with STH. For instance, rats given enormous doses of cortisone would normally die with intense tissue catabolism and multiple microbial foci throughout their organism, but they can be saved by conjoint administration of purified STH.

... experimental tuberculosis, ...

The rat is normally resistant to human type tuberculosis bacilli. Following pretreatment with ACTH or cortisone, its ability to combat infections deteriorates so much that it can be readily infected with these microbes. The animal then rapidly loses weight and develops rather characteristic tubercles in various organs, particularly the lung. This decrease in weight and resistance is in turn abolished by simultaneous administration of STH. Our preliminary studies suggest that in species normally susceptible to infection by tuberculosis (e.g., the mouse), STH can even raise resistance above normal [10].

Since currently available STH preparations are not suitable for clinical purposes, it remains to be seen whether these observations will prove to be of practical value. You should keep in mind, however, that encapsulation of microbial foci and healing by scar formation are important normal biologic defense reactions against topical irritants and, particularly, against tuberculosis. Their more or less efficient regulation through STH, as secreted by the patient's own pituitary, is probably an important factor in the pathogenesis of some infectious diseases.

... the effects of ionizing rays.

Another beneficial effect of STH is its action upon the acute X-irradiation syndrome. While we were performing autopsies of rats overdosed with antiphlogistic hormones, we were impressed by the many similarities between the syndrome of intoxication with ACTH or cortisone and that elicited by whole-body X-irradiation. Both the antiphlogistic hormones and the ionizing rays cause: a pronounced acute loss of body weight, a rather selective involution of the thymus, lymph nodes and spleen, an atrophy of the liver, loss of hair with atrophy of the skin, a delay in wound healing, a diminution of the inflammatory potential and a great sensitivity to infections. Since all these manifestations of antiphlogistic hormones had been so effectively counteracted by STH, I thought that this hormone may be active also in combatting these changes if they were elicited by ionizing rays.

Up to now, we have not yet studied the long-range effect of such hormonal therapy, hence nothing can

[10] Lemonde, P. and H. Selye (in press).

be said about the value of STH in combatting the lethal actions of total-body X-irradiation. However, we could definitely establish that the hormone, even if given only after X-irradiation, prevents the subsequent loss of body weight, as well as the atrophy of the thymico-lymphatic tissue, spleen and skin. Thus, we learned at least that X-irradiated cells are still receptive to certain actions of STH and that several typical manifestations can be artificially separated from the radiation syndrome by such hormonal treatment. Here again, much further work will be necessary before we could assess the possible clinical implications of our observations [11].

Rôle of adaptive hormones in the production of the diseases of adaptation.

The preceding discussion of the mutual interactions between the direct effects of topical or systemic stress, on the one hand, and of the adaptive hormones, on the other, has important implications upon our general interpretation of the "diseases of adaptation."

At first, it seemed that the most important factors in the production of the diseases of adaptation are either the direct effects of non-specific stress itself (shock, inflammation), or its indirect effects, which are mediated principally through the pituitary-adrenal system. For instance, diseases might be caused by an excess or a deficiency or an abnormal combination of such hormones as STH, ACTH, P-Cs and A-Cs.

Now, a third possibility begins to attract attention. In many instances, the hormones merely determine the responsiveness of the body to one or the other of the direct effects of pathogenic agents. For example, a great excess of A-Cs will not cause infection, but

[11] Selye, H., E. Salgado and J. Procopio: "Effect of somatotrophic hormone (STH) upon resistance to ionizing rays." Acta Endocrinol. *9*: 337 (1952).

merely a danger of infection. Microbes are obviously also necessary for the actual occurrence of this complication. Similarly, necrosis of tissues, thymolysis, lympholysis, catabolism and many other pathologic manifestations, may be facilitated, even though not produced, by A-Cs. Conversely, inflammation, nephrosclerosis, hypertension, etc., are disease manifestations whose development is enhanced, though not necessarily produced, by P-Cs.

This brings the chronological development of my story up to date.

We have seen how the mechanism of stress responses has been subjected to a systemic analysis and how the chief hormonal pathways at least appear to have been largely elucidated.

The story is, of course, still very incomplete. I do feel, however, that the evidence which came to light definitely supports the concept that the body responds to stress with a rather uniform, standard reaction, the general adaptation syndrome. I believe to have demonstrated furthermore that this reaction can derail and thus become the principal, though never the sole, cause for the development of disease. These "diseases of adaptation" are not due to hormones alone, nor to any one pathogen alone, but to the development of *pathogenic situations*, in which many factors participate. The principal ones among these are:

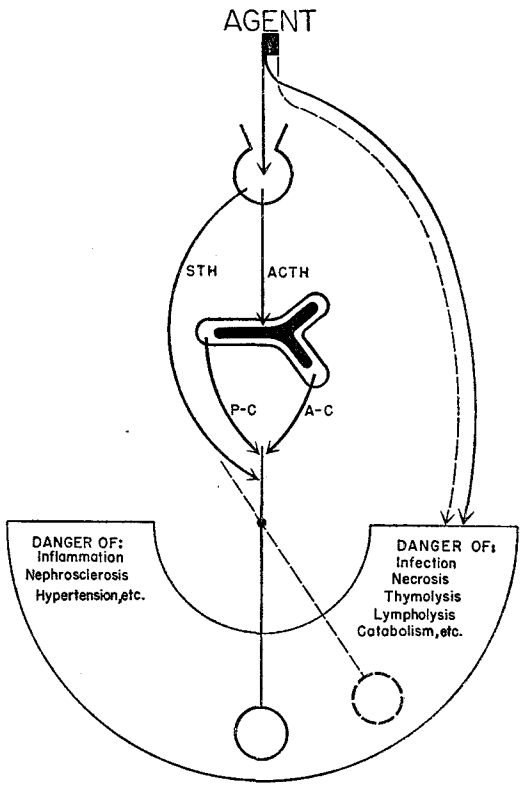
(1) the stressor effect of the pathogen,

(2) the specific effects of the pathogen,

(3) the adaptive hormones present in the body at the time of exposure, or produced during stress, and

(4) such conditioning factors as heredity, a preexistent organ lesion, the diet, etc.

This complex interrelationship between the direct and indirect effects of potentially pathogenic agents is illustrated in the next schema. (See p. 156.)



This drawing reminds us again that all potentially pathogenic agents have three essentially distinct types of actions: specific effects (interrupted curved arrow), non-specific actions, which are not mediated through the pituitary-adrenal axis but affect tissues directly in the form of systemic or topical stress (solid curved arrow which runs parallel to the former), and non-specific actions mediated through the pituitary-adrenal system (solid arrow connecting agent with hypophysis). By way of the latter system, through the production of antagonistic adaptive hormones, the condition of disease susceptibility (pendulum) can be set at different levels.

A shift of the pendulum to the right does not necessarily produce disease (especially if the deviation is not very pronounced), but it greatly augments the danger of infection, necrosis, thymolysis, lympholysis, catabolism, etc., if the direct (non-specific and specific) actions of the potential pathogen tend to produce such changes.

Conversely, the prophlogistic hormones shift the pendulum of susceptibility towards the left and thus predispose the body to inflammation, nephrosclerosis, hypertension, etc.

Deviations of the pendulum to either side of the mid-line diminish the danger of the lesions listed on the opposite side of our diagram.

Thus, to my mind, there begins to emerge a new and somewhat more complex pathology, in which the main objects of our study are no longer individual "pathogens," but rather "pathogenic situations."

I hoped to make my thesis more interesting and easier to follow by developing it historically. Along this lengthy path, factual observations led us to theories and theories suggested experiments, which in turn brought forth new observations. Unfortunately, this type of presentation tends to make it difficult to distinguish clearly between solidly established facts and theories.

As I have said elsewhere, it has always been my guiding principle in research that: *"Our facts must be correct. Our theories need not be, if they help us to discover important new facts."* It is indispensable, however, to separate fact from fancy. To help you with this, we will examine, next time, a purely factual "balance-sheet" of our "assets," the data brought to light by this approach to medicine, and of our "liabilities," the doubts and uncertainties which it created.

It is not particularly stimulating to follow a dry factual enumeration of data, hence, I shall present them in the form of an "illustrated catalogue" with photographs objectively reproducing our most important and most photogenic exhibits.

SIXTH LECTURE

An Illustrated Catalogue of the Facts Brought to Light by the Adaptation Syndrome Concept and an Enumeration of the Doubts It Raised.

Ladies and Gentlemen!

Object and structure of today's lecture.

IN THE PRECEDING LECTURE, I tried to re-live with you the story of our work on the adaptation syndrome by evoking the status of our knowledge at various crucial points, from the time the idea of biologic stress originated up to the present day. I hoped that through this historic approach I could best elicit in your minds those same thoughts and feelings which we experienced in the laboratory while the story was actually developing.

A purely technical description is based on measurable intellectual values alone; yet in actual life science is far from being purely a product of conscious thought. Indeed, I think that as a rule the greater a scientific creation, the more is it conceived by instinct and emotions. Pure intellect is largely a quality of the middle-class mind. The lowliest hooligan and the greatest creator in any field of human endeavor are motivated mainly by imponderable instincts and emotions, especially faith. Curiously, even scientific research, the most intellectual creative effort of which

man is capable, proves no exception in this respect. That is why the objective, detached form of an original scientific publication or of a textbook falls so ludicrously short of really conveying the spirit of an investigation.

By presenting my story as it was actually born, so largely intermixed with blind faith in success and profound discouragement, I hoped that I could — even if at the expense of my "academic decorum" — let you participate in the real fun of it all. At the same time, I was sure this would teach you more about what really matters than the heavily documented descriptions in the more reserved and factual reviews on the adaptation syndrome, which others and myself have written in the past.

As I told you last time, the trouble with this simple, narrative, historic technique of presentation is, however, that fact and fancy, measurements and theory, tend to become confusingly intermixed.

That is what I want to correct in the remaining last two lectures.

In the first part of today's address, I plan to present you with a rigidly objective balance-sheet of the principal facts, the tangible, solid "assets" gained from all this research on stress and the adaptation syndrome. To facilitate their evaluation, I propose to list them with the conclusions my previous lectures have implied that they support. Whenever possible, they will also be illustrated through the rigorously objective medium of the photograph.

As a result of this purely enumerative technique, today's lecture will be somewhat cut and dry; it will not be entertaining, nor give you any stimulus for research, but entertainment and stimulation do not

belong in an objective balance-sheet. I shall also spare you my usual diagrams, replete with arrows, for these symbolize interactions — or rather our interpretation of interactions — which must be banned if this lecture is to serve as a simple record, a clean score-sheet of the conclusions supported by the tangible facts which have come to light so far.

The second part of this lecture will be an enumeration of the principal doubts and uncertainties raised by our work, the "liabilities" of the stress concept.

Conversely, in my next, and last lecture, I shall let imagination go wild, depicting my dreams and hopes about the implications and probable future of this research. This will help us separate fact from fancy clearly, without sacrificing either.

ASSETS.

To my mind, the following are the twelve principal conclusions which are supported by objective facts that have been revealed through research on stress and the adaptation syndrome.

Biologic stress and the G-A-S.

(1) *The existence of biologic stress and of the general adaptation syndrome is established.*

This, our principal conclusion, is supported by the following facts:

During adaptation to a variety of essentially dissimilar agents (such as cold, fatigue, infections, intoxications or emotions), a number of objective and measurable somatic changes appear conjointly, as a syndrome. We called this the "general adaptation syndrome." Prominent among these manifestations are the involution of the thymico-lymphatic apparatus, eosinopenia, the appearance of gastro-intestinal ulcers, an enlargement of the adrenal cortex with discharge of its lipids and cholesterol, as well as increased elimination of corticoids and corticoid metabolites.

The common property of these diverse agents, by virtue of which they elicit this standard response, has been termed their "stressor" effect and the condition which they create, "stress."

(2) *The stress-response is triphasic.*

Three phases: I. Alarm, II. Resistance, III. Exhaustion.

The tangible somatic manifestations of stress do not remain the same continuously during prolonged treatment with an invariable dose of any one stressor. As judged by its objectively measurable manifestations, the stress-response is fundamentally triphasic.

To give at least one concrete example, the adrenals of a rat continuously exposed to the same degree of cold over a period of months, first discharge their secretion granules, then accumulate an excessive amount of them and finally become depleted again. Most, if not all, of the measurable indicators of stress follow a triphasic course. These three phases of the general adaptation syndrome have been designated respectively: the "alarm reaction," the "stage of resistance" and the "stage of exhaustion."

The G-A-S can be useful or harmful.

(3) *The adaptation syndrome can be useful or detrimental, depending upon the circumstances.*

Exposure to any one stressor may either increase or decrease resistance to another stressor, depending upon the circumstances. For instance, immediately after an acute and severe trauma or burn, a rat responds with less than the normal degree of anaphylactoid inflammation to an intraperitoneal injection of egg-white; it develops a less intense arthritis upon juxta-articular injection of formalin; it can withstand otherwise fatal doses of adrenaline without developing the usual pulmonary edema.

Crossed resistance.

This has been termed "crossed resistance." It is largely due to an increased secretion of A-Cs during the alarm reaction produced by these stressors.

Crossed sensitization.

Conversely, prolonged exposure to one stressor, such as cold, tends to render animals hypersensitive to other agents, for instance to morphine, and vice versa. This phenomenon of "crossed sensitization," (and also of course the occurrence of the exhaustion stage after continued exposure to the same stressor), led us to suspect that adaptability or "adaptation energy" is a finite quantity which can be exhausted. It should be clearly stated that the nature of this adaptability factor has not yet been established.

Clarification of relationships between:

(4) *An important part of the adaptation syndrome is dependent upon the anterior pituitary.*

Hypophysis and the G-A-S.

In hypophysectomized animals, exposure to stressors causes no morphologic changes in the adrenal cortex and no thymus involution.

The excessive urinary elimination of corticoids, normally produced by stressors in various species, including man, likewise fails to occur after hypophysectomy.

Conversely, in both intact and hypophysectomized animals, overdosage with ACTH reproduces some of the principal manifestations of the adaptation syndrome (such as adreno-cortical stimulation, thymico-lymphatic involution, catabolism, lymphopenia, eosinopenia, and suppression of inflammatory response). It also decreases resistance to various microbes.

STH tends to counterbalance most of these effects of ACTH, so that the final result depends not only upon the absolute amounts of ACTH and STH produced, but largely upon the relative proportion between these two adaptive hormones.

Adrenals and the G-A-S.

(5) *An important part of the adaptation syndrome is dependent upon the adrenal cortex.*

After adrenalectomy, neither stressors nor ACTH injections cause thymico-lymphatic involution, increased urinary elimination of corticoids or inhibition of inflammation.

Conversely, overdosage with A-Cs (such as cortisone or hydrocortisone) reproduces rather accurately the symptom complex obtained with ACTH, while overdosage with P-Cs (DCA or desoxocortisone) imitates many, although not all, of the changes obtained by STH. In particular, the P-Cs stimulate connective tissue proliferation, raise the inflammatory potential and, under suitable experimental conditions, cause nephrosclerosis and hypertension. The P-Cs do not share with STH the ability of stimulating the growth of the body as a whole or of the thymico-lymphatic tissue in particular.

After adrenalectomy, STH exerts no toxic effect upon the kidney, but the corresponding nephrotoxic action of DCA is independent of the adrenals.

DCA tends to produce no nephrosclerosis after hypophysectomy, yet it can still increase diuresis and raise the blood-pressure in the absence of the hypophysis.

Inflammation and the G-A-S.

(6) *The A-Cs and P-Cs are antagonistic in some, but not in all, respects.*

Interactions between adaptive hormones.

The suppression of inflammatory responses by A-Cs (e.g., cortisone) can be blocked by P-Cs (e.g., DCA).

The thymico-lymphatic involution, the eosinopenia, the general tissue catabolism and the decreased resistance to infections caused by A-Cs remain uninfluenced by P-Cs.

The renal lesions and adreno-cortical atrophy caused by P-Cs are further aggravated by A-Cs.

(7) *The A-Cs and STH are antagonistic in almost all respects.*

The thymico-lymphatic involution, the inhibition of inflammatory responses, the decrease in resistance to infections, the adreno-cortical atrophy and the general tissue catabolism caused by A-Cs can all be suppressed by STH.

We have no definite evidence that the diabetogenic or nephrotoxic effect of A-Cs could be similarly blocked by STH, but it is indeed striking that almost all the characteristic actions of cortisone and hydrocortisone are so effectively prevented by simultaneous STH treatment.

Conditioning of stress-responses.

(8) *Most of the actions of adaptive hormones are largely dependent upon "conditioning factors."*

The production of nephrosclerosis, hypertension, periarteritis nodosa and polyuria by DCA is greatly facilitated in animals in which a certain degree of renal deficiency has been produced by partial nephrectomy. In these same respects, a high-sodium intake also acts as a sensitizing factor. Maximal sensitization is obtained by partial nephrectomy plus a high-sodium intake. The protein content of the diet has little, if any, effect upon these actions of P-Cs.

The production of adrenal enlargement, nephrosclerosis, myocarditis, hypertension and polyuria by STH is augmented by partial nephrectomy, diets rich in sodium or rich in protein. Maximum sensitization to such actions is obtained by a combination of all three of these conditioning factors.

The pathogenic effects of the hypertension produced by the "endocrine kidney" technique, particularly the development of nephrosclerosis on the opposite side, the periarteritis nodosa, myocarditis and hypertension,

do not appear to be significantly influenced either by the sodium or by the protein content of the diet.

Many of the actions of ACTH and of A-Cs (such as cortisone or hydrocortisone) are dependent upon conditioning by stress itself. Adrenalectomized animals do not respond with hyperglycemia or thymolysis upon exposure to stressors. However, if they are treated with doses of cortisone which are in themselves almost inactive, they show pronounced hyperglycemia and thymolysis during subsequent exposure to stressors. Here, apparently, there is a peripheral synergism between the antiphlogistic corticoids and some unidentified metabolic consequences of systemic stress.

Naturally, the effect of both pro- and antiphlogistic hormones upon inflammation itself is conditioned by the existence of topical stress capable of producing a phlogistic response. In other words, there must first be an inflammation before the hormones can regulate its course.

We have already mentioned the interactions between the various adaptive hormones, which could be interpreted as a conditioning of one hormone's effect by another hormone.

Progressive lesions caused by brief hormone overdosage.

(9) *Temporary overdosage with certain adaptive hormones can cause progressive lesions.*

A short treatment with DCA or STH preparations may be tolerated without any obvious immediate disease manifestations and yet, through some trigger-mechanism, it initiates a morbid process which eventually kills the animal with nephrosclerosis and hypertension. — This shows that a normal urinary and blood-concentration of adaptive hormones in a patient does not necessarily exclude the possibility that his malady can be a disease of adaptation due to abnormal hormonal responses to an earlier stress episode.

The "endocrine kidney."

(10) *The participation of renal hypertension in the stress-response has been somewhat clarified, but remains largely conjectural.*

With the aid of the "endocrine kidney" operation, it is possible to abolish the urine-producing ability of the kidney selectively, while its pressor effect rises. Hence, urine secretion is not indispensable for the production of renal pressor substances, as had been previously assumed.

After the "endocrine kidney" operation, the glomeruli and most of the tubules involute and lose their lumina. Only the spiral segments of the descending convoluted tubules undergo actual proliferative changes. — This was taken to show that the renal pressor mechanism is located in the spiral segment.

The morphologic aspect of the "endocrine kidney" bears some resemblance to that of animals which developed nephrosclerosis due to prolonged treatment with DCA or STH. The extra-renal manifestations of the "endocrine kidney" are also reminiscent of those produced with prophlogistic hormones: there is hypertension, periarteritis nodosa, myocarditis and nephrosclerosis on the opposite side. — This was the evidence which suggested that prophlogistic hormones may activate the renal pressor mechanism.

Unlike the corresponding syndrome produced by DCA or STH intoxication, that elicited by the "endocrine kidney" remains uninfluenced by the sodium and protein content of the diet and is not accompanied by hypokalemia. — The effect of prophlogistic hormones upon the blood-potassium is apparently not mediated through the kidney.

Assessment of therapy with antiphlogistic hormones.

(11) *Antiphlogistic hormones proved useful in a number of experimental and clinical diseases characterized by excessive inflammation.*

A variety of the rheumatic-allergic and other diseases characterized by excessive inflammation (experimentally produced in animals or spontaneously occurring in man) are favorably influenced by treatment with ACTH, hydrocortisone or adreno-cortical extract, all of which are essentially antiphlogistic substances. The clinical use of these hormones was not suggested to its discoverers by the G-A-S concept; it is mentioned here only for the sake of completeness.

Assessment of therapy with prophlogistic hormones.

(12) *Prophlogistic hormones proved useful in a number of experimental diseases characterized by lympholysis, a diminished inflammatory potential and increased sensitivity to infection.*

In the rat, the inhibition of growth, catabolism, thymolysis and lympholysis produced by stress, ACTH or cortisone, can be prevented by STH.

The high sensitivity of ACTH- or cortisone-treated rats to infection by normally saprophytic organisms, or even virulent human type tuberculosis, can be restored to normal by STH.

The loss of weight and intense involution of the thymus, spleen and liver, which are part of the acute radiation syndrome in the rat, can be counteracted by treatment with STH. It remains to be seen, however, whether this treatment is also effective in increasing the eventual survival rate following treatment with otherwise fatal doses of ionizing radiations.

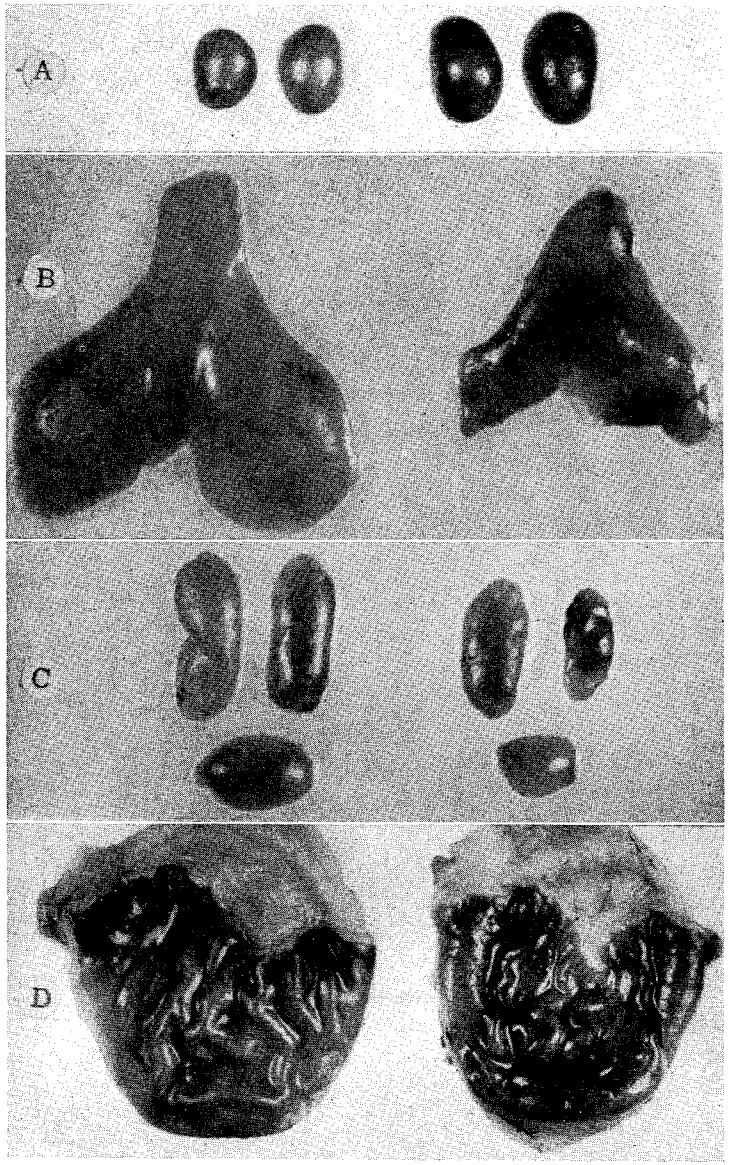
Up to now, it has not been possible to prepare STH preparations suitable for clinical use; our animal experiments are merely meant to point out the probable fields of its clinical applicability.

These are, to my mind, the principal facts derived from research on stress and the adaptation syndrome. They are enumerated here according to the conclusions we deduced from them. I hope that the list so arranged will help you in assessing objectively, for yourselves, not only the present status of this field, but also the significance of future pertinent communications.

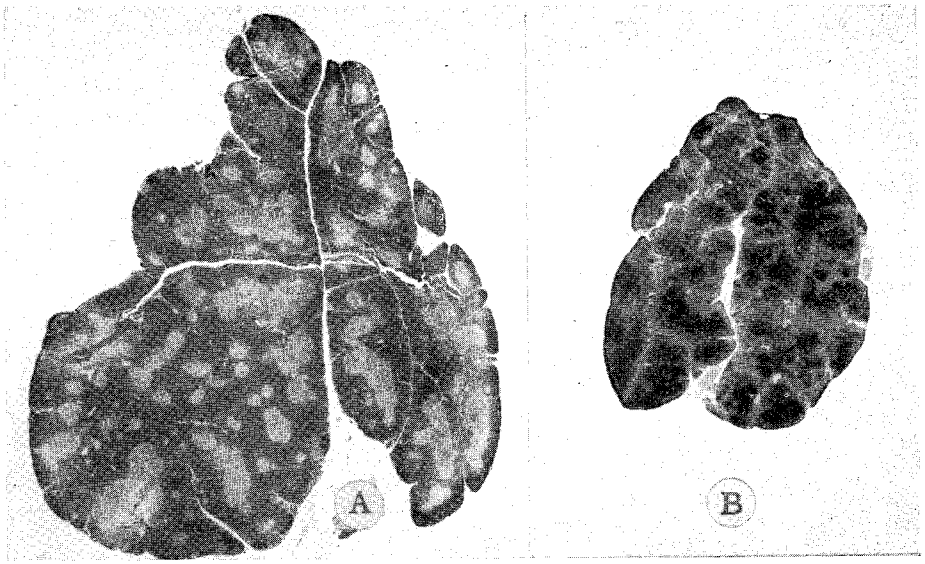
It is well to ask from time to time: has anything come to light that is an additional fact not foreseen in this list, or actually contrary to the conclusions we drew ? If so, can we now arrange all the definitely established facts into a better system than that of the adaptation syndrome and the diseases of adaptation as hitherto formulated ? I for one found this technique of analysis most useful throughout the years in building up, adjusting and extending my concept of stress, as more and more information became available.

There is no doubt that readjustment and extension of our theories will always be indispensable in this field of science, as in any other. Nothing could be more detrimental to progress than to remain undauntedly faithful to our preconceived ideas. From time to time, we must reassess the validity of our data. But this reassessment must be objective. A vague and essentially emotional evaluation of scientific data (often unfortunately based upon an excess, or a lack, of enthusiasm for them) is highly misleading. An inventory does not make fascinating reading, but it is certainly useful in assessing, objectively, the data it lists. This is my excuse for having submitted you to this lengthy, dry enumeration of facts.

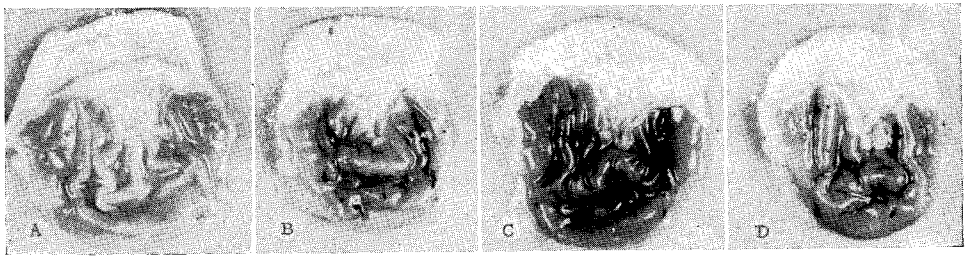
To make my catalogue a little more palatable, I shall now show you photographs illustrating a few among our basic facts which happen to lend themselves to pictorial representation.



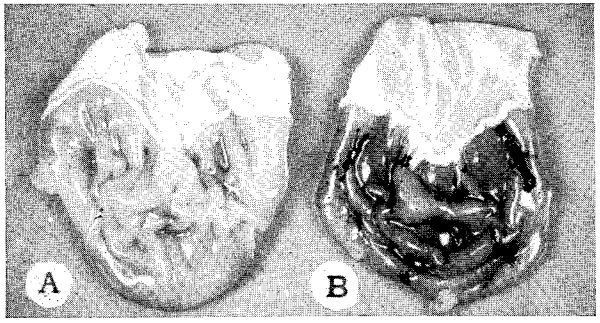
The typical triad of the alarm reaction. — **A.** Adrenals, — **B.** thymus, — **C.** iliac lymph nodes, — **D.** gastric mucosa of a normal rat (left) and one which was exposed to the frustrating mental stress of being immobilized on a board for 24 hours. Note the marked enlargement with lipid discharge and hyperemia of the adrenals (which consequently became reddish-brown), the intense atrophy of the thymus and lymph nodes and the numerous blood-covered gastric ulcers in the alarmed rat (right).



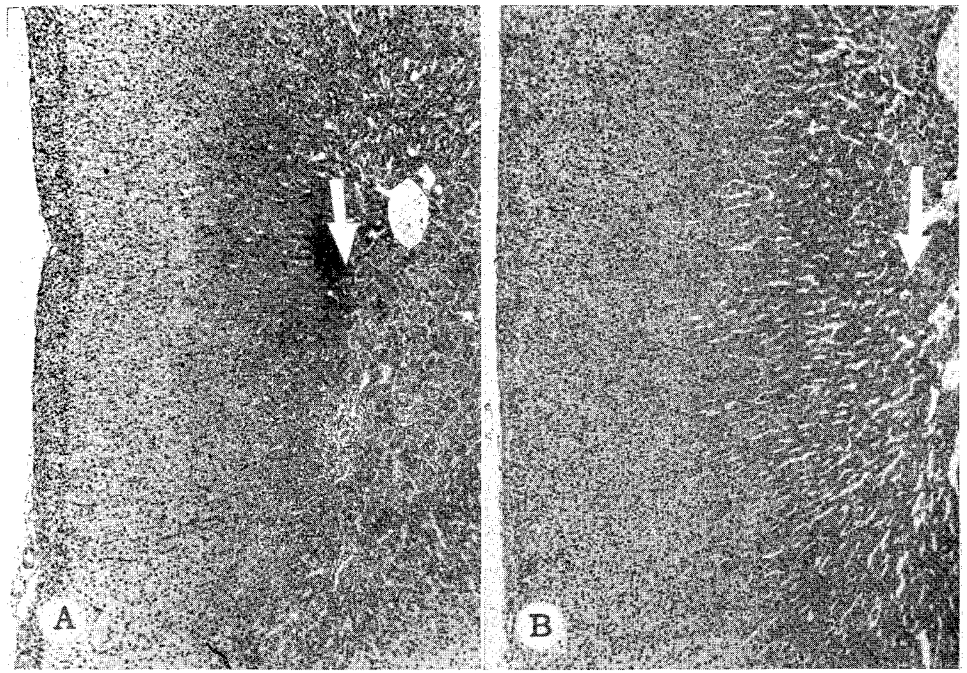
Thymus during the alarm reaction in the rat. — **A.** Low magnification of a cross-section through the normal thymus. Medulla light, cortex dark due to the presence of numerous thymocytes. — **B.** Cross-section through thymus in alarm reaction produced by formalin. Note "inversion of the thymus pattern" due to depletion of the cortical thymocytes whose debris migrates into the medulla. [After Selye: J. Clin. Endocrinol. **6** : 117 (1946)]



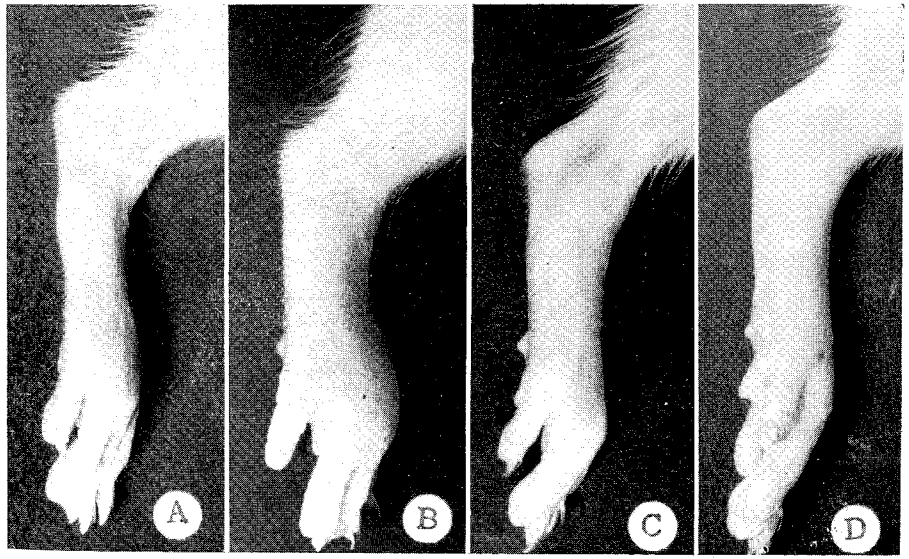
Acute gastric ulcers during the alarm reaction in the rat. — **A.** Normal control. In the other three animals an alarm reaction was produced by: — **B.** High spinal cord transection, — **C.** Exposure to cold, — **D.** Forced muscular exercise. Note hyperemia and bleeding ulcers, which are similar irrespective of the agent used. [After Selye: "STRESS"]



Gastric ulcers during the exhaustion phase of the adaptation syndrome in the rat. — **A.** Normal control. — **B.** Ulcers following 30 days of exposure to cold. [After Selye: "STRESS"]

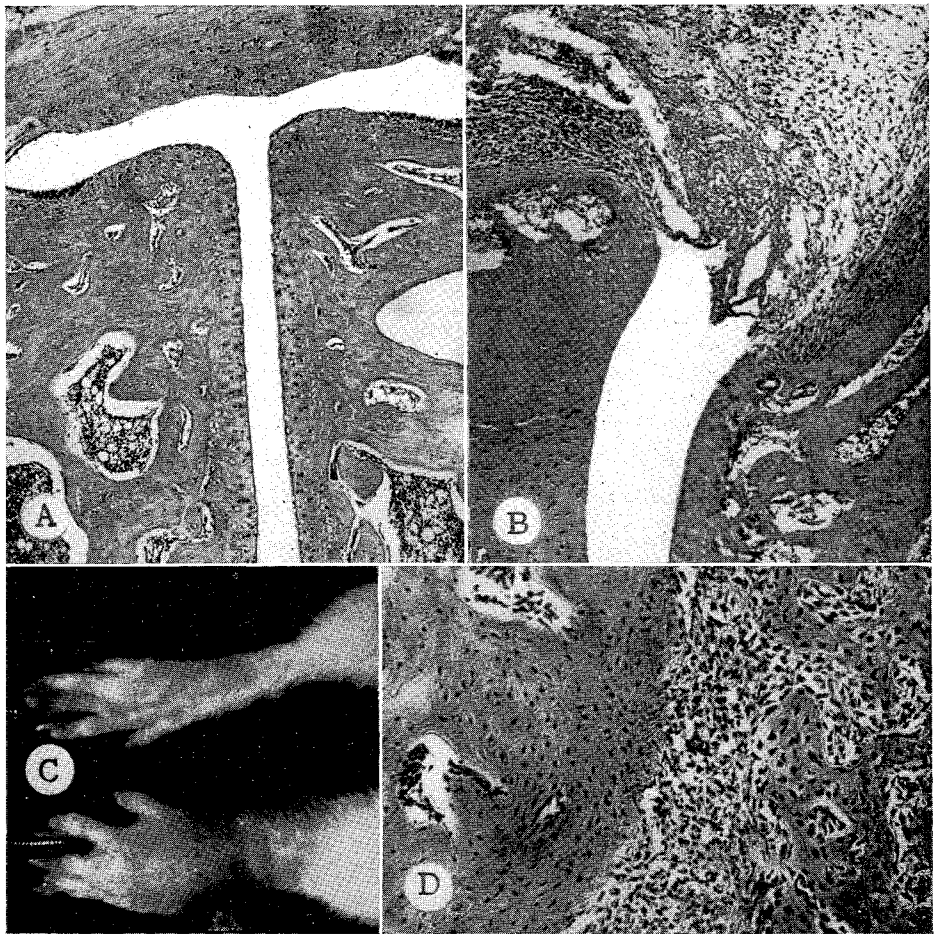


Adrenal cortex during the alarm reaction. — **A.** Untreated control rat. — **B.** Cortical enlargement and lipid discharge after 48 hrs. of formalin intoxication. [After Selye: J. Clin. Endocrinol., **6** : 117 (1946)]



Antiphlogistic effect of the alarm reaction in the rat. — **A.** Untreated control. All other animals received a local formalin injection underneath the plantar skin to produce a "topical irritation arthritis." — **B.** Otherwise not treated rat showing full development of inflammation and edema. — **C.** Alarm reaction produced by spinal cord transection. — **D.** Alarm reaction produced by cold. Other stressors exerted similar antiphlogistic effects, presumably due to endogenous ACTH discharge.

[After Selye: Brit. M. J. **2** : 1129 (1949)]

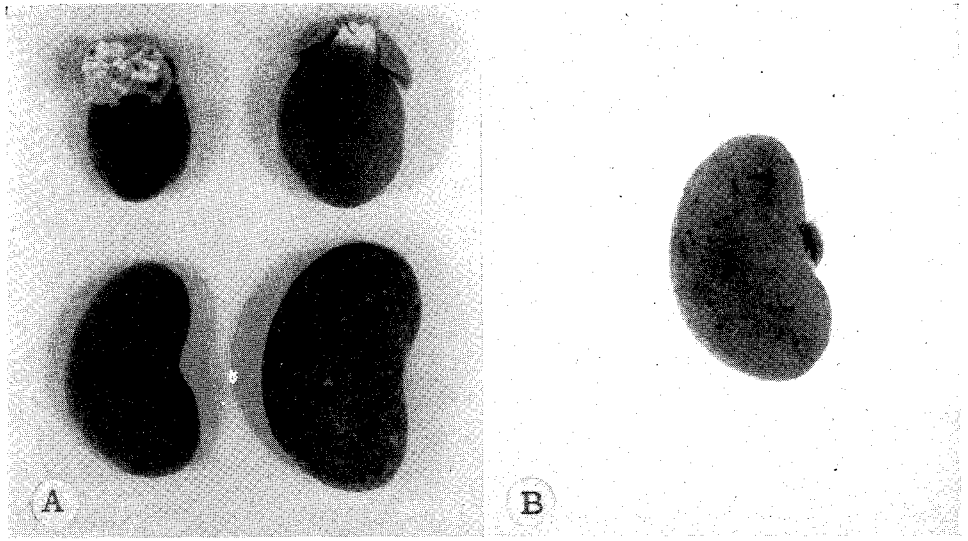


Hormonal production of arthritis in the rat. — **A.** Normal metatarsal joint. — **B.** Acute arthritis produced by DCA. Edematous and inflamed synovial membrane. — **C.** Arthritis in left hind paw of a rat chronically treated with STH-containing pituitary extract. — **D.** Newly formed periarticular bone in metatarsal region of rat treated with such pituitary extract.

[After Selye et al.: J.A.M.A. **124** : 201 (1944) and Selye: J. Clin. Endocrinol. **6** : 117 (1946)]

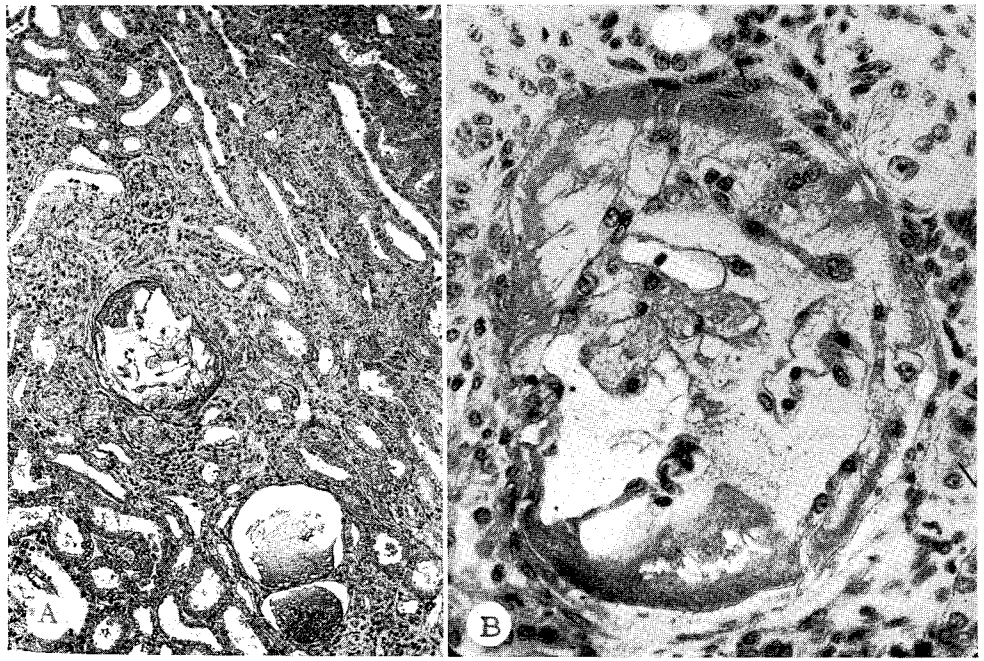
Motor disturbances due to encephalopathy caused by DCA. — **A.** DCA-treated rat with periarteritis nodosa of the brain, shown during rest between two spells. — **B.** Same rat shown during typical epileptoid spell with rotation of the shoulder girdle and head towards the left. — **C.** Brain of normal control rat. — **D.** Brain of DCA-treated rat. Note hemorrhages and edema.

[After Selye: J. Clin. Endocrinol. **6** : 117 (1946)]



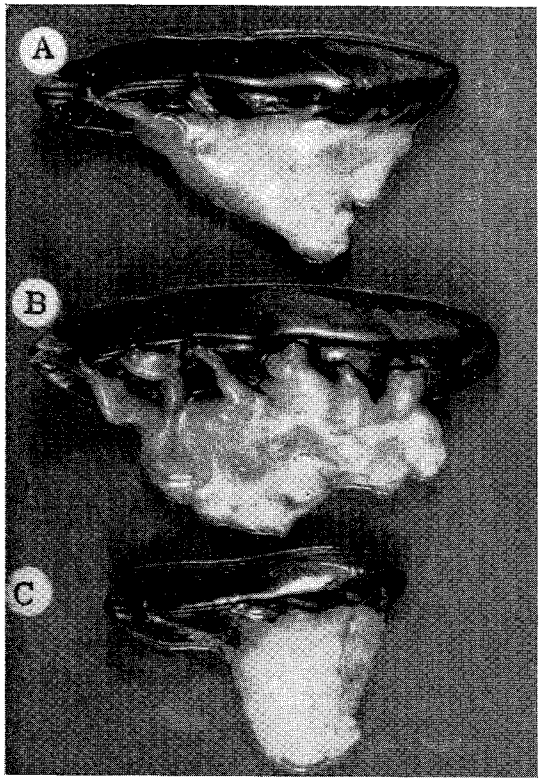
Effect of corticoid overdosage upon the rat kidney. — All these animals had been sensitized by unilateral nephrectomy and 1% NaCl. — **A.** On the left, heart and kidney of control; on the right, enlargement of the heart and nephrosclerotic nodules in kidney, after DCA overdosage. — **B.** Glomerular hemorrhages after concurrent overdosage with DCA and cortisone.

[After Selye: "STRESS"]



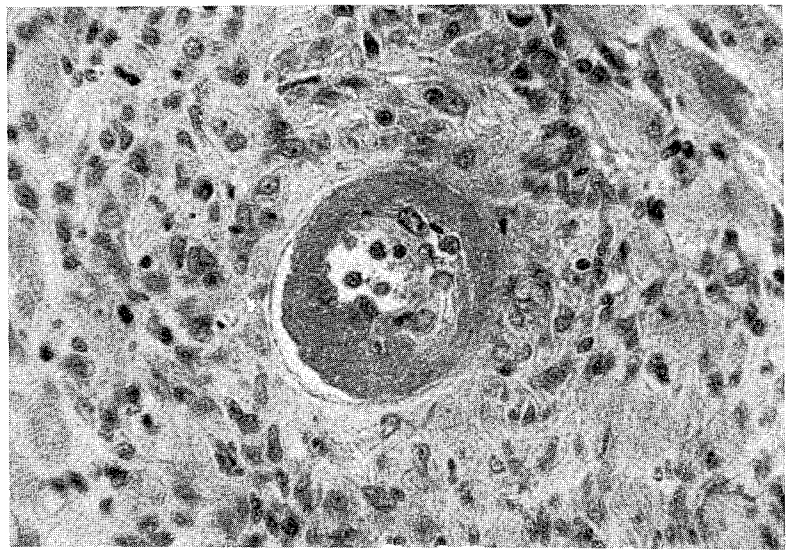
Histologic aspect of renal changes caused by simultaneous overdosage with DCA and cortisone in the rat. — **A.** Low magnification. — **B.** High magnification of renal tissue. Note disintegration of glomeruli, cast formation and dilatation of some tubules while others become solid and assume the aspect of "endocrine nephrons."

[After Selye: "STRESS"]



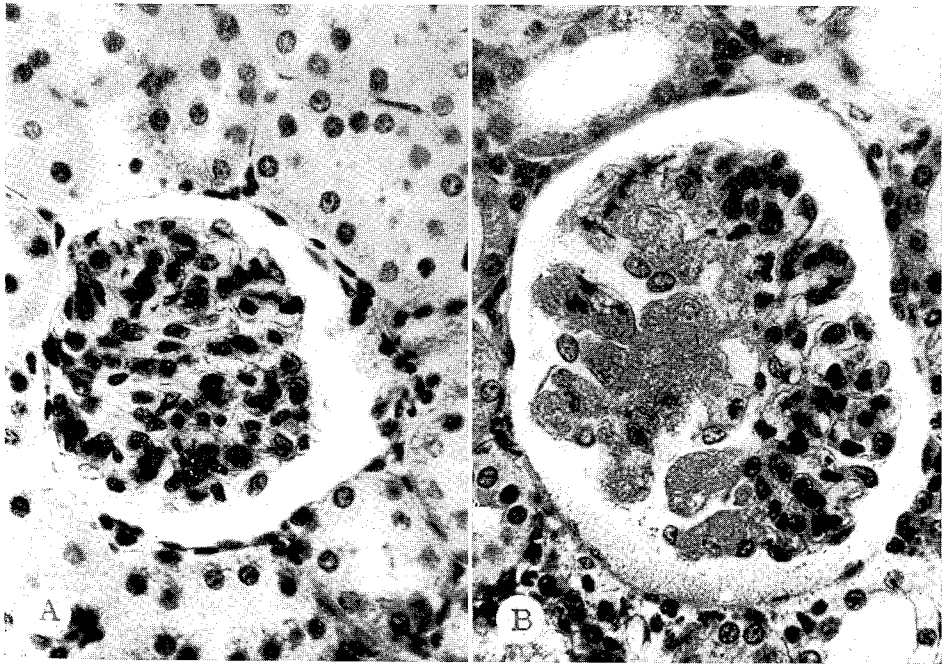
Effect of pro- and antiphlogistic corticoids upon the spleen and its vessels in the rat. — All the animals in these experiments had been unilaterally nephrectomized and given 1% NaCl as a drinking fluid in order to sensitize or "condition" them to the prophlogistic corticoid actions. — **A.** Spleen with the attached tail of the pancreas, through which the vessels reach the hilum in an untreated control. — **B.** Corresponding tissues of a rat treated with DCA for 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 figure B, but at the same time was also treated with equivalent amounts of an antiphlogistic hormone, namely cortisone. Note great reduction in the size of the spleen (lympholytic effect of antiphlogistic corticoids) and complete absence of periarteritic lesions (antiphlogistic effect).

[After Selye: "STRESS"]



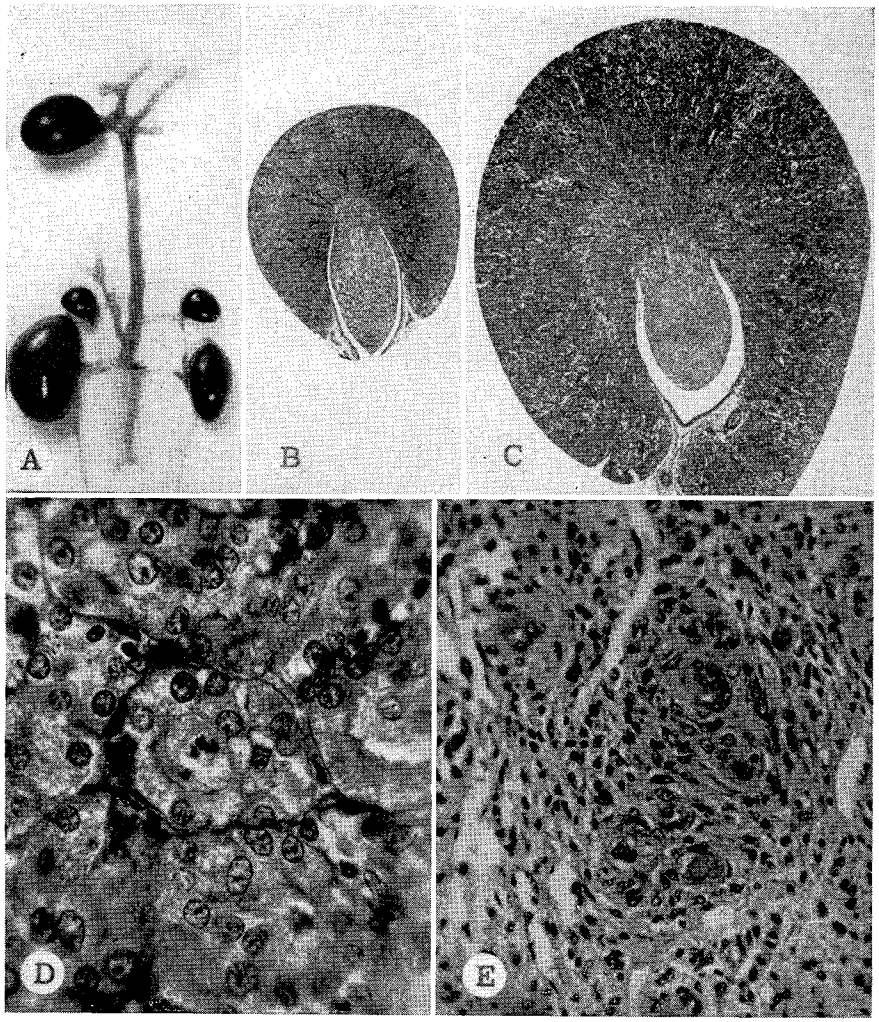
Periarteritis nodosa in the heart after STH overdosage in the rat. — Typical periarteritis nodosa in a small cardiac arteriole of a rat which had received STH following the usual sensitization to prophlogistic actions by unilateral nephrectomy and sodium chloride. Underneath the endothelium, there is a thick layer of homogenous hyalin material and the walls of the vessel are disorganized by granuloma tissue.

[After Selye: Annual Report on Stress — 1951]



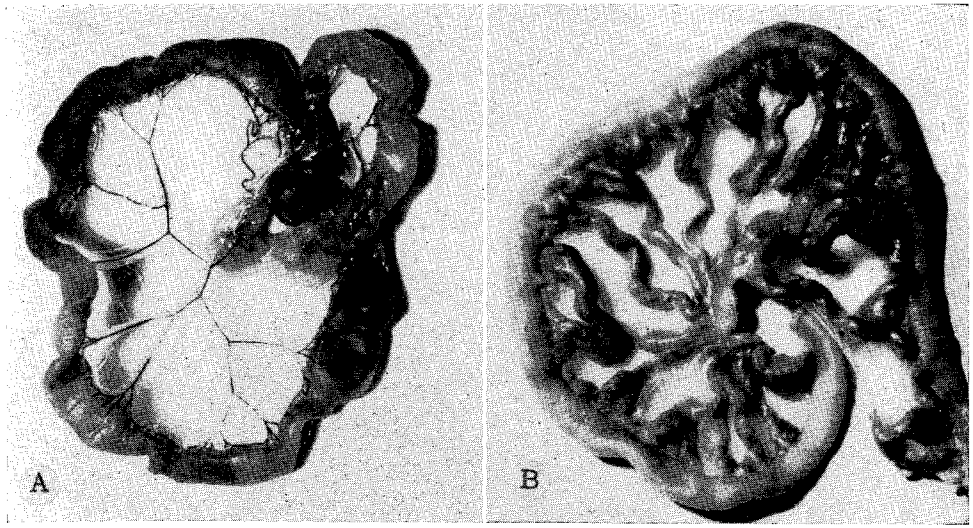
Glomerular hyalinization caused by desoxocortisone in the rat. — **A.** Glomerulus of normal control. — **B.** Glomerulus of desoxocortisone (another prophlogistic corticoid) treated rat. Several glomerular loops are completely hyalinized and the surrounding tubules are dilated.

[After Selye: Annual Report on Stress — 1951]

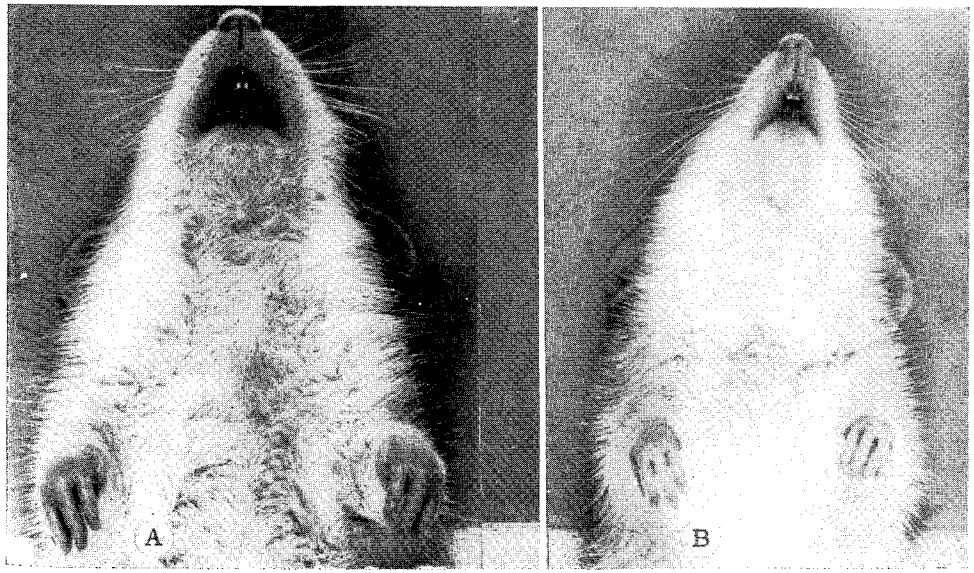


"Endocrine kidney" in the rat. — **A.** Macroscopic view of heart, aorta, kidney and adrenals after "endocrine kidney" operation. Note great enlargement of heart, adrenals and right kidney. In the heart, macroscopically visible Aschoff (?) nodules; the surface of the right kidney is irregular (beginning nephrosclerosis), the adrenals are enlarged and there are several periarteritic nodules on the superior mesenteric artery. The left kidney (whose artery originates below ligature) is atrophic but free of nephrosclerosis. — **B.** Cross-section through the "endocrine kidney" shown in figure A. — **C.** Cross-section through nephrosclerotic right kidney of the same animal. — **D.** High magnification of the "endocrine kidney". Tubular lumina have disappeared, but the cells are well preserved and there is a mitotic figure in the center of this field in a spiral segment. — **E.** A myocardial "Aschoff nodule" of another "endocrine kidney"-bearing rat.

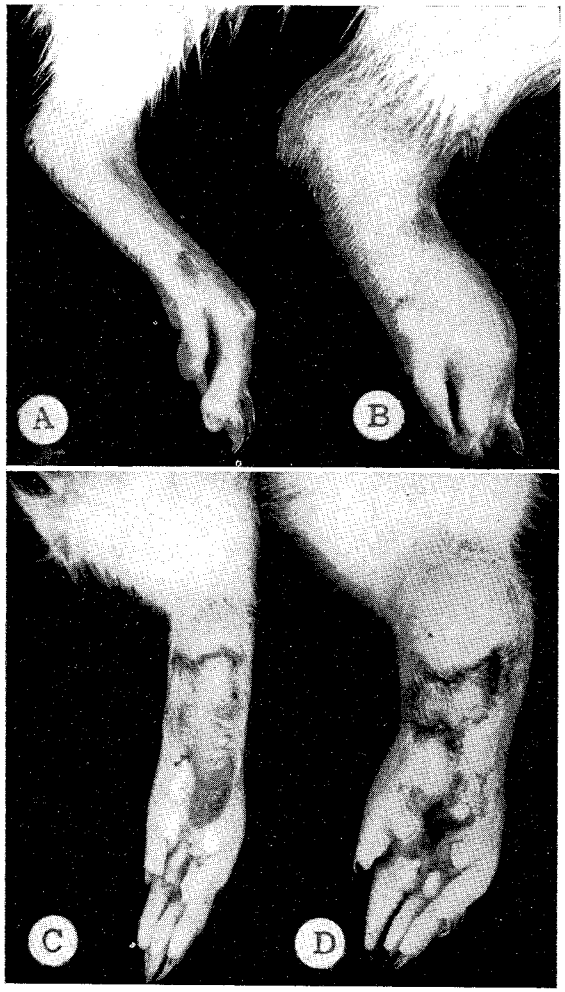
[After Selye and Stone: J. Urol. **56** : 399 (1946)]



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, the "endocrine kidney" operation had been performed 38 days previously and caused complete "endocrine transformation" of the left kidney, accompanied by marked hypertensive disease. [After Selye: "STRESS"]

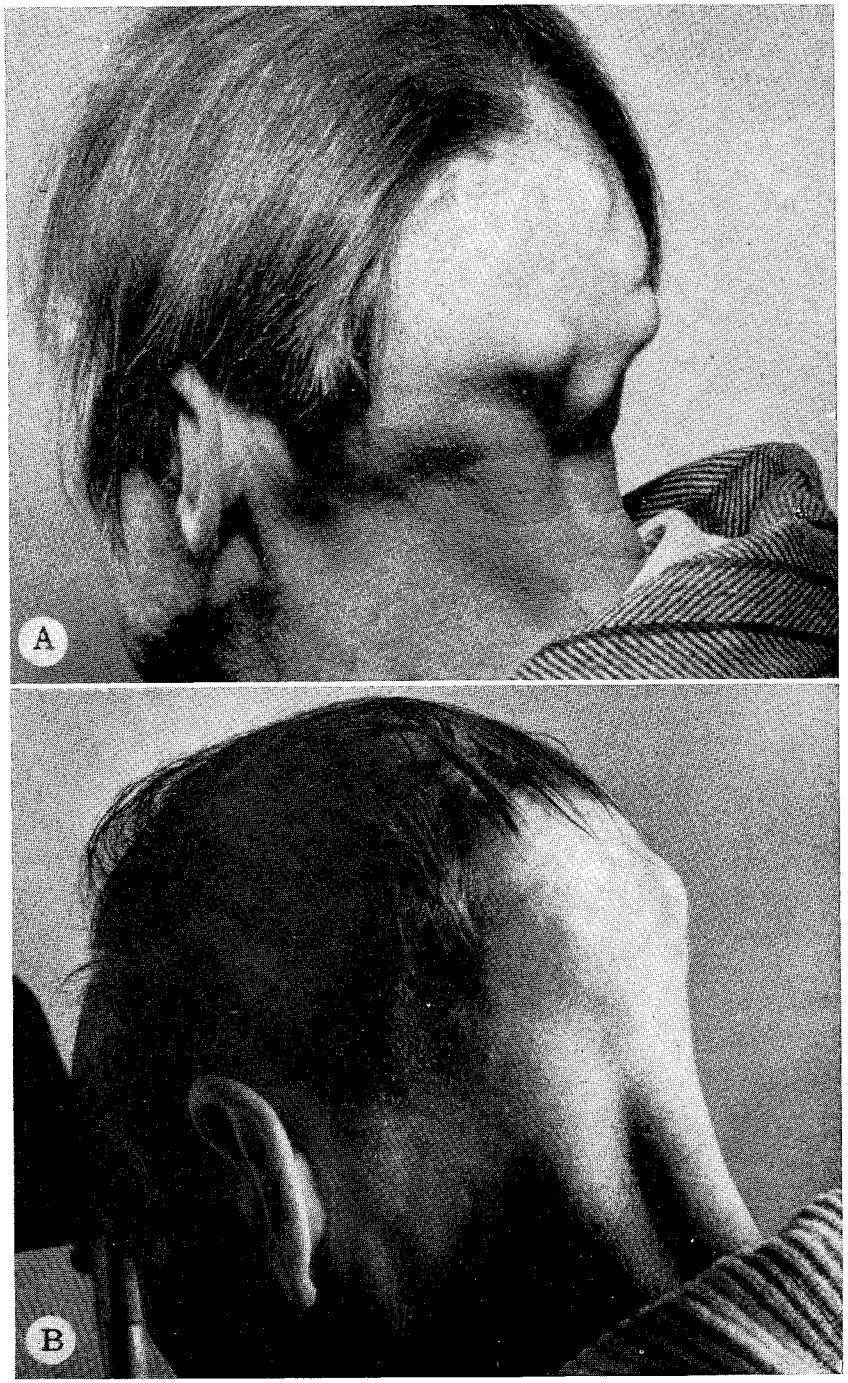


Effect of ACTH upon hyperergic inflammation in the rat. — **A.** Not hormone-treated rat injected with egg-white. Note marked edema and hyperemia of the paws, lips and nose. — **B.** This rat received ACTH just prior to treatment with egg-white. Note complete absence of hyperergic inflammation. [After Selye: Canad. M.A.J. **61** : 553 (1949)]



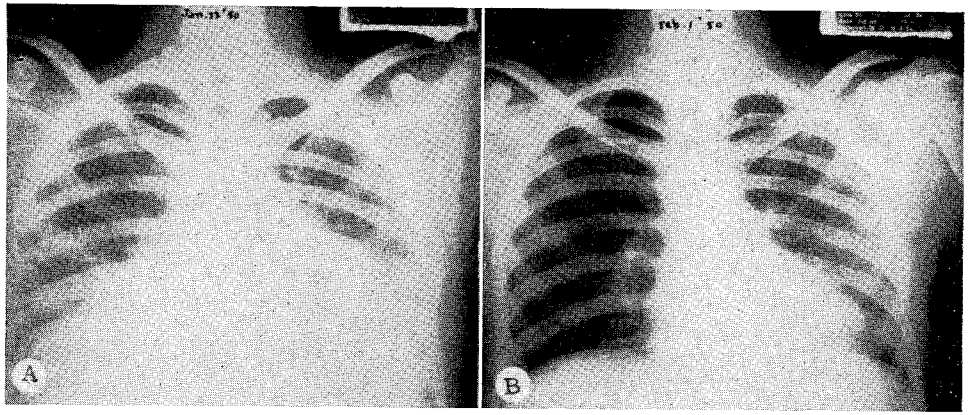
Effect of ACTH on "topical irritation arthritis." — **A.** ACTH pretreated rat, — **B.** not pretreated control. Both these animals were given repeated injections of the same amount of formalin into the paw. The controls (B) developed marked indurative chronic arthritic and periarthritic lesions; the 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 formalin 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: Brit. M. J. Nov. 19. 1129 (1949)]



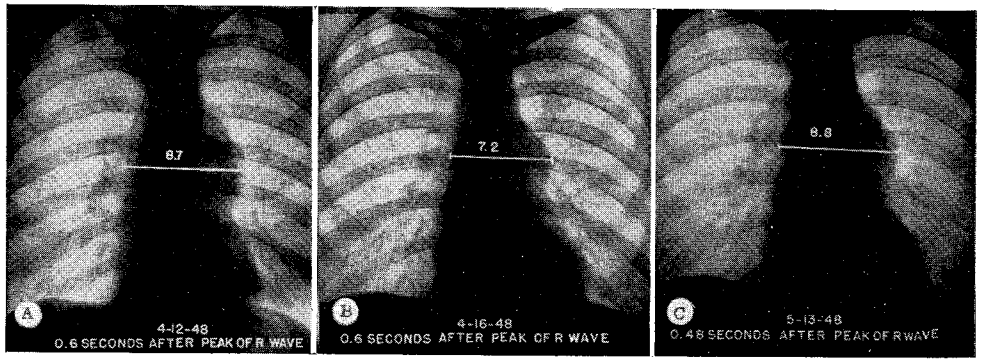
Effect of cortisone upon rheumatoid nodules. — **A.** Before treatment. — **B.** After 44 days of cortisone.

[After Engleman et al.: Cortisone Research (Symposium) Washington. Aug. 15. p. 18 (1950). Merck and Co., (Publs.), Rahway, N.J.; by courtesy of Veterans' Administration Hospital, San Francisco.]



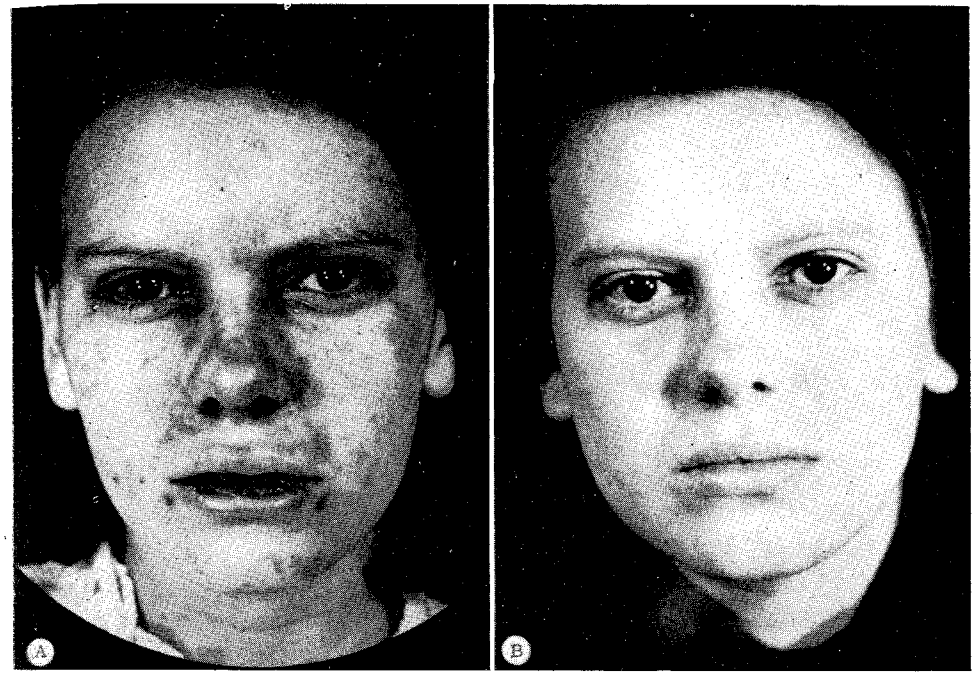
Effect of cortisone upon rheumatic pancarditis. — **A.** X-ray of the chest in an 18-year-old boy with a history of recurrent rheumatic fever, taken during a very severe attack of rheumatic pancarditis. The heart shadow is enlarged (chiefly the left ventricle); there is considerable infiltration in the 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.

[Courtesy of Drs. G. I. Bell, D. R. Wilson and R. E. Bell, University Hospital, Edmonton, Alberta.]



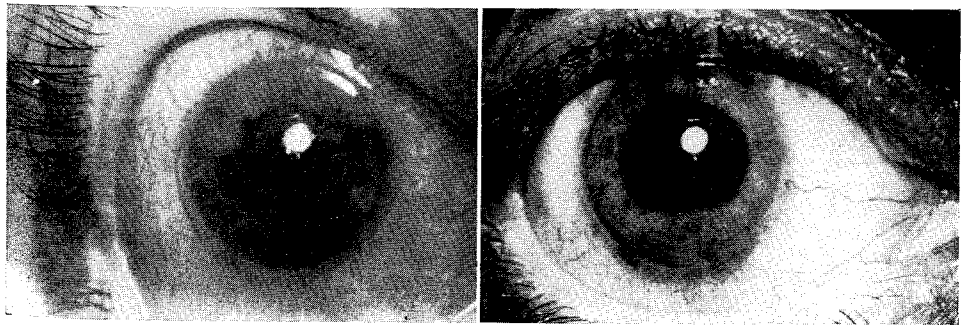
Effect of ACTH upon thymic tumor in myasthenia gravis. Roentgenograms made during diastole. — **A.** Before treatment. — **B.** Immediately after completion of treatment with ACTH. — **C.** Four weeks after discontinuation of treatment. Note that mediastinal mass greatly decreased under the influence of ACTH, but regained its original size within a month after treatment was discontinued.

[After Soffer et al.: J. Mt. Sinai Hosp. 15 : 73 (1948)]



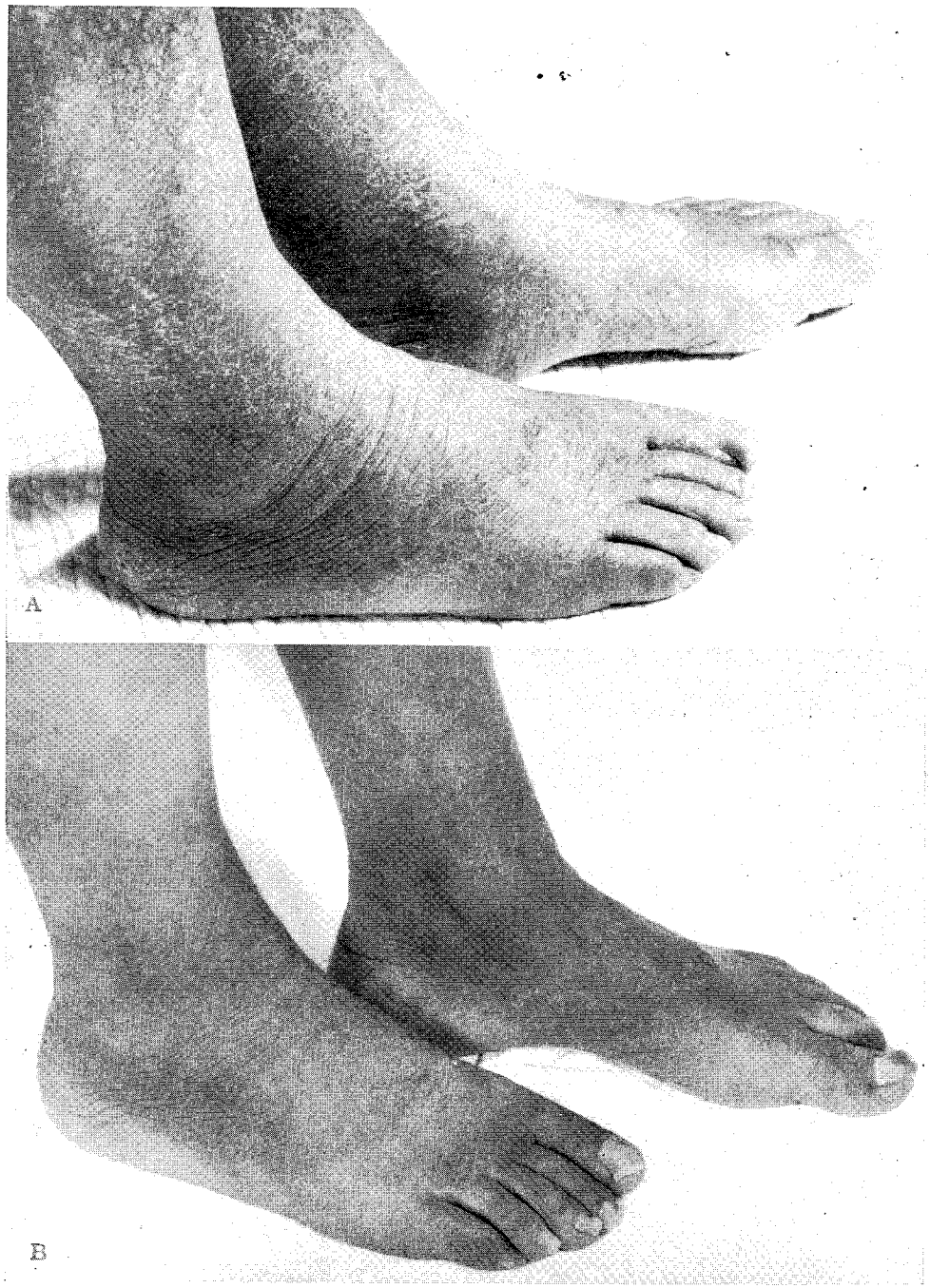
Effect of ACTH in lupus erythematosus disseminatus. 17-year-old girl with lupus erythematosus of seven months duration. Typical lupus erythematosus cells ("L.E. cells") were found in the bone marrow. — **A.** Appearance of face on admission. — **B.** Appearance of face after one month of ACTH treatment. Note that the skin lesions have disappeared. Curiously in this (as in several other cases) the lesion first became fiery red after about one week of ACTH.

[After Selye: "STRESS".
Courtesy of Dr. D. Markson, Wesley Memorial Hospital, Chicago.]



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.

[After Selye: "STRESS".
Courtesy of Dr. E. H. Steffensen, Henry Ford Hospital, Detroit.]

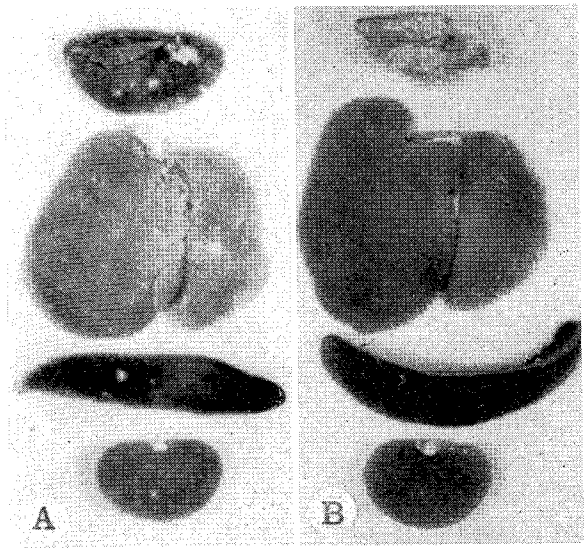


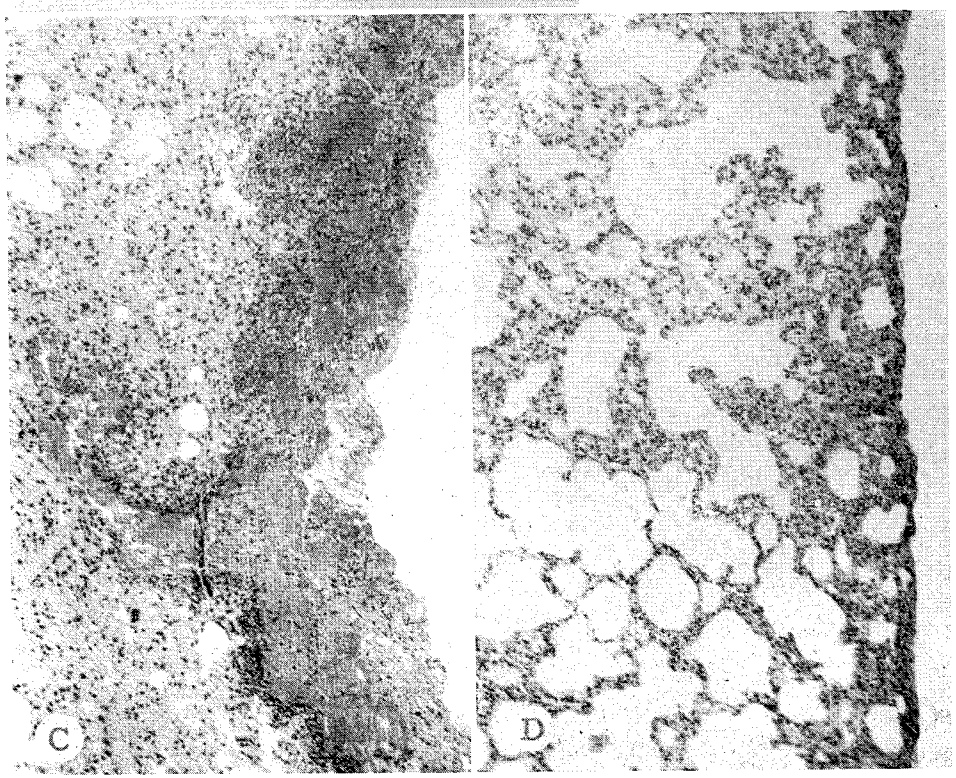
Effect of ACTH in psoriatic erythrodermia. 48-year-old male in whom the skin condition was quite refractory to all usual types of therapy. — **A.** Before, — **B.** After several weeks of ACTH treatment.

[After Selye: "STRESS".
Courtesy of Dr. D. Markson, Wesley Memorial Hospital, Chicago.]

Effect of STH and cortisone upon resistance to infection. — **A.** Macroscopic appearance of the lung, liver, spleen and kidneys of a rat which received toxic doses of cortisone (20mg./day) and — **B.** of one which received the same doses of cortisone conjointly with STH (6mg./day). — The marked hyperemia of the lung, in the region surrounding the abcesses, as well as the greater involution (catabolism) of the liver, spleen and kidney are quite evident in the rat treated with cortisone alone. — **C.** Pleural surface of the lung in a rat treated with cortisone alone. Note intense proliferation of micro-organisms on the visceral pleura, with little suppuration and almost no encapsulation. — **D.** Corresponding portion of the lung of a rat treated both with cortisone and with STH. Note complete absence of pathologic processes.

[After Selye: Canad. M.A.J. 64 : 489 (1951)]





Effect of STH upon resistance to X-rays in the rat. — Both these animals were exposed to the same degree of X-irradiation. Note stunting of growth in the (lower) animal which received no hormone treatment. Here the fur became irregular and fell out easily; the thymus, spleen and liver became intensely atrophic. All these changes were markedly counteracted by STH, as illustrated by the treated animal (upper). These experiments proved that the catabolic and lympholytic actions of ionizing rays can be counteracted by the anabolic "growth" hormone. It is not yet established whether such protection also increases resistance to the fatal actions of ionizing rays but experiments along these lines are now under way.

[After Selye et al.: Acta Endocrinol. 9 : 337 (1952)]

And now, let us consider our "liabilities," the doubts and uncertainties raised by the adaptation syndrome concept.

In medicine, as in most other fields, any new solution, no matter how advantageous, introduces new complications. The concept of the adaptation syndrome is certainly no exception to this rule. In order to highlight these "complications," I list them all as "liabilities," but bear in mind that they are actually questions which could not even have been asked without first formulating the adaptation syndrome concept.

I think many of them can now be satisfactorily answered in keeping with the original tenets of our theory; others, which were not in agreement with it, showed us the weak spots where further research was needed to clarify or complete the picture. In these respects, the questions brought up were, to me, the most valuable assets of this theory since they showed us the way to new and unexpected facts. I believe that a theory which says "nothing but the truth and all the truth" no longer possesses any heuristic value — indeed, it is no longer a theory but a mere enumeration of facts.

The following list includes every serious objection that has been raised against any part of the whole stress concept, as outlined in my lectures. You will note that not a single criticism is levelled against the general adaptation syndrome itself; all the points in my list deal with the interpretation of the "diseases of adaptation." In my opinion, however, this is the most important aspect of our work as regards clinical medicine, and I must admit that here disagreements were many and sometimes formulated with great violence and emotion.

Being quite emotional myself, I cannot claim to have registered such attacks with complete equanimity, but I tried to find consolation in the thoughts expressed, almost a hundred years ago, by the father of modern experimental medicine:

"Comme tous ceux qui ont eu le bonheur d'introduire dans la science des faits inattendus ou des idées nouvelles, j'ai été et je suis encore l'objet de beaucoup de critiques" [1]. [As all those who have had the joy of introducing into science unexpected facts or new ideas, I have been, and still am, the object of much criticism.]

This should give me enough courage to start my list.

Is desoxycorticosterone a natural substance?

(1) *Desoxycorticosterone may not occur in the adrenals.*

This seemed to be an important point because all our basic observations concerning the diseases of adaptation have been made in animals treated with excessive amounts of DCA. It is this work which led to the concept that diseases could be due to an excess of P-Cs; but we used DCA only because it happened to be a readily available example of a P-C compound. Other P-Cs, such as desoxocortisone, whose natural occurrence has never been doubted, proved to exhibit qualitatively similar inflammation-enhancing properties. Besides, so much evidence has accumulated in the meantime to show that desoxycorticosterone itself is also secreted by the adrenal cortex, that this objection is no longer seriously upheld and need not detain us.

(1) Bernard, C.: "Introduction à l'étude de la médecine expérimentale." Les Éditions du Cheval Ailé, Genève, p. 358 (1945).

Just how much P-C could the adrenals secrete?

(2) *The doses of DCA which we used to produce lesions may exceed the amounts that could ever be secreted by the adrenals.*

This criticism has come up particularly in connection with our 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, high-sodium diets, STH, etc.), much smaller amounts of the hormone proved to be disease-producing. Indeed, it is quite conceivable that in individuals specifically sensitized to the toxic actions of P-Cs by such "conditioning factors," the syndrome of DCA overdosage could appear without any appreciable increase in the total production, or urinary elimination of corticoids.

This whole situation has its parallel in enzyme actions. In common parlance, we often say that the content of the blood in a certain enzyme is increased or decreased, although the determinations upon which such statements are actually based do not measure absolute amounts of enzymes, but enzyme activity. The latter does not depend only upon total amounts, but also upon "conditioning factors," such as pH, the presence of certain metals and so forth.

Absolute versus relative hypercorticoidism.

In clinical endocrinology, when we observe specific changes of unknown etiology which we can duplicate only by excess administration of a certain hormone, we are tempted to ascribe their spontaneous occurrence to endogenous overproduction of this same hormone. If we find that a patient spontaneously shows signs which simulate the changes caused by an excess of thyroid hormone, we conclude that he probably produces too much thyroid hormone. Similarly, I used the term "hypercorticoidism" too loosely in connection with my experiments on the pathogenesis of the diseases of adaptation. The changes actually observed are only indicative of increased corticoid *activity*, not *production*. Special investigations will be necessary in each case to determine whether a lesion of this type, when it occurs spontaneously in a patient, is actually due to

increased production of corticoids, to changes in the internal milieu which sensitize certain target organs to such corticoids, or to both of these factors.

You must remember, on the other hand, that there is no objective reason to doubt that the pathogenic amounts of P-Cs are beyond the limits of what could be produced in the body during stress. The quantities excreted in the urine of men who have received DCA in toxic doses (that is, in amounts 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 A-Cs required to produce clinical remissions (in those spontaneous diseases which have been simulated in animals by DCA), then this objection appears to be even more unjustified. About 10 mg. of DCA a day, given over a period of weeks, would certainly be pathogenic in man, while 80-100 mg. of cortisone daily is usually required to produce a pronounced remission, for instance in rheumatoid arthritis or lupus erythematosus. The two types of hormones just cannot be compared on a weight-for-weight basis.

Furthermore, the toxicity of the corticoids largely depends upon the functional capacity of the adrenal cortex itself. It is a generally known clinical fact that a dose of DCA readily tolerated by a normal man, tends to prove highly toxic in an addisonian. Any similar defect in the adrenal or in other organs concerned with steroid metabolism, such as the liver, may render normal amounts of corticoids pathogenic. This could occur even without any accompanying rise in the urinary elimination of their metabolites. After all, the activity of hormones does not depend so much upon the rate of their complete turnover as upon the length of

time during which they remain active in their target cells.

Relationship between absolute amounts of corticoids and their toxicity.

(3) *The urinary elimination of corticoids is not always demonstrably abnormal in the diseases of adaptation.*

This objection has already been answered by my preceding comments. As I said, diseases of adaptation do not necessarily result from an absolute deficiency or excess of corticoids; they can also ensue as a consequence of unfavorable "conditioning" of their actions, for instance, by dietary factors or by an improper balance between antagonistic pairs of adaptive hormones (ACTH/STH, A-C/P-C, ACTH/P-C, etc.). Such a deranged hormone balance is in turn not necessarily due to abnormalities in the secretion of these substances by the hypophysis or adrenal. It may be caused by derangements in hormone metabolism (e.g., hepatic detoxification) or abnormal end-organ sensitivity (conditioning).

Absolute versus relative hypocorticoidism.

Diseases of adaptation can also 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 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 secretion can be assessed only in proportion to the *pathogen which creates a need* for cortical 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, remain in perfect health throughout life because — by way of 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.

What is a "normal" hormone production?

What is a "normal" level of hormone production anyway? Sex hormone secretion during pregnancy may exceed that of the non-gravid state a hundredfold. If it were to drop to "normal" suddenly during mid-pregnancy, the result would be a very abnormal occurrence, an abortion.

> Normalcy is indeed a very relative concept. My pulse is "normally" 70 per minute when I am resting. But I am not always resting. The elevator which leads up to the eighth floor of our building, at the University of Montreal, is frequently out of order. It is my custom, on such occasions, to run upstairs at full speed, just to prove to myself that I can still do it. When I arrive at the eighth floor, my pulse is 140 per minute. If it were still at a "normal" 70, I fear I would be in a state of severe circulatory collapse. A pulse rate which is normal for rest is not normal for a person performing intense muscular activity, just as a level of corticoid production which is normal for rest would not be normal during stress; for instance, in a patient with widespread inflammatory changes.

Chronic disease caused by temporary hormone excess.

In this connection, remember also our experiments which showed that temporary overdosage with certain adaptive hormones (e.g., DCA alone, or in combination with STH) was often tolerated without obvious manifestations of disease while the injections were given; yet all the animals so treated eventually died from nephrosclerosis, hypertension and arteritis,

at a time when the hormone overdosage had long been interrupted. Such observations suggest that a transitory episode of excessive adaptive-hormone production could elicit diseases of adaptation when the increase in the production (and hence excretion) of the causative hormonal factors no longer exists.

Basal hormone excretion is an inadequate indicator of responsiveness to stress.

Furthermore, most pertinent hormone excretion studies have been made on hospitalized patients protected against the usual stresses and strains of their daily lives. This is certainly not the best way to detect hormonal "hyperreactors to stress." Do you remember my sketch with the pendulum? Well, in a predisposed individual, the pendulum may swing into the danger zone frequently enough to cause disease by the accumulation of injury; it need not necessarily stay in this zone, even at rest. A person suffering from chronic carbon monoxide poisoning would never be recognized as such on the basis of blood-CO determinations performed in hospital. A chromaffinoma does not necessarily secrete large amounts of adrenaline in the resting patient.

The discussion of this particular question would not be complete without mentioning — at least here at the end — recent investigations which did bring forth objective evidence that derangements of steroid metabolism can occur in certain diseases of adaptation. Quite independently, several investigators [2, 3, 4] reported an absolute or relative increase in the urinary

(2) Dobriner, K., S. Lieberman, H. Wilson, M. Dunham, I. F. Sommerville and C. P. Rhoads: "Adrenal function and steroid excretion in disease." In: Proc. 2nd Clin. ACTH Conf., Blakiston Co., New York, *1*: 65 (1951).

(3) Marrian, G. F.: "Hormonal disturbances associated with rheumatoid arthritis and related conditions." Practitioner, *166*: 43 (1951).

(4) Weissbecker, L. and W. Ruppel: "Trennung der Desoxycorticoide von den 11-Oxycorticoiden im Harn und ihre quantitative Bestimmung." Verhandl. deutsch. Gesellsch. f. inn. Med., 57 Kongr., p. 37 (1951).

elimination of the 11-desoxycorticoids (presumably P-Cs or their metabolites) in the rheumatoid diseases. Unfortunately, research along these lines has been severely handicapped because of the technical difficulties which stand in the way of assaying blood or urine specifically for P-C activity. However, recent improvements in the relevant techniques hold great promise as regards the elucidation of this important problem.

Should one distinguish between P-Cs and A-Cs?

(4) *The distinction between P-Cs and A-Cs is fundamentally unsound.*

This objection is hardly justified and, in fact, it has only been raised by those who failed to appreciate that the terms prophlogistic (or mineralo-corticoid) hormones on the one hand, and antiphlogistic (or gluco-corticoid) hormones on the other, were never meant to suggest that any one chemical compound can possess *exclusively* one or the other of these activities. As I have said in my previous lectures, I proposed these terms to denote the *predominant* pharmacologic property of the two types of corticoids. An overlap between them in any one pure steroid — for instance, the presence of some mineralo-corticoid activity in a predominantly gluco-corticoid compound such as cortisone — does not obviate the necessity of distinguishing between these two actions.

> Let me add also that such an overlap of pharmacologic activities in the same steroid is by no means without precedent. Testosterone is a predominantly "androgenic" or testoid compound, although it also possesses considerable "estrogenic" or folliculoid activity. No one will doubt that it is pharmacologically indispensable to distinguish between testoids and folliculoids, although we do not know of any testoids completely devoid of folliculoid potency.

Most of you probably feel that it is quite superfluous to insist so much upon these self-evident facts,

but this point is still often misunderstood in the current literature.

Are rheumatic diseases aggravated by P-Cs?

(5) *DCA does not aggravate rheumatoid arthritis.*

It has been claimed that an excess of P-Cs could not be a factor in the pathogenesis of rheumatoid arthritis, since, here, treatment with DCA does not further aggravate the joint lesions. So far, this is one of the most justified objections levelled against the concept of the diseases of adaptation. It must be kept in mind, that up to now patients with rheumatoid arthritis have been treated only with very small doses of DCA. In the few rheumatics who have received toxic amounts, the availability of P-Cs may not have been the limiting factor in the progress of the disease. In any event, none of the cases so treated has as yet been reported in detail; therefore it is difficult to assess them.

Acute overdosage with large amounts of DCA tends to cause threatening derangements in water and electrolyte metabolism; hence, these experiments were probably not carried on long. Just which manifestation of DCA overdosages will become most prominent in any one case depends largely upon dosage, length of treatment, diet, the functional capacity of the adrenal cortex, and other conditioning factors.

It is certainly well established, on the basis of many case reports (I have seen at least six such cases myself), that DCA treatment often produces rheumatic-like joints lesions in addisonians. This does not prove that P-Cs *do* usually produce this disease (or even that they participate in its pathogenesis), but it does show that they *can* be the cause of such joint lesions in man.

Are rheumatic diseases accompanied by manifestations of P-C overdosage?

(6) *Rheumatoid arthritis is not accompanied by any marked disturbances in mineral or water metabolism.*

In this connection, it should be pointed out that even in rats in which rheumatic-like changes are produced by DCA overdosage, the hormone does not necessarily, at the same time, cause any characteristic mineral and water metabolism disturbance. Depending upon a variety of conditions, DCA may either increase or decrease sodium chloride and water elimination. On the other hand, the hypokalemia, which is rather constant during DCA intoxication, is not particularly marked in the case of other prophlogistic hormones. Even the inflammation stimulating effect of DCA does not depend upon the hypokalemia which it produces. If hypokalemia is overcompensated by giving excess potassium chloride, DCA still raises the inflammatory potential of the rat. In view of all this, it is quite plausible that whatever steroids may play a part in sensitizing tissues to inflammation in patients with rheumatism, they could do so without any manifest and persistent alterations of mineral and water metabolism.

It is also pertinent that the rheumatoid granuloma itself is very rich in sodium chloride and water; hence, some retention of these components must necessarily exist, at least at the site of the lesions.

Finally, several investigators did claim to have observed a definite salt and water retention in rheumatoid arthritis, although this is inconstant and rarely pronounced.

Despite all this, I do not feel that any of my counterarguments answer the criticism under consideration. They merely show that the absence of marked

disturbances in sodium and water metabolism is not incompatible with the assumption of an adreno-cortical participation in the pathogenesis of rheumatic diseases, but they do not explain why such metabolic disturbances fail to occur in these maladies.

Do ACTH and cortisone act merely as "pharmacologic" agents?

(7) *The therapeutic actions of ACTH and A-Cs may be purely "pharmacologic" and unrelated to the adaptation syndrome mechanism.*

Immediately after it had been shown that ACTH and cortisone can cause remissions in those same clinical conditions which we had experimentally imitated by prophlogistic hormones, several investigators expressed the view that there may be no relationship whatsoever between the clinical and the laboratory observations. It had been pointed out, for instance, that just because digitalis is helpful in heart disease we do not conclude that the latter is due to a digitalis deficiency.

Surely, the case for the adaptive hormones, as factors in the development of disease, is on an entirely different level!

A variety of useful drugs, such as digitalis, may influence the course of a disease favorably, but there is no reason to expect that they are ever produced in the body's effort to combat disease, or indeed that they ever occur naturally in animal tissues. The adaptive hormones, on the other hand, are demonstrably manufactured by our endocrine glands, and we have irrefutable evidence that, during stress, they are secreted in excessive amounts. No one doubts that a deficiency of these pituitary and adreno-cortical hormones (e.g., after hypophysectomy, adrenalectomy, in Simmond's or in Addison's disease) decreases resistance to a variety of essentially dissimilar agents,

— that is, non-specific resistance. Conversely, a pathologic excess of these hormones, even if they are endogenously produced by the endocrine glands themselves, can elicit tangible pathologic changes in man (e.g., accidental thymus involution during acute stress, hypertension due to adreno-cortical hyperplasia).

Relationship between adaptive hormones and "non-specific therapy."

During an acute stress situation, such as is created for instance by intense "non-specific therapy," enough ACTH is discharged from the patient's pituitary to induce a temporary remission in rheumatoid arthritis. Under these conditions, the accompanying increase in the urinary elimination of corticoids is approximately the same as that obtained by therapeutically effective doses of injected ACTH. In view of this, I would find it difficult to speak of a "purely pharmacologic" action of ACTH or A-Cs in the rheumatic diseases. Surely, here we are imitating a physiologic "auto-pharmacologic" self-defense mechanism of the body.

The last three Heberden Orations.

It is amusing, in this connection, that the last three Heberden Orations in London [given by P. S. Hench [5], myself [6] and E. C. Kendall [7], in this order] all dealt extensively with this problem and yet no definite agreement was reached.

Doctor Hench pointed out that such varied conditions as pregnancy, jaundice, surgical trauma or malnutrition may cause remissions in rheumatoid arthritis and hence, the disease must be considered to be essentially reversible. He argued that some "X-factor" (not to be confused with the "X-factor" in

(5) Hench, P. S.: "The potential reversibility of rheumatoid arthritis." Ann. Rheumat. Dis., *8*: 90 (1949).

(6) Selye, H.: "Stress and the General Adaptation Syndrome." Brit. M.J., June 10-17, pp. 1362, 1383 (1950).

(7) Kendall, E. C.: "The adrenal cortex and rheumatoid arthritis." Brit. M.J., Dec. 1, p. 1295 (1951).

our LAP preparation) must be produced under the influence of all these conditions. At that time, he did not mention stress, the pituitary or the adrenal, but these considerations subsequently led him and his co-workers to attempt the therapeutic use of ACTH and cortisone for the artificial induction of similar remissions. This extraordinarily successful clinical research undoubtedly resulted from an attempt to imitate a physiologic defense mechanism of the body.

The following year, before this same Society, I outlined my work on the adaptation syndrome, including the production of inflammatory lesions with the aid of prophlogistic hormones and their inhibition by antiphlogistic hypophyseal and corticoid hormones. I thought that the therapeutic effects of the latter were not pharmacologic, but based on principles of natural defense measures.

Yet, the next year, when Doctor Kendall described his classic studies concerning the chemistry of corticoids, he said to the Heberden Society that, in his opinion, "No combination of overactivity or underactivity of the ductless glands appears to be important in the aetiology of rheumatoid arthritis."

Several other prominent investigators (F. Coste, G. Sayers and others) expressed the view that ACTH and the A-Cs act merely by virtue of purely "pharmacologic" effects which have nothing to do with self-defense through adaptive responses.

Let me re-emphasize that, personally, I definitely regard these beneficial actions as not merely coincidental pharmacologic side-effects of hormones, whose physiologic rôle lies in an entirely unrelated field. I believe that these therapeutic measures are based upon our ability to improve or correct certain natural, hence

essentially physiologic, defense measures of the body. This was the keynote of my pertinent investigations and — right or wrong — it helped me to learn most of the facts which I presented to you during these lectures. Yet, you must keep in mind that, even today, several first rate investigators do not agree with me on this point.

The mystery of how they can be many and yet one.

(8) *Why are the diseases of adaptation so polymorphic in their manifestations, if they are all due to stress?*

We believe that the principal reasons for this polymorphism are the so-called "conditioning factors": the specific effects of the evocative stressor and other exogenous or endogenous factors (heredity, pre-existent diseases of certain organs, diet, previous exposure to stress, etc.), which can selectively effect certain pathways or target organs of the G-A-S response.

Individual constitution and susceptibility to disease.

(9) *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 cannot be expected to produce such maladies unless the defense-reaction is inadequate. Thus, for instance, in our experimental efforts to produce the nephrosclerotic-hypertensive-rheumatic 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 factors 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 cardio-vascular lesions, nephrosclerosis and a rise in blood-pressure.

It is very probable that in man also, under the influence of stress, similar diseases tend to develop only when, as a result of adverse conditioning factors, the adaptation syndrome is prevented from evolving in a normal manner.

On changing one's opinion.

(10) *The theory of the diseases of adaptation is constantly being changed as new facts come to light.*

This objection is perhaps the one usually made with the greatest display of irritation. Surprisingly, many investigators seem to feel that changing one's views is shameful and that such a disgrace could have been avoided by not publishing any interpretations before they had been supported by all the pertinent facts known today. But we must change our views when they are no longer tenable; and anyway which day is "today"?

It has been said — not without acrimony — that my theories are too plastic, almost "protean" in nature. Of course, the concept of the adaptation syndrome and of the diseases of adaptation is pliable; if it were not, each new discovery would outdate it. Only a flexible theory, handled by investigators who are willing to alter it or add to it, can long survive.

If you draw a preliminary map of a country you are just beginning to explore, it is wise to insert even the few well-identified points lightly in pencil, while you are not quite certain of their positions relative to each other. Thus, the map will be most useful as long as it

is the best available; furthermore, it will maintain this superiority at all times by additions and changes as new information comes forth. I have always felt that theories, even those in our minds, should invariably be drawn in pencil; they can be replaced by indelible ink only after they cease to be theories and become facts.

Every addition involves a change.

In these lectures, I have taken special care to show you how the stress concept was formulated at different times between 1936 and 1952. In retrospect, we have actually changed very little, but we have added a great deal. For instance, while we first thought there is only one cortical hormone, we now have to invoke several to make the theory fit the known facts. But, as I said, it is a necessary prerequisite of a concept which tends to embrace many hitherto unknown (or only partly known) facts, that it should be expressed in a form which is not too rigid and hence lends itself to extension as objective observations require it.

Imagine an investigator who has lived through, and participated in, the development of any other field of medicine — say, bacteriology, allergy or vitaminology. How often would he have had to change or extend his views? Just as often as an important fundamental contribution was made. Nowadays, research is rapidly progressing, and a good deal has happened since 1936 in this intensely studied field of stress.

Of course, I participated in only a small fraction of it, but — alas! — I lived through it all. During many a dangerous storm, I tried to keep the basic tenets of the adaptation syndrome concept alive when they were threatened to be abandoned by others, just because some new facts did not seem to fit the whole.

It would have been impossible to do this had I stuck stubbornly to my every previous dictum. For some time — not for long — I might have maintained a semblance of being right, but I preferred to be right by admitting that I was wrong.

(11) *Anticipated objections.*

There are a few additional doubtful points which have not yet been hurled against me, although they should have been and I suppose they will be.

Is STH secreted during stress?

(A) It has not yet been proven objectively that STH is ever discharged during stress. Of course, up to now there was no particular reason to examine the blood for excesses of this hormone in any condition other than acromegaly or gigantism. Besides, the methods for such bio-assays are far from satisfactory. We must keep in mind however, that this point remains to be proven.

Even should there be no change in STH secretion during stress, we already know that there certainly is a marked increase in ACTH and A-C secretion; hence, anomalies due to deviations from the normal $\frac{\text{prophlogistic}}{\text{antiphlogistic}}$ ratio undoubtedly occur during the adaptation syndrome.

The possible rôle of the kidney in systemic inflammation.

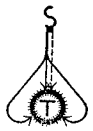
(B) The relationship between renal pressor substances and prophlogistic hormones is not clear. P-Cs (e.g., DCA) certainly can produce nephrosclerosis and hypertension, but it is not yet known to what extent renal pressor substances participate in determining the inflammatory potential of connective tissue in general. The possible participation of the kidney in systemic inflammatory disease would deserve to be studied from this viewpoint.

The possible rôle of the thyroid in the G-A-S.

(C) The part played by the thyroid in the adaptation syndrome has not been adequately examined. Thyroxin and thyrotrophic hormone: increase the nephrotoxic actions of STH and DCA. Without doubt, certain types of Graves' disease can be elicited by non-specific stressors, for instance, by emotional strain. The basal metabolic rate is an important conditioning factor of all biologic phenomena and, hence, presumably also of the adaptation syndrome.

To take a specific point, DCA fails to cause nephrosclerosis in hypophysectomized animals. It has been assumed that a deficiency in STH is responsible for this, but hypothyroidism is no doubt also a contributing factor since thyroidectomy delays and thyroxin accelerates the development of the P-C intoxication syndrome. However, the mechanism through which the thyroid participates in stress phenomena remains quite obscure.

There are many other problems of this kind, doubts and uncertainties which would not have arisen without the formulation of the adaptation syndrome concept. But I consider these as "liabilities" only in that they are hazy spots, one would almost say flaws, in the picture; actually, they are our most valuable assets since they show us where to look for more knowledge.



SEVENTH LECTURE

General Summary and Outlook

Ladies and Gentlemen!

THROUGH FIVE LONG LECTURES, I have tried to reconstruct for you the story of the adaptation syndrome, from the moment when its outlines had first been faintly suggested by a few incidental observations, up to the present day when it has grown into one of the most complex and most rapidly developing branches of contemporary medicine.

My sixth lecture was meant to be an objective summary of the principal facts which were brought to light with the help of this theory and of the most commonly voiced doubts and objections against some of its tenets. Through this impersonal résumé, I hoped to make certain that you will not confuse the facts which I observed with the ideas which led me to them or which I derived from them.

Now, in this seventh and last lecture, I shall permit myself the luxury of an entirely subjective summary of this field and of a personal assessment of its significance and future.

Let me first try to list here what I think are the principal doctrinal acquisitions derived from the adaptation syndrome concept.

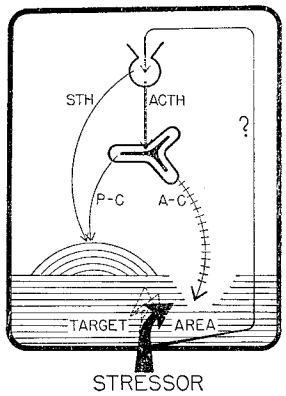
Principal gains derived from the G-A-S concept.

All agents which act upon the body or any of its parts exert dual effects:

(1) Specific actions with which we are not concerned in this study, except insofar as they modify the non-specific actions of the same agents.

(2) Non-specific or stressor effects whose principal pathways (as far as we know them today) are illustrated in the adjacent drawing.

The *stressor* acts upon the *target* (the body or some part of it) directly (thick arrow) and indirectly through the pituitary and adrenal.



Through some *unknown pathway* (labelled by a question mark), a stimulus travels from the directly injured target area to the *anterior pituitary*. It notifies the latter that a condition of stress exists and thus induces it to discharge *ACTH*.

It is quite possible that this "first mediator" of hormonal defense is not always the same. In some instances, it may be an adrenaline discharge, in others a liberation of histamine-like toxic tissue metabolites, a nervous impulse or even a sudden deficiency in some vitally important body constituent, such as glucose or an enzyme.

ACTH stimulates the *adrenal cortex* to discharge corticoids. Some of these, the *prophlogistic corticoids (P-C)*, stimulate the proliferative ability and reactivity of connective tissue; they enhance the "inflammatory potential." Thus, they help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the pathogenic stressor agent.

However, under ordinary conditions, ACTH stimulates the adrenal much more effectively to secrete *antiphlogistic corticoids (A-C)*. These inhibit the ability of the body to put up granulomatous barricades in the path of the invador; in fact, they tend to cause involution of connective tissue with a pronounced

depression of the inflammatory potential. Thus they open the way to the spreading of infection.

As far as we know, ACTH always stimulates the adrenal to produce the various corticoids in the same proportion and always with a great predominance of A-Cs. However, the *somatotrophic hormone (STH)* of the pituitary also increases the inflammatory potential of connective tissue, somewhat as the P-Cs do; hence, it sensitizes the target area to the actions of the latter.

It is possible that the hypophysis also secretes some special corticotrophin which induces the adrenal to elaborate predominantly P-Cs; indeed, STH itself may possess such effects, but this has not yet been proven. In any event, if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence can be vastly different, depending upon "conditioning factors" (such as STH), which specifically sensitize the target area for one or the other type of corticoid action. Actually, conditioning factors could even alter the response to ACTH of the adrenal cortex itself, so that its cells would produce more A-Cs or P-Cs. In any event, during stress, one or the other type of effect can predominate.

The fundamental reaction-pattern to topical stressors is "inflammation," to systemic stressors, the "G-A-S." Various combinations of these two basic responses constitute the essence of most diseases.

The regulation of tissue reactivity through "adaptive hormones" often determines whether the body succumbs to disease or resists a potential pathogen by means of adaptation. The nervous system and humoral agents, other than those which we have considered here, also participate in the adaptation syndrome, but the nature of their pertinent actions is not yet sufficiently understood to deserve detailed consideration at the present time.

Thus, stress affects the body through multiple pathways; its effects are always modified by the variable specific actions of the eliciting agent and by the conditioning factors (diet, heredity, constitution, previous exposure), the "terrain," which is different in every individual.

The sum of all these non-specific reactions is what we call the "general adaptation syndrome." It comprises both non-specific damage and non-specific defense.

The hormonal defense reactions of the adaptation syndrome are not, in themselves, pathogenic; on the contrary, they are indispensable physiologic reactions to damage as such. However, the adaptation syndrome — like any other biologic response — is not always optimally effective. I believe that its imperfections play an important part in the pathogenesis of most diseases. The maladies in which such inadequacies are even more important than the specific actions of the pathogen itself are considered to be primarily "diseases of adaptation."

Pathogenicity of G-A-S derailments.

Let us now consider how derailments of the adaptation syndrome could become the principal causes of disease.

For the maintenance of the body's integrity, inflammation is sometimes useful, sometimes detrimental.

If the stressor is virulent and invasive . . .

If the stressor is a virulent living microbe, for instance the tuberculosis bacillus, it is manifestly of the utmost importance to put up a strong barricade of inflammatory granuloma tissue around it. This process of active encapsulation helps us to keep the microbes from proliferating unduly and from invading the entire organism. Our experiments have shown how even saprophytic micro-organisms can cause death, if the possibility of inflammation and encapsulation is abolished by heavy overdosage with A-Cs, such as cortisone.

The many patients in whom a hitherto latent and inoffensive focus of tuberculosis has been reactivated under the influence of ACTH or cortisone therapy for rheumatoid arthritis, bear witness to the dangers of this antiphlogistic type of treatment. In such patients, the absorption of granuloma tissue from the joints is no doubt desirable, but the hormones fail to distinguish between "useful" and "useless" granuloma tissue. When they remove a purposeless connective tissue barricade around a joint affected by rheumatoid

arthritis, they also destroy the vitally important connective tissue capsule around the tuberculous focus in the lung of the same patient.

If the stressor is neither virulent nor invasive . . .

If the stressor is not very injurious and has no tendency to multiply or spread from the site of invasion throughout the body, a prophlogistic response is of little value. For example, in our rats with the topical irritation arthritis, the formalin injected into their paws can neither multiply nor spread through the body; it is immediately precipitated with the proteins of the cells in its immediate surroundings. The egg-white, which causes hyperergic inflammatory changes in rats, belongs to this same category. Under these experimental conditions, neither the formalin nor the egg-white represent a major threat to survival; indeed, they produce "disease" only by way of the excessive inflammatory response which they evoke. Numerous allergens and other irritants act similarly in man.

Such a purposeless inflammatory response is particularly detrimental when it affects especially mobile or vital regions; for instance, the joints, the central nervous system, the heart and the eye. In all these sites, the connective tissue reacts by essentially the same imflammatory response as elsewhere. As in other locations, granulomatous barricades help to protect the rest of the body against the possible dangers of invasion; but here this benefit is bought at a prohibitive price. Especially if the irritant is not invasive anyway, its imprisonment by a thick granulomatous wall serves no purpose while the inflammatory tissue itself may become the principal cause of disease. In a joint, it may cause stiffness and pain; if it localizes in the brain, it may elicit epileptiform convulsions; a myocardial infarct can kill the patient

if the granuloma develops in a coronary vessel and blindness may ensue if it renders the cornea opaque.

Dynamics of G-A-S derailments.

I can imagine that the body does not always respond optimally to injury. The following are the most obvious ways in which the adaptation-syndrome-mechanism could so derail as to become the major cause of illness:

(1) A *dysreactive pituitary* may not always respond with the proper balance of prophlogistic (STH) and antiphlogistic (ACTH) hormone secretion. To give but two examples: excessive ACTH secretion in tuberculosis, or excessive STH production in rheumatoid arthritis, would almost certainly be unfavorable "adaptive" responses. In the former instance, the necessary granulomatous encapsulation of the site of infection would be prevented by the antiphlogistic hormone, and this could open the way to a generalization of the infection. In the second instance, topical granuloma formation around the affected joints would be further enhanced, thus aggravating the arthritis. Such rheumatoid granulomas are evidently of no defensive use, since their removal by ACTH or A-Cs causes a welcome remission without opening the way to any great spreading of the malady.

(2) A *dysreactive adrenal* cortex may respond to ACTH by a disproportionate excess of A-C over P-C or vice versa.

(3) A generally *hyperreactive pituitary or adrenal cortex* may respond during stress by an excessive, though balanced, production of their hormones.

(4) A *hyporeactive pituitary or adrenal cortex* may respond during stress by an insufficient, though balanced, production of their hormones.

In all of these four possibilities of derailment, there is some disturbance in the total amount of hormones produced or in the proportion of the various hormonal principles secreted.

(5) Finally, we must also consider the derailments of the adaptation-syndrome-response which could arise from an abnormal *increase or decrease in the sensitivity of the target organs* themselves to one or more adaptive hormones; such anomalies could be due to selective conditioning factors.

Undoubtedly, all these possibilities must be envisaged and I imagine that several, if not all of them, can actually participate in the development of the diseases of adaptation.

Again about the value of a theory.

At this point, permit me one last "aside."

Many of you will remember the innumerable criticisms of which I became the target when I first formulated the concept of the diseases of adaptation, because I then spoke only of the possibility that maladies may be due to an excessive production of adaptive hormones, particularly of M-Cs.

As I told you, the first factual observations which led me to think along these lines were that DCA caused arthritis, periarteritis nodosa, myocarditis, nephrosclerosis, hypertension, etc. We also knew that the adrenals are enlarged and hyperactive during the adaptation syndrome and that an excessive secretion of "corticoids" during stress can cause organic lesions, such as thymus involution or nephrosclerosis.

At that time, we did not clearly understand the difference between A-Cs and P-Cs, nor did we know anything about the possibility of increasing a hormone *effect* (by conditioning factors) without any change in actual hormone *concentration*. Surely, it would then have been futile to enter into lengthy dialectic arguments about the ways in which a "hormone excess" could occur. Yet, here again, the concept was useful since even the question "In what way could hormone activity become excessive and pathogenic?" could not have been asked before we formulated the theory that "A corticoid excess could be pathogenic."

Diabetes had been regarded by Banting as a form of hypoinsulinism because pancreatectomy reproduced it in animals, and insulin had a therapeutic value. It is surely not always as simple as that! Yet, without this "false" theory, the possibility of differentiating pancreatic from extra-pancreatic diabetes could hardly have been considered, and insulin would not have been discovered.

I do hope my habit of breaking up this account of the adaptation syndrome by side-remarks concerning the philosophy of research does not make it too difficult for you to follow my principal arguments. Try as I may, in telling my story I just cannot resist the urge to transmit to those of you who are on the threshold of your scientific career, the most important lessons that I have learned from it myself.

The horror of abstract thinking.

The value of handling a theory correctly is certainly near the top of my list! It is particularly important to emphasize this because, nowadays, there is a veritable horror of abstract thinking in medical research. Of course, most people abhor what they cannot master and the primitive intellect is tempted to justify its inability to follow a complex argument by accusing it of being "vague speculation."

1 + 1 = 2

It is pardonable if a child cannot understand that $1 + 1 = 2$, because figures are abstract and do not mean anything to him. Hence, we first teach the child that 1 apple + 1 apple = 2 apples, and after having gone over a number of examples showing that the same is true of 1 + 1 pencils, books, rabbits, etc., he is finally led to the abstract generalization according to which $1 + 1 = 2$ *of no matter what.* Of course, all generalizations are fraught with danger — the danger of not being applicable in every instance. Their utility depends upon the breadth of their applicability, which may be great but is hardly ever infinite. [Even the above example, which seems so safe, has its limitations; 1 rabbit + 1 rabbit does not necessarily = 2 rabbits . . . if they are of different sexes.]

You will understand why I belabor this point if you remember what I said during my first lectures about the objections against the concept of non-specific biologic stress. I shall never forget the air of self-righteousness with which some of my colleagues pointed out that a conscientious scientist should not speak of an "alarm reaction" (which is an abstraction) as a manifestation of "stress" (which is also an abstraction), but of an adrenal enlargement caused by cold, a gastric ulcer produced by forced muscular exercise, a thymus involution elicited by formalin, etc., which is what he can actually observe. The implication was that abstractions are fantasies and hence revolting to the truly scientific mind which refuses to deal with anything but honest, measurable facts.

The two meanings of the verb "to speculate."

We must learn that speculation has two meanings: "to ponder a subject in its different aspects and relations," that is, to meditate or think, and "to theorize from conjectures, without sufficient evidence." (Webster's dictionary.) Even if they occupy the highest academic positions (and they often do!), you must refuse to be intimidated by those who, being unable to speculate efficiently in the former sense, imply that the word possesses only the latter meaning.

Although the more recently formulated concept of the diseases of adaptation is still debated now, after 16 years of constant checking, the concepts of the G-A-S and of non-specific biologic stress are generally accepted. Yet I remember that not so long ago, I was accused by a novice in medical research that my theories on the adaptation syndrome have "retarded medical progress by a century." [I am still most grateful to a very mild-spoken, elderly scientist who helped out, while I was speechles, by replying: "I hope you find it consoling that no one could possibly say that about your work."]

A theory should not be expressed if it is based on insufficient evidence, but if we are certain that its basic tenets are solid we must not give it up easily just because it is unpleasant to be attacked. Faith, persistence and courage despite opposition, are almost as indispensable to a scientist as intellect or training, for no fundamental progress can be made by one who cannot face criticism.

I mention all this because you too will be criticized if you look at things from a new viewpoint.

Of course, we must carefully check our facts and if they are incompatible with our dreams and theories, the latter must be abandoned; but hope and optimism about what can be accomplished encourage us to try, while skepticism tends to inspire nothing but a supercilious sterile inertia.

Objections against the germ theory of disease.

It is not so long ago that skeptics still discounted the germ theory of disease. They gave reasons singularly reminiscent of the objections levelled against the con-

cept of the diseases of adaptation. They pointed out firstly that in some patients with manifestly contagious maladies, no germs had been demonstrated; secondly, that certain supposedly pathogenic organisms are often plentiful in people who exhibit no signs of illness. Of course, these objections were made only because the fundamental tenets of the germ theory had been too rigidly applied in their first oversimplified form. These findings were not really exceptions; they merely required a further elaboration of the concept to become fully understandable. Now we know that most of the so-called exceptions of the first type were due to the transmission of disease by viruses and other not readily identifiable micro-organisms, while those of the second category can be ascribed to congenital or acquired immunity. These and many other apparent exceptions to the original germ theory were responsible for its transformation from the first formulation that "a certain disease is due to the introduction into the body of its specific causative micro-organism," to the complex edifice of contemporary microbiology and serology. It would have been a pity to abandon the original theory because it was "false."

But let us get back to our discussion of the diseases of adaptation.

In what sense can a malady be viewed as a disease of adaptation?

We must keep in mind that there is no such thing as a disease of any one organ or a malady caused solely by any one pathogen. We classify diseases according to the *relative* importance, for their development, of individual organ-lesions or pathogens. Just as there are diseases whose manifestations are principally cardio-vascular or nervous, so there are principally adaptive diseases, but no system of nosologic classification can avoid overlap.

For instance, a case of scarlet fever may be listed among the infectious (according to etiology), or among the renal or cardiac diseases (according to manifestations) if it causes nephritis and myocarditis.

Any among the "diseases of adaptation" could also be listed under some other heading, but this, as

all other nosologic systems, has been proposed to illuminate disease from a new viewpoint. Those of us who study the stress-factor in pathology, find this system of classification to be the most convenient. Adaptation (or the lack of it) is an important factor in any physiologic or pathologic process. Hence, all maladies are to some extent diseases of adaptation, but only those in which the maladaptation factor is of special importance should be listed in this category. A nervous breakdown precipitated by the patient's inability to adapt himself to mental stress, or the rapid spreading of a previously dormant infection caused by a stress-induced A-C discharge, are examples of predominantly adaptive diseases. Conversely, in blindness or the muscular paralysis due to a traumatic nerve lesion as in acute carbon monoxide poisoning, the maladaptation factor is negligible, since the body possesses no adaptive mechanisms with which it could counteract the principal derangements caused by these pathogens.

Let us point out here that the therapeutic efficacy of adaptive hormones, such as ACTH or A-Cs, in a patient does not mean that his *is* a disease of adaptation. Yet, the effectiveness of such treatment is a rather useful indicator of the *degree* to which a malady is a disease of adaptation.

Unified theory of medicine.

Now, just a few words about the adaptation syndrome as a unifying concept in medicine.

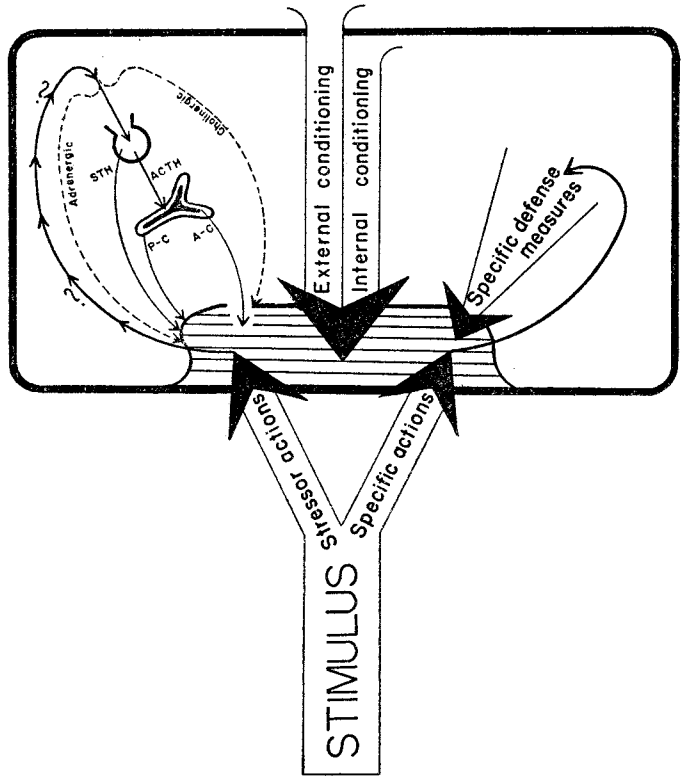
Whenever a large number of facts accumulates concerning any branch of knowledge, the human mind feels the need for some unifying concept with which to correlate them. Such integration is not only artistically satisfying, by bringing harmony into what

appeared to be discord, but also practically useful as it helps to visualize a large field from a single viewpoint. When surveyed from a great elevation, some details in the landscape become hazy, or even invisible; yet, it is only from there that we can see the field as a whole in order to establish where more careful exploration of the ground would be most helpful for its further development.

Efforts to arrive at a unified concept of disease have been made by physicians ever since the beginning of medical history. Whenever objective observations revealed any one structural or functional characteristic that appeared to be common to all the parts of the body, or to all of its diseases, efforts were made to single out this characteristic as a lookout post from which to obtain a co-ordinated view of medicine in its entirety.

None of these efforts were wholly successful and I am inclined to doubt even the theoretic possibility of ever arriving at an interpretation of medicine which will be truly unifying. There are many distinct diseases and they could not all be wholly due to any one thing.

We have said that whether we call a certain malady a disease of the heart, a disease of the kidney or a disease of adaptation, depends upon the relative predominance of its various characteristics. Similarly, the value of a "unifying theory" of medicine can only be measured in relative terms. The adjacent drawing will illustrate the manner in which we visualize that pathology and pharmacology could be partly unified through the stress-concept.



Any *stimulus* (e.g., a potential pathogen, a drug) acts upon the body both by way of its specific actions and through its non-specific stressor actions. Some stimuli may affect all cells of the body directly, but in most cases their immediate action is more or less selectively concentrated upon a certain *"target"* (shaded area).

The *specific actions* provoke specific defense measures (e.g., antibody formation by antigens).

The *stressor actions* provoke non-specific defense measures (e.g., adaptive-hormone secretion), that is, responses whose protective effect is not limited to the stimulus which elicited them. These non-specific reactions may be purely local (e.g., inflammation) or systemic (the G-A-S).

The specific defense measures (right side of the field) are not part of the adaptation syndrome. Hence, we shall merely indicate their existence here without

discussing them in detail, although they can be secondarily influenced by stress.

The stressor actions elicit the *typical hormonal manifestations of the G-A-S* (left side of the field) which have already been discussed in sufficient detail. They are pictured here only in order to indicate their position within our system.

In the course of my lectures, I frequently emphasized that the adaptive-hormone mechanism is not the only means of non-specific defense. *The nervous system* also plays an important rôle, but I did not discuss this in any detail because I have little personal experience in this field and, besides, the mechanism of nervous participation in the G-A-S has not yet been sufficiently clarified. — There exist many synergisms between prophlogistic hormones and adrenergic compounds on the one hand, and between antiphlogistic and cholinergic compounds on the other hand. Hence, I have tentatively inserted these two roughly antagonistic pairs of nervous regulators (interrupted lines) into the G-A-S part of our drawing.

The important investigations of Ricker, Reilly and Speransky focused our attention upon the nervous system as an important link in the pathogenesis of disease in general. Our work on the adaptation syndrome re-emphasized this point by showing that nervous irritation is an extraordinarily powerful stressor. Transection of the spinal cord, psychic stress, hypothalamic lesions, all tend to produce G-A-S manifestations qualitatively similar to those elicited by other agents, but of unusual intensity. This may be due to the fact that, through its many intercommunicating pathways, the nervous system can readily affect large areas of the body even if it is injured only at one specific point. This may help the rapid diffusion of the stressor-effect throughout the body. Certainly, much could be gained by a further elucidation of the manifold interrelations which exist during stress, between the two great co-ordinating systems of the body: the nervous and the humoral systems.

The schema implies — perhaps too definitely — that non-specific actions evoke non-specific reactions, while specific actions call forth specific reactions on the part of the body. This is largely correct, but it must be kept in mind that there is some overlap between the two categories. For instance, an agent such as insulin which produces a particularly pronounced hypoglycemia, tends to elicit a greater gluco-corticoid discharge than other equally damaging stimuli. Here the drop of the blood-sugar itself apparently acts as a selective conditioning factor, enhancing the G-C discharge. Since G-C secretion is also a non-specific response, this example helps to illustrate that the distinction between specific and non-specific reactions is not as sharp as our schemas may imply.

Both *external* (temperature, diet, light) and *internal* (heredity, constitution, pre-existent organ lesions) conditioning factors influence the reaction of the body to both specific and non-specific actions. As mentioned above, they also help to integrate specific and non-specific factors along the mid-line of our drawing.

Cells are capable only of a limited number of qualitatively distinct responses (e.g., degeneration, necrosis, increase and decrease in mitotic rate, in size and function). Depending upon the pathogen, the specificity of these responses varies between the most non-specific type of reaction that any pathogen can elicit when applied in suitable dosage (e.g., necrosis), to the most highly specific (e.g., the Koplik spots of measles). Yet, probably no pathogen produces any response "de novo," that is, one for which there exists no mechanism in the normal life of the cell at any time (e.g., transmutation of elements). Hence, presumably all normal and abnormal reactions can be effected by various combinations of simple stimulations and inhibitions of pre-existent biologic mechanisms (e.g., through the directing enzyme systems). I mention this because it means that even specific actions and specific diseases could be due to mere "stress" if the latter were directed selectively upon certain structures or chemical mechanisms. *In this sense, specificity would merely be a consequence of unusual patterns in the distribution, the "mosaic," of topical stresses.*

It remains to be seen whether this outline of a "unified theory of medicine" will be of heuristic value. Its principal weakness is its vagueness, its failure to explain the ultimate causes of disease. However, it appears to include and to be compatible with all the important facts concerning disease in general which are well established today; I do not think a theory can be useful if it attempts to be more explicit than verified observations warrant.

This is all I can tell you now about the adaptation syndrome, its history, its mechanism, its clinical implications and the light it begins to shed upon our understanding of disease in general.

●

Assessment of stress-research.

Now let me close with a few words about what I think is the most important outcome and probable future of research on stress and the adaptive hormones.

The "ACTH and cortisone era" 1949-1952.

When ACTH and cortisone were first introduced into clinical medicine, there was much hope that treatment with these hormones might cure a large number of hitherto incurable diseases; indeed, it was felt that these drugs — and they were considered as merely pharmacologic agents, which means drugs — would have such a wide spectrum of practical applications that they would "revolutionize medicine." Not only the lay press but even many usually conservative medical journals spoke of the beginning of a special "ACTH and cortisone era" in the treatment of disease.

During the first year or two, the purely empirical evaluation of these hormones as drugs has yielded so many interesting results that this kind of research truly dominated medical thought throughout the world. I think it is no exaggeration to state that, in

1949, there began an "ACTH and cortisone era" but, stimulating as it was, it unfortunately did not last long. Now, in 1952, we may say that treatment with these hormones has already been tried empirically in almost every disease. That is, as far as one can go without any rationale or theoretic background, using these hormones as pharmacologic agents which happen to be useful in certain maladies. We have already learned enough about the limitations and complications of this kind of treatment to conclude that further major progress is unlikely along these lines. In other words, this oversimplified, though very "honest" and objective approach of mere screening has been fully exploited within three years! To go further, more depth and more imagination will be necessary.

Of course, even without any fundamental study of their actions, ACTH, cortisone and other antiphlogistic corticoids will, no doubt, continue to be useful additions to our therapeutic armamentarium. This is true particularly in the treatment of certain inflammatory diseases of the eye, which do not tend to recur soon after discontinuation of such treatment or can be controlled by the purely local application of A-Cs, without introducing the danger of systemic complications. Perhaps, by pure chance and empiricism, we might overcome even some of the toxic side-effects of systemic treatment with these hormones sufficiently to make their continued use desirable also in the so-called rheumatic and other connective tissue diseases. But if their significance in medicine is to be thus limited, we can no more speak of contemporary medicine as being in the ACTH and cortisone era than we could put upon it the imprint of thyroxin, insulin, or the sex hormones. All these substances proved to

be of great therapeutic value and their practical utility is certainly not exceeded by that of ACTH or cortisone.

The real significance of it all.

What then is the real significance of all this work on stress and the adaptive hormones? Why is it that an ever increasing number of investigators is engaged in assessing the implications of these new concepts in every specialty of medicine?

In order to give my own answer to these questions, I have to go back to the very beginning of this lecture course. You remember what I said about my early student days when I was so deeply impressed by the "syndrome of just being sick"? It seemed to me, at that time, that a systematic inquiry into the mechanism of this syndrome might teach us how the body defends itself against "just being sick" and that, having learned more about this, we might be in a position *to improve upon Nature's own defense against injury as such,* no matter how produced.

Even today — after more than a quarter of a century — to me the most important outcome of relevant research is that this dream is now beginning to come true, although so far only to a very modest extent, because the practical applicability of treatment with adaptive hormones, the conditioning of stress-responses with dietary means or any other procedure based upon a better understanding of the G-A-S, are still very limited.

Yet, we have made some progress!

Now we know, by actual observation — not only intuitively — that Nature's defensive responses during stress are not always optimal and that they really can be improved, for instance by certain hormone preparations.

We have also acquired irrefutable evidence to prove that, in addition to their specific actions, all potential pathogens and all drugs exert some stressor effects.

Specific causal therapy.

Ever since Pasteur, medical thought was dominated by the conviction that each specific disease has its specific cause. This belief brought as its corollary the view which we have learned in medical school and subsequently taught to our students, that in order to treat any disease effectively, we must diagnose its specific cause and eliminate this by specific treatment. If the causative pathogen is a micro-organism, this should be killed by some anti-microbial agent; if it is a beginning cancer, it must be excised or destroyed by rays to make certain that it will not spread through the body and kill. This is what we call "causal therapy."

Specific symptomatic therapy.

Of course, we also admitted the utility of specific symptomatic therapy. For example, a patient suffering from an intractable headache will benefit from aspirin, even if we fail to determine just what caused the headache. Here, as in all instances where a diagnosis of the specific pathogen is impossible or where means for its elimination are unavailable, we must be satisfied by therapeutic agents which will at least free the patient from some of his most troublesome specific disease manifestations. This is what we call "symptomatic therapy."

Non-specific therapy.

The "stress-therapy" we advocate is neither "causal" nor "symptomatic" in this sense. Yet, up to now, classic medicine did not recognize as reliable any other approach to the treatment of disease. Of course, since time immemorial, efforts have been made to cure by "non-specific therapy". Even if we could not make a diagnosis or prescribe any useful specific causal or

symptomatic treatment, we found it advisable to recommend that the patient be protected against the usual stresses and strains of daily life, should take a long holiday and perhaps even a rest in bed, should receive a nutritious and readily digestible diet, and so forth. Some physicians would recommend climatologic or balneologic therapy or procedures such as the parenteral administration of foreign proteins, milk, blood, heavy metals, etc. However, this non-specific type of treatment was hardly mentioned in the classic textbooks of medicine. It was too unreliable and, since we knew practically nothing about the possible mechanism of its action, it did not lend itself to scientific analysis.

In retrospect, it seems that all these "non-specific therapeutic procedures" are actually the closest approximations to "stress-therapy" that medicine has been able to make on a purely empirical basis.

Research guided by the G-A-S concept.

Using the concept of the G-A-S as our guide, we can now translate much of this into truly scientific terms, separating what is real and valuable from what is mere superstition. The whole of medicine and pharmacology will now have to be re-examined in order to delimit specific from non-specific effects, both in disease and in treatment, since, up to now, the "typical" manifestations of every disease and of every drug-effect were always seen as they appeared through the mask of the accompanying non-specific manifestations. You know how intensely a simple treatment with ACTH or cortisone can "mask" the manifestations of a disease by eliminating such typical signs as fever, inflammation, etc. You know also that all major diseases cause a considerable increase in the endogenous production of ACTH, corticoids, as well as innumer-

able other manifestations of non-specific stress. These changes necessarily clouded our picture of disease and of drug-actions up to the present time.

With the help of the adaptation syndrome concept, however, we are now in a position to identify the various components of the non-specific stress-response. By separating these from the specific actions, we can see both facets of disease and treatment — the specific and the non-specific — much more clearly than ever before.

Summary.

Thus, to my mind, the most important contribution of research on stress is that it has furnished an objective, scientific basis for the development of a new approach to the treatment of disease.

This is neither specific causal nor specific symptomatic therapy, but a treatment based upon the imitation and perfection of Nature's own auto-pharmacologic responses. These defensive reactions have become exquisitely adapted to our needs, through countless centuries of evolution so that we may meet all the usual assaults against health and life to which man is commonly exposed. A therapy which thus attempts to co-operate intelligently with the natural healing powers of the body could not fail to inspire confidence.

Of the many facts concerning stress and the adaptation syndrome which have come to light by now, only a small fraction was contributed by my associates or myself. However, this fraction was based upon the theoretic implications of the adaptation syndrome in our effort to consolidate our knowledge of its principal tenets. That is why these lectures could be built up almost exclusively around this small segment of available relevant data.

As I told you so often during these past days, many investigators still disagree with some of our concepts. The latter helped by leading us to new facts, but they can still not be considered as generally accepted pillars of classic medicine. In most branches of science, whenever a complex problem arises that has not yet been fully solved, there are several schools of thought which advocate different possibilities of interpretation. Hence we can compare divergent points of view and select what we think is best.

Unfortunately, this is impossible in the field of stress and the adaptation syndrome. Some investigators agree with my concepts and use them as a guide to their research; others disagree with certain or even all of their aspects. But, curiously, in this field, complex as it may be (or perhaps precisely because of its complexity?), no other correlative theories have yet been formulated. In other words, here the choice is not between one school of thought and another, but between the adaptation syndrome concept and empiricism without a concept.

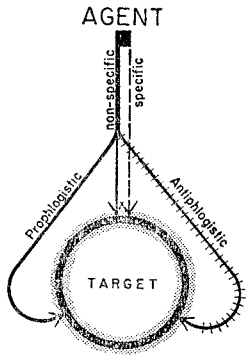
I venture to say that, today, few if any serious investigators doubt that, to take a list at random, stress, ACTH, periarteritis nodosa, allergies, inflammation, hyaluronidase, the adaptation syndrome and rheumatoid arthritis, have enough in common to make it desirable to correlate them somehow; yet no system other than the G-A-S has been proposed for this. It would certainly be most stimulating for all of us in this field, if alternative explanations were forthcoming.

I myself can think of no better way of systematizing our knowledge of stress than through the concept of the adaptation syndrome. I have handled this concept very flexibly, making the theory grow into the

mold furnished by the very facts which it unearthed. Thus it went through a number of stages between 1936 and 1952, as illustrated in my successive synoptic drawings.

In concluding this lecture series, let me express the hope that the last drawing, that of 1952, will soon be outdated by important new facts which you and I may be able to bring forth, now that our ideas have been crystallized to this extent. For our efforts — yours, of listening to me, and mine, of preparing these lectures — will have been worthwhile only if in the Story of the Adaptation Syndrome this does not prove to be

THE END.



Printed by
THÉRIEN FRÈRES LIMITÉE
Montreal, Canada