

HANS SELYE, M.D.

IN VIVO

THE CASE FOR SUPRAMOLECULAR BIOLOGY



IN VIVO

The Case for Supramolecular Biology

Presented in six informal, illustrated lectures

By HANS SELYE, M.D.

Professor and Director of

The Institute for Experimental Medicine and Surgery,

University of Montreal

With a Foreword by Albert Szent-Gyorgyi, M.D., Prix
Nobel 1937

* * *

In this age of molecular biology, IN VIVO pleads the case for "supramolecular biology", the large-scale correlation of the manifestations of living matter in health and disease. As Dr. Selye says: "Throughout my life, I have been guided by a *precept* which is now inscribed over the entrance of our Institute:

'Neither the prestige of your subject and the power of your instruments, nor the extent of your learnedness and the precision of your planning can substitute for the originality of your approach and the keenness of your observation.'

Says Nobel Laureate Albert Szent-Gyorgyi in his Foreword: Anybody who goes into research is urgently advised to read through these pages to find his poise amidst the complexity of problems, guard the freshness of his mind. Dr. Selye speaks in many languages but the most important one he knows is the *language of life*, and it is in this language that he teaches us the pleasure and excitement of being out in the unknown with no footsteps to guide us.

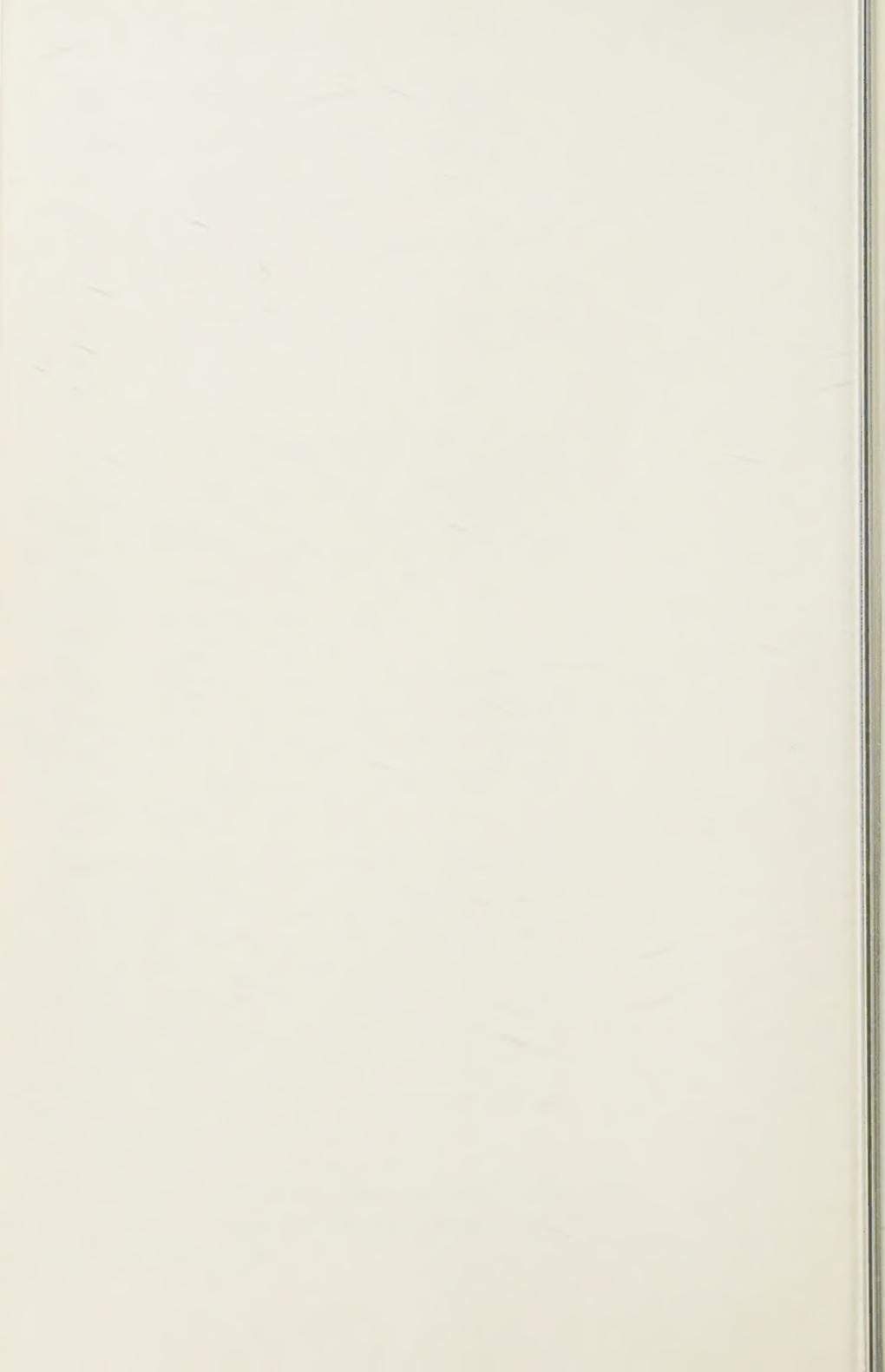
IN VIVO is very accessible to the educated reader and carries a special message for young people contemplating a research career.

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IN VIVO

"In studying life, you keep diving from higher levels to lower ones until somewhere along the way life fades out, leaving you empty-handed. Molecules and electrons have no life." [Albert Szent-Györgyi: Internat. Sci. Techn. June 1966.]

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presented in Six Informal, Illustrated Lectures

by

HANS SELYE

M.D., Ph.D., D.Sc., F.R.S.(C), F.I.C.S. (hon.)

Professor and Director of the
Institute of Experimental Medicine and Surgery,
University of Montreal.

with a Foreword by

ALBERT SZENT-GYÖRGYI, M.D., Ph.D.

Nobel Prize Laureate



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Dedicated to *Humberto Fernández-Morán*
as a token of my great admiration for
his work on the finest particles of life.

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[In order to bring this lecture series within reach of readers who have had no medical training, this glossary gives at least brief dictionary definitions even of common biologic terms. A more detailed discussion, especially of novel concepts, will be found in the text at the pages indicated in parentheses.]

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Foreword

When I was a medical student there was no Bohr Atom, no orbitals, no quant, no nucleus, no electrons, no electron microscope, and no X-ray crystallography. We only knew that there were about twenty amino acids and a similar number of sugars, and could classify, roughly, the main ingredients of a cell. Then, these were wonderful achievements. Judged from our present outlook, then, we knew practically nothing. All the same, we felt obliged to explain life and he who said that our knowledge was insufficient to understand it was called a vitalist or mysticist. Now we know much more, and again try to explain life, "molecular biology" being the password, but we do not know, as we did not know in my student days, how many more sciences wait still to be discovered, and again we call him a mysticist or vitalist who ventures to say that our present knowledge may still be insufficient to understand life, and molecular biology may not be the last word.

I do not mean to say that the achievements of molecular biology do not deserve all admiration. We have to know and find out all we can about the molecules, quants and electrons to approach an understanding of life, but we must not forget that the molecular level is but one of the many levels on

the gamut of organization and what we call "life" is an integral of *all* functions and *all* reactions. No judge will acquit me for my saying that by shooting through a fellow's head I damaged only a small part of that man, whose heart went on beating, muscles twitching and hair growing for awhile, for life is linked to the entity. This integrated level of the whole is the most complex and also the most difficult field of research. It is this level which also has all the charm and whimsicalness of life. To approach it we must be in most direct personal contact with it, and not only observe it by watching pointers of involved hardware. I would go even further and say that in order to understand the living system one must love it, and to reach a deeper intuitive understanding we must use all our senses, including two outdated instruments: eyes and brains. I should almost say that to grasp life one must be something of a poet.

Life has its special charm, but this charm is more and more fading out of biology. We frighten our youngsters of taking the chances of being wrong, and teach them to think, not in terms of problems but in terms of results and papers.

It is a great pleasure for me to be allowed to write these lines for a book of Dr. H. Selye, who, from the beginning, saw life as an entity with all its charm, and who approached it with the intuitive grasp of a poet and showed that this approach can be most fruitful, not only for our understanding but even for our ability to cure disease. He even showed how intelligent mistakes, eventually, can lead us to a deeper understanding. With his present book he does an invaluable

FOREWORD

service to science, giving a profound analysis of the mental process of discovery and development. Anybody who goes into research is urgently advised to read through these pages to find his poise amidst the complexity of problems, guard the freshness of his mind.

Dr. Selye speaks many languages but the most important one he knows is the language of life, and it is in this language that he teaches us the pleasure and excitement of being out in the unknown with no footprints to guide us.

Albert Szent-Györgyi, M.D., Ph.D.

April 1967

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Preface

Today, molecular biology is "*the* thing." Let me admit from the start that I am deeply impressed by its intricacies. Who could fail to stand in awe before such astounding successes of the human brain as the elucidation of RNA, DNA, ATP, ADP and all the other complex biochemical entities of life that have now become so commonplace as to require acronyms to save time in daily laboratory conversation.

This line of research needs no protagonist. If I have come here to plead the cause of old-fashioned supramolecular biology,* it is only because almost no one else is willing to do it anymore and I would hate to see the art become obsolete. As I look around me, I see virtually no more simple, general practitioners of medical research. Even the few who have survived tend to camouflage their true allegiance by "pseudo-molecular" lingo (instead of heredity, they say genome, instead of calcification, calcium-hydroxyl-apatite nucleation) for fear that seen through modern eyes, they may look obsolete.

And yet, it seems to me that no matter how much we shall learn about the most intimate mechanisms of biologic phe-

* The term "Supramolecular Biology" was suggested to me by Professor Paul Weiss of Rockefeller University who coined the term "Molecular Biology" in 1951 when he reorganized the scheme of Biological Sciences as Chairman of the Division of Biology and Agriculture of the U.S. National Research Council.

nomena, we will always need the old-fashioned holistic approach; for an over-all view, we will continue to depend upon the broad-scale correlation of simple observations in which the chips are handled as units although we know that, in fact, they are intricately-structured complexes. Indeed, the closer we come to breaking down the chips into subunits of subunits, the more the bruised bits become artefacts—mere ashes of life.

The principal object of the present volume is to document this point of view. It is based in part on some of my earlier books * but mostly on notes and tape recordings of lectures given to diverse groups of physicians and medical students in Canada, the U.S.A. and Europe. I hope my readers will forgive the unusual informality of the style but the transcripts were only slightly edited in order to preserve the spontaneity inspired by direct contact with an audience. A glossary (p. 152) has been provided to bring the text within the reach of readers unfamiliar with certain technical terms used in medical research.

I wish to take this opportunity to express my heartfelt thanks to Mrs. Y. Côté, Miss L. Traeger and Mr. J. Douglas who helped me with the arduous task of collecting and editing my sometimes rather cryptic lecture notes and transcripts. I also wish to thank Mr. K. Nielsen and Mr. J. A. Blascheck for preparing the illustrations.

* SELYE, H.: *The Story of the Adaptation Syndrome*. Montreal: Acta Inc., Med. Publ., 1952.

SELYE, H.: *The Stress of Life*. New York: McGraw-Hill, 1956.

SELYE, H.: *From Dream to Discovery*. New York: McGraw-Hill, 1964.

Introduction

An extremely intelligent but non-human messenger found his way from Mars to Paris. His name is MARTIUS DNA-RNA. What interests him most is life as we know it on earth and he soon realizes that there is a lot of it in the city around him. He cannot communicate with the people, nor can his transparent, amorphous self be perceived by others; but, blowing through the streets, Dna-Rna is fascinated by the pulsating life of the French capital. Yet, his eager analytical mind asks for more "understanding" so he begins to probe for detail.

He diffuses into the Folies Bergères, Maxim's, up the Eiffel Tower and down into the subway cars of the Métro; he investigates private homes, schools, and the booksellers' stalls along the Seine. With his extraordinary intellectual capacities, he is quick to perceive that all there is around him here consists of a limited number of elements, in turn composed of still smaller elementary particles (neutrons, electrons, and the like) quite similar to those in outer space—indeed, quite similar to those constituting himself. He becomes confused. Just what makes life on this earth so characteristic and fascinating? Suddenly, it dawns on him and he inclaims (Dna-Rna has no mechanism for exclaiming): "Communication!"

Now he begins to investigate interpersonal relationships and immediately he discovers the telephone. This finding he regards as a turning-point in his research, a subject worthy of being explored in great depth. Of course, a telephone is not inside living beings, yet, it is obviously a characteristic manifestation of life in Paris.

Dna-Rna begins to collect facts for a systematic investigation. He notices that when people talk into one of these little black objects on their desks, they can communicate with others at a distance. He discovers that the talking machines are connected by wires to a central exchange and gradually he disentangles the system of interconnections. However, being analytically-minded, he feels impelled to dig deeper in search for elementary components. After studying the electricity and the switch system of the exchange, he progresses to an analysis of what seems to be the unit end organ, the little black gadget on the desk. Yet, he finds that this is still composed of innumerable parts, each of which consists of several among the well-known chemical elements which in turn have the same atomic structure as they have anywhere else. There is nothing characteristic of the telephone in them—certainly nothing typical of life.

Dna-Rna is very disappointed, but being endowed with superhuman intelligence, he now realizes that life as it occurs on earth, disappears as we progress from the living whole to the inanimate constituent. Life just isn't the sum of its parts. The life of Paris is in its streets, public buildings and private homes: the life of Parisians in their whole bodies,

INTRODUCTION

the life of a cell in its undissected matter. The more you take these living things apart, the further you get from biology and finally there remain only the majestic, eternal, and all-embracing physical laws of inanimate matter.

First Lecture

Instinct vs. Intellect in Research. "Problem Finders" and "Problem Solvers." Triumphs of Eminent Problem Finders: Mendel's Laws. Penicillin.

MR. CHAIRMAN, LADIES AND GENTLEMEN:

Instinct vs. Intellect

It was not easy to find a proper title for what I want to discuss here; "Instinct vs. Intellect in Research" would have been better, but I was afraid to scare away my audience. Today the use of the word "instinct" in connection with research is taboo; it smacks of sheer guesswork which, by definition, is not research. But now that I have you here, a captive audience in this crowded hall (whence it is not easy to escape without causing a disturbance) let me admit frankly that it is precisely this supercilious attitude towards instinctive research that I propose to deplore. I hope to show you that even in modern medicine the simple approach of the general biologist, the naturalist or clinician is not yet and will never become obsolete. His exploration of life is still aided much more by keen observation and an instinctive feeling for Nature than by complex instruments

and elaborate planning. Forty years in the laboratory and a critical analysis of research psychology, have unshakably convinced me of this. I shall therefore try to plead my cause by many examples, some grandiose taken from medical history, others modest but self-experienced.

I realize that my task will not be easy. Nowadays, instruments of such complexity as the computer, the electron microscope, or the mass-spectrometer are the fashion in biology, and planned research is held in the highest esteem. Today, the rank beginner can get no fellowship and the seasoned scientist no institutional grant to support his research without submitting a detailed outline of what he intends to discover during the years to come. But let me point out emphatically at the outset that I am opposed neither to the use of complex instruments nor to meticulous planning. These are indispensable for the development and exploitation of a discovery; yet, there must first be a discovery and, if a finding is entirely new, it cannot be planned, nor can we predict what instruments will be most suitable for its exploitation. We can plan to study the adrenal glands or the mechanism of anaphylaxis and list the methods and instruments to be used, but our predecessors could not have planned to find that the adrenals exist or that there is such a phenomenon as anaphylaxis. It is impossible to work out something by logic before suspecting its very existence on the basis of some earlier observations.

The first step in research, the discovery of a problem, will always have to depend on subconscious intuitive feelings

which suggest that among the thousands of things we see, one or the other holds the key to something great and entirely new. A guess if you wish, a guess unwittingly guided by all that we have experienced before, but still nothing but a guess, not a planned process controlled by logic.

It is odd that in science, the most intellectual activity of man, the first and most decisive step should depend upon vague hunches. Yet, that is how it is, we might as well admit it. Man is so proud of being bright that he named himself *homo sapiens*; and yet a dog's nose can often find a murderer where all the intellect of the best criminologists fails. Some of the most impressive original creations of mankind have been in the arts. Yet, few artists would feel ashamed for having to rely more on feeling than on intellect. Why should we scientists be so reluctant to admit that the same is true of scientific creativity?

Who is the Fairest in the Land?

Now, having said this, let us be sure not to put any mistaken value judgments on the relative importance of discovery and development in our sense of these words, that is of problem finding and problem solving. What good would it be to know that the adrenals exist, if this discovery had not been followed by carefully planned investigations on the structure and function of these glands or the isolation and synthesis of the useful hormones that can be obtained from them? This second stage of research has required much more intellect and a much more complicated methodology

than was needed by Bartolommeo Eustachio to find the glands in the first place. But surely we need not justify the most impressive achievements of modern analytical research in molecular biology.

Far be it from me to overrate discovery in comparison with development as regards either the intellectual satisfaction or the practical advantages that can be expected from them. Besides they are wholly interdependent. All I want to say is that the qualifications needed for discovery and development are not the same, and that the modern fashion at our universities of directing all the most gifted students in the life sciences toward molecular biology is not justified.

“Problem Finders” and “Problem Solvers”

Now that we have fairly well defined what we mean by discovery and development, let us agree on some terms to designate the type of scientists who practise these arts.

The first depend mostly on instinctive feeling for the ways of Nature, a keen sense for importance behind observations and for correlations on a broad scale; let us call them the “Problem Finders.” They are essentially phenomenologists or “gestalt biologists” interested in new configurational wholes rather than in structural detail.

The second are the “Problem Solvers.” They start with something already known and try to take it apart to understand its composition and mechanism. Hence, they must lean heavily upon the use of logical analysis and the methodology of chemistry and physics; these are really exact scientists be-

cause, in essence, they merely apply the results of the exact sciences to biology. I was tempted to call them the "exact biologists" but, of course, this would be wrong because biology is not an exact science. It is very instructive to apply chemistry, physics, and sometimes perhaps even mathematics to biology, but the more you dissect living matter into its constituents, the further away you get from life. The chemist who synthesizes a hormone, the physicist who elucidates the crystal structure of bone minerals, supply data important to biology. Yet, they are not biologists, no more so than the gunsmith is a soldier, or the telescope designer an astronomer.

The old-fashioned naturalists were ecologists; they took the individual as the ultimate unit which they did not attempt to break down and analyze further. They studied only his external relations with other living beings and with inanimate nature. The modern naturalist, the phenomenologist, in the sense in which I am using the term here, is still a kind of ecologist, but he studies the relationship of entire organized living systems within the individual. If he is to scan a broad field in search of new problems, unexpected correlations between distant parts of the body, he cannot be encumbered by the loss of time and the many artifacts and fallacies inherent in all the complex instruments and rationalizations that tend to separate the more sophisticated exact scientist from Mother Nature. Most of all, he cannot afford to limit the breadth of his horizon by zeroing in too sharply on any one target.

You will say there is no reason why the analyst, the prob-

lem-solving kind of exact scientist, could not also make a discovery just because he is looking at one particular aspect of life, a minute structural detail or a single biologic process. Of course he could; but the more sharply we focus on detail the more we reduce the likelihood of unexpected discoveries by the "peripheral vision" of things that turn up accidentally where we are not looking for them. It would hardly have been possible to discover anaphylaxis, yellow fever or the phenomenon of homograft rejection by the use of the electron microscope or of cell chemistry.

It may also be objected that there is no point in encouraging neophytes to become Problem Finders instead of following formal courses and learning sophisticated techniques useful for problem solving, because intuitiveness cannot be taught. This is true, but only up to a point. The blind cannot be taught to paint, nor the deaf to play music; but in science as in the arts, innate talent can be suppressed by excessive obligatory course work and routine technologic training—just as much as it can be developed by personal apprenticeship under experts in action whose style is worth emulating. Besides, the Problem Finder's career is not for the masses in any case since the gift for it is rare and each new discovery occupies countless Problem Solvers for many years. Few have talent for problem finding, but few are needed, and these few are badly needed. I do feel, therefore, that we should make every effort to maintain the naturalist's tradition by raising a few of them, say one percent, among all those who plan to specialize in biologic research. These few will do much for

their colleagues by opening up new fields, by finding new problems that can be solved through the application of the exact sciences.

Triumphs of Problem Finders

Let us now see whether careful planning and sophisticated technology have been important during the most decisive stage, the birth of great biologic discoveries.

Mendel's Laws

About a century ago, the Austrian monk, Gregor Johann Mendel, amused himself in the garden of his monastery by cross-breeding several varieties of peas. In each cross between plants differing in color, size or other features, he found that only one of the alternative characteristics (he called them dominant characters) appeared in the hybrid, but when the latter produced a single generation by self-fertilization, both grand-parental types always reappeared in the same constant proportion, about $\frac{3}{4}$ with the dominant character, $\frac{1}{4}$ with the recessive. By testing the second generation hybrids he found that in any given character under observation, $\frac{3}{4}$ of them resembled one of the pure parent varieties from which it was derived, $\frac{1}{4}$ resembled the other pure variety, while $\frac{1}{2}$ resembled the first generation hybrid both in appearance and in breeding behavior. Mendel concluded that "it is now clear that the hybrids form seeds, having *one or the other* of the two differentiating characters." The essential point here was the demonstration that visible alternative characteristics appear

in constant varieties and in their descendants, due to the occurrence of paired elementary units of heredity which are now known as genes.

These simple findings served as a basis for modern genetics. They represent one of the most important discoveries in the life sciences, and yet Mendel's momentous publication was completely ignored by his contemporaries. It is characteristic of discoveries of totally unexpected new phenomena that contemporary "classical science" is unprepared to appreciate their importance and applicability. It was not until thirty years later that several other investigators obtained similar results. Then, in searching the literature they found that both the observations and their correct interpretation had been published by an amateur who used only the technology of a vegetable-gardener and obviously could not have planned beforehand to find that heredity is transmitted in units by genes.

By contrast, the development and exploitation of Mendel's ideas took not only a great deal of careful planning but also all the complicated methodology required for the study of the ultrastructure and chemical composition of genes. Countless highly specialized scholars armed with powerful instruments have gone to work on the problem discovered by Mendel. The progress they made is truly impressive. Yet, the identification of each link in the complex chain of events governing the transmission of hereditary characteristics revealed the existence of yet another preceding link. Man's brain cannot penetrate to ultimate causes—the problem of the genes will never be completely solved.

Penicillin

One of the most important milestones in the history of medical research, an observation which probably saved more lives than any other, was the discovery of antibiotics. It has been described as a "triumph of accident and shrewd observation." Among these compounds, penicillin was the first which could be put to practical use. Here is the history of its birth:

While the English bacteriologist, Sir Alexander Fleming, was engaged in research on influenza, a mould had accidentally developed on a staphylococcus culture plate and created a bacteria-free circle around itself. Fleming immediately concluded that some principle (he called it penicillin) produced by the mould kills bacteria; this substance, he thought, might be used to combat infections.

You may say that anyone faced with the same fact would have come to the same conclusion, but history shows that this is just not so. Actually, the same observation had been made with different moulds and bacteria many times before, yet no one thought seriously of making use of it. At first sight, a mould appears to be such a dirty thing that it seems unbelievable that anyone would want to put it on a wound or inject it into a sick person. Moulds usually grow on spoiled food, and we have become so accustomed to considering them damaging that only a highly creative, original mind, one that can completely free itself from established patterns of thought, could have made such a discovery. All the earlier

bacteriologists who had seen that cultures of microbes are spoiled when exposed to moulds, merely concluded that moulds must be kept out of such cultures. It took a stroke of genius to see the promise of this basic observation.

"Peripheral Vision"

Fleming could hardly have planned his discovery; there was no precedent to justify the assumption that moulds elaborate useful antibacterial drugs. What distinguished Fleming from his predecessors was precisely that he alone had the "peripheral vision" necessary to see what he had not planned and hence could not look for. He certainly required no sophisticated technology or complicated machinery to aid his powers of observation. In fact, were it not for my great respect for the "Father of Antibiotics", I would be tempted to say that his technique was rather sloppy. Surely no self-respecting bacteriologist should allow moulds to get into his cultures!

As in the case of Mendel's publication, Fleming's lead was not picked up by others until much later when Florey and Chain fully demonstrated its practical value. Indeed, it may be asked whether even Fleming himself fully appreciated all the potentialities of what he had found, since he abandoned this field for many years in favor of less important investigations.

The discovery of the problems posed by penicillin subsequently occupied many highly specialized scholars who used sophisticated techniques. Thanks to them, we can now extract and even synthesize penicillin and many related sub-

stances. Yet, each time we learn something about the mechanism of antibiotic actions, we hit upon new unknowns—the problem of antibiotics as that of genes, will never be completely solved.

Countless similar examples could be cited: The Sanarelli-Shwartzman Phenomenon, the Arthus Phenomenon, Cushing's Disease, conditioned reflexes, indeed most biologic phenomena and diseases have been found by simple observation. They could never have been discovered through the electron microscope or any of the complex methods of molecular biology, yet they were indispensable to supply the Problem Solvers with fundamental questions worth exploring in depth.

Today, I have tried to illustrate my point by truly great historic examples, and it is not without trepidation that I contemplate the task of turning to my own investigations right after these. So let us pause here, at least for a day, to avoid embarrassing comparisons.

Second Lecture

My Own Ventures: Stress and the General Adaptation Syndrome (G.A.S.). The three stages of the G.A.S. Mechanism of Reaction to Stress.

In my first lecture, I tried to define the difference between phenomenologists, or if you wish "gestalt biologists", who are primarily interested in configurational wholes, and the analytical biologists whose main preoccupation is with structural and chemical detail. The former are more likely to find new problems, the latter to solve them. We saw that the work of both types of scientists is equally important, but the Problem Finder must lean more heavily upon intuition and the gift of seeing the unpredictable, whereas the Problem Solver depends primarily upon logical planning, powerful instruments and a sophisticated methodology. It is in the nature of things, therefore, that the Problem Finder is in a better position to discover something utterly new, while the analytical Problem Solver is better equipped to clarify mechanisms and to come closer to the ultimate causes of phenomena.

My Own Ventures

Last time, I tried to illustrate the work of the Problem Finder by describing the discoveries of some of our most illustrious predecessors. To document my views on the ways of these intuitive biologists, I could cite many additional great landmarks in the history of the life sciences, but instead I would like to tell you a little about my own work, though its results are not nearly as impressive. For this choice, I have several excuses:

First, I can discuss only my own findings from firsthand observation without having to worry about all the distortions that tend to creep into stories reconstructed from the writings of others.

Second, to make my account instructive, I shall have to be quite frank about the limited credit the "Problem Finder" deserves for ultimate success. This can best be done, without giving offense, when the work is your own.

Third, I know from discussions with colleagues and students that one of the most common criticisms of the old-fashioned naturalist's ways is the feeling that most biologic phenomena that can be discovered by our unaided sense organs, without planning, have been described long ago. I cannot agree with this defeatist attitude; it is contradicted every day by experience. On the contrary, I think we have only begun.

Stress and the G.A.S.

I shall speak first of my work on stress and the general adaptation syndrome because all I did before was a preface, and all I did later, a postscript to this central topic of my scientific life.

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: "nonspecific stress", "corticoids", "general adaptation syndrome", diseases of adaptation"—or even "Selye", as far as that goes.

The First Glimpse

I am often asked just what made me think of the adaptation syndrome in the first place. In retrospect, after so many years, it is rather difficult to single out precisely the beginning of a long trend of thoughts. Nonspecific reactions have always held a singular fascination for me, perhaps because they were generally neglected (not to say despised) and blocked out of 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,

gastrointestinal disturbances with loss of appetite and loss of weight (also an increased elimination of nitrogen, phosphates and potassium). Less constantly there was fever, an enlarged spleen or liver, proteinuria, an inflamed tonsil, a skin rash, etc. However, our teacher attached very little significance to all this.

Then, he enumerated a few "characteristic" signs which, should they subsequently appear, would help the diagnosis of a specific disease. These, we were told, are the important changes to which we must give all our attention. Until they develop, 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, for they were "nonspecific" and, hence, "of no use" to the physician.

These were my first patients; I could still look at them without being biased by current medical thought. Had I known more, I would never have asked questions because everything was handled "just the way it should be", that is, "just the way every good physician does it". Had I known more, I would certainly have been stopped by the biggest of all blocks to improvement: the certainty of being right. But I did not know what was right and I was puzzled.

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. But, novice that I was, it impressed me much more that so few signs are actually characteristic of any one disease while 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 "nonspecific 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 forty years—the extraordinarily profound impression that this consideration made upon me at the time. I could not understand why, 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 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 nonspecific. They 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.

Nonspecific Derangements of Sexual Cyclicity

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), and convinced him to join me in a study of neuroendocrine correlations during pregnancy.

As an incidental observation, we noted that some of our animals exhibited anomalies of the sexual cycle following treatment with pituitary or placental hormone preparations; they went into what is called a condition of "pseudopregnancy."

It soon became clear, however, that this was in no way a characteristic effect of our preparations; overdosage with desiccated thyroid, various vitamin deficiencies, starvation, adrenalectomy and other damaging procedures all caused such a derangement of the sexual cycle. Thus, it became ob-

vious that the phenomenon is entirely nonspecific and hence, we promptly lost interest in it. Yet, we went so far as to conclude that through some condition of "nonspecific stress", a number of agents may so inhibit the pituitary that insufficient amounts of follicle-stimulating hormone are secreted and the sexual cycle stops.

First Use of the Term "Stress"

This was the first time we used the word "stress" in its present connotation, that is for a state of nonspecific tension in living matter, which manifests itself by tangible morphologic changes in various organs and particularly in endocrine glands under pituitary control. Yet, these findings had largely been overlooked and this is hardly surprising, since we also failed to discover their main implications. They were described in the appendix of a paper entitled "Studies on the physiology of the maternal placenta in the rat",¹ a caption hardly suitable to call attention to this kind of work.

A little later during this same year, I stumbled upon the "stress problem" again in another connection. Quite independently of our histophysiologic placenta studies, my chief, Professor J. B. Collip, directed an active research program concerning the hormones of the placenta, ovaries and pituitary. In this project, it was my task to assay many glandular extracts for their possible sex-hormone effects on ovariectomized or hypophysectomized rats, using histologic changes as

¹ SELYE, H. and McKEOWN, T.: Studies on the physiology of the maternal placenta in the rat. Proc. Roy. Soc., Lond.; B, 119, 1 (1935).

indicators of potency. I was handed this work only because of my earlier training in experimental surgery and morphology.

Hypophysectomy Poses a Problem

Ovariectomy posed no problem, and a few years earlier, Philip Smith had succeeded in hypophysectomizing rats, but his method required extraordinary surgical skill and was far too time-taking and unreliable for routine bioassay purposes. It had taken most of my time in 1932-1933 to develop the greatly simplified technique now generally employed. Once I had it, I wanted to find some use for it in the study of the many problems that can be solved only by experimentation on a large number of hypophysectomized animals.

At that time, it was already known that hypophysectomy causes involution of the adrenal cortex with cessation of growth and that crude pituitary extracts restore the growth rate and the adrenals to normal. However, it was impossible to demonstrate with certainty whether these effects were exerted by the same or by separate hormones of the anterior lobe. Using various pituitary extract fractions prepared by Professor Collip, we could show on my hypophysectomized rats that fractions capable of actively stimulating growth did not exert any appreciable degree of adrenal, 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 (which I named STH) and the adrenocorticotropic

hormone (ACTH) of the anterior pituitary, must be chemically distinct entities.²

Search for a New Hormone

Then, in the course of 1935, certain theoretic considerations led me to suspect that in addition to the estrogens and progesterone, which were already known by then, the ovary might produce hormones having qualitatively different actions. I shall not detain you with a detailed 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 to show that 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.

As it is customary in sex hormone studies, we had to inject both ovariectomized and hypophysectomized rats with the extracts of ovaries and placentas, 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.

The Triad

Much to my satisfaction, such lesions were immediately obvious, even when the most impure extracts were used. In

² COLLIP, J. B., SELYE, H. and THOMPSON, D. L.: Beiträge zur Kenntnis der Physiologie des Gehirnanhanges. Virchows Arch. pathol. Anat., 290, 23 (1933).

ovariectomized rats these preparations caused: (1) a considerable adrenocortical enlargement (with a discharge of the secretory granules from the cortical cells and intense mitotic proliferation), (2) acute involution of the thymicolumphatic apparatus, and (3) bleeding ulcers in the stomach and duodenum. Hypophysectomized rats did not tolerate these extracts well and never responded with adrenocortical stimulation or thymicolumphatic atrophy; yet, many of them developed gastrointestinal ulcers.

This peculiar triad of manifestations (adrenocortical stimulation, thymicolumphatic atrophy and gastrointestinal 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—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 even had a perfect bioassay method which would serve as a basis for its (no doubt imminent) isolation.

Unfortunately, this happiness was not to last long.

It did not worry me much that both ovarian and placental extracts gave positive results (as judged by the above-mentioned indicators); after all, we knew that the placenta also produces ovarian hormones. However, when it became evident, a little later, that extracts of the kidney, skin, spleen or any other organ would produce the same syndrome, I became

puzzled. Was the causative factor some kind of "tissue hormone", a 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 only to a diminution of their potency. By that time almost our whole Department joined in the hunt for the "new hormone", but the crudest preparations (mine) were invariably the most active, the purest (made by the chief) were virtually inert. The extracts made by the others ranged somewhere in between these extremes, their potency being inversely proportional to the academic rank of the chemist who made them. I could not understand the reason for this singular lawful relationship but, whatever the explanation, I was very proud of my talent.

The Great Unhappiness

Then came the day of the great disappointment. I shall never forget that dark, rainy afternoon in the spring of 1936. I was sitting in my small lab, brooding over the ever increasing mass 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 struck me: for all I knew, this entire syndrome could be due merely to the impurity and toxicity of my extracts. If so, all my work meant

nothing. I was not on the track of a new ovarian hormone after all. Indeed, I was not even dealing with any specific "ubiquitous biologic principle", but merely with damage. My extracts were "the best" because they were the most impure and toxic, in other words, because I was the worst chemist in the Department.

At that very moment, my eyes fell on a bottle of formalin which happened to be on the shelf in front of me. Formalin is a particularly damaging substance which precipitates the proteins of cells, thus "fixing" them for histologic study. If my syndrome was really due to tissue damage only, I should be able to reproduce it by injecting rats with this fixative. I immediately proceeded to try this. Within forty-eight hours, when these animals came to autopsy, they showed intense adrenocortical enlargement, thymic lymphatic atrophy and gastrointestinal ulcers. Formalin was more potent than even my best 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 had been published about the "new hormone", so nothing had to be retracted. I tried to tell myself over and over again that such disappointments are inevitable in a scientist's life; occasionally anyone can be led astray; 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 lab meditating about how all this could have been avoided.

Eventually, I decided that, of course, the 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 being 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 antihormones. These were also interesting topics, and in any of these fields, I had the singular advantage of being able to count on the guidance and co-operation of one of the great masters of hormone biochemistry, my chief, Professor Collip. Yet, somehow I could not bring myself to do anything in the lab for several days.

A New Viewpoint

As it turned out, the ensuing period of introverted contemplation pointed the way for all my subsequent scientific efforts. As I continued to brood over my ill-fated experiments, it suddenly occurred to me that one could look at them from an entirely different angle. If there is such a thing as a single nonspecific reaction of the body to damage of any kind, this may be worthy of study for its own sake. Indeed, such a stereotyped "syndrome of response to injury as such" may be

much more important than the isolation of yet another sex hormone.

◆

Flashback to Student Days

As I repeated to myself: "a syndrome of response to injury as such", my early lecture-room impressions of the clinical "syndrome of just being sick" gradually began to emerge out of the dimness of my subconscious, where they were buried for so many years. Could it be that the clinical manifestations in man (the feeling of being ill, the diffuse pains in joints and muscles, the gastrointestinal disturbances with loss of appetite, the loss of body weight, etc.) were in some manner clinical equivalents of the experimental syndrome (adrenocortical stimulation, thymicolumphatic atrophy and gastrointestinal 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 cessation of menstruation 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 nonspecific damage is undoubtedly superimposed upon the specific changes produced by any disease and any drug used to treat disease.

Why, 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 nonspecific response to damage. The latter may even mask specific actions!

...one might combat damage as such

If this were so, it would mean that my first classroom impressions about the onesidedness of medical thinking were quite justified. Evidently, if the "damage syndrome" is superimposed upon the specific manifestations of all diseases and all remedies, a systematic inquiry into its mechanism should furnish us with a solid scientific basis for the treatment of damage as such.

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. The patient is advised to go to bed and to avoid physical and mental exertions; he is given an easily digestible diet and protected against great variations in temperature, humidity and draught. Indeed, for many quite unrelated maladies, certain "nonspecific therapeutic agents" have been prescribed empirically 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, ultra-violet rays, diathermy, blood-letting). Stress may even have a curative value!

Through an objective, truly scientific analysis, we might learn to improve upon the mechanism by which Nature defends herself against injuries of various kinds.

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 the safety of orthodox endocrinology, I was now prepared to spend the rest of my life studying this unknown nonspecific response. I have never had reason to regret this decision.

The Voice of Experience Offers Advice

Probably many of the younger people in the audience, struggling to find their proper medium for research, are facing similar decisions now. It may help them to know that all of us have to overcome considerable mental inhibitions in carrying out our tasks. Nowadays, it is perhaps difficult to appreciate just how absurd my views and plans seemed to most people in 1936, before we had enough facts to substantiate them.

I especially remember the objections of one senior investigator whom I admired very much and whose opinion meant a great deal to me. I knew he was a real friend and always ready to help me. 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 go off on 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 nonspecific damage which must accompany all diseases and all but the mildest medications.

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

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

The "Pharmacology of Dirt"

Of course, he was right. Nobody could have expressed it more poignantly; that is why it hurt so much. I still remember the phrase after some thirty years. But to me, the "pharmacology of dirt"—which meant the response to nonspecific damage as such—seemed the most promising subject in medicine.

Still, as time went by, I often doubted the wisdom of my decision. So few among the recognized, experienced investigators whose judgement I could trust, agreed with my views and, after all, was it not silly and presumptuous for a begin-

ner to contradict them? Perhaps I had just developed a warped point of view, perhaps I was merely wasting my time?

Banting's Pat on the Back

In such moments of doubt, I derived much strength and courage from the fact that one of the most respected Canadian scientists, Sir Frederick Banting, was manifestly interested in my plans right from the beginning. At that time, he was often visiting university laboratories throughout Canada as an advisor to the National Research Council. When in Montreal, he often dropped in quite informally. There was not much space in my somewhat overcrowded little laboratory 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 me to get my first grant (\$500), but more than anything else, 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 encouraging pat on the back.

The Time for Planning

The next point to decide was how to go about studying the new syndrome. At this stage it was suspected, some clues were noted, but it was certainly not yet discovered. The very fact that it created so much opposition showed that it was not yet ready for an analysis in depth by the methods of the

exact sciences—the methods of the Problem Solvers. How could I characterize this syndrome sufficiently to make it acceptable to them? In which part of the body should morphologists look for revealing details in structure? Where should chemists search for defensive substances? Right from the start, a multitude of questions arose:

- (1) To what extent is the syndrome nonspecific?
- (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 proportionate 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 and *vice versa*?
- (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?
- (6) Is this a defense reaction and, if so, could defensive substances (e.g., hormones) produced by the body during stress be used for treatment?

These and many other questions not only presented themselves quite spontaneously, but became immediately amenable to objective scientific analysis. Before the theory of a single “stereotypical response to damage” had taken form, we could not even have asked these questions.

How Nonspecific 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.*

It is at this point that I first became painfully aware of the purely semantic difficulties created by 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 they are so often proposed merely to give a semblance of a new point of view. But now we clearly needed terms for two things: the nonspecific reaction itself and its evocative stimulus.

First Semantic Difficulties

My first paper on stress (which incidentally took up only 74 lines of a single column) came out on the 4th of July (!) 1936 as a Letter to the Editor of the British journal "Nature." It was entitled: "A syndrome produced by diverse nocuous agents."³

By that time, I had temporarily abandoned the term

³ SELYE, H.: A syndrome produced by diverse nocuous agents. Nature, (Lond.), 138, 32 (1936).

"stress" (as employed in the paper on the stress-induced anomalies of the sexual cycle), because there was too much criticism of my use of the word for somatic reactions. I hoped that "nocuous" or "noxious" would be less obnoxious until the concept was better understood. In any event it is no exaggeration to say that, at the time, this epistle attracted little immediate attention and certainly, I would never have thought of it as the guidepost for all the experimental research I was to do during the rest of my life.

The "Alarm Reaction"

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

However, this alarm reaction was evidently not the entire response. Upon continued exposure to any noxious agent capable of eliciting this reaction, a stage of adaptation or resistance ensued. In other words, no organism can be maintained continuously in a state of alarm. If the agent is so drastic that continued exposure becomes incompatible with life, the animal dies during the alarm reaction within the first hours or days. If it can survive, this initial reaction is necessarily followed by the "stage of resistance".

The "Stage of Resistance"

The manifestations of this second phase were quite different from—and in many instances, the exact opposite of—those

which characterized the alarm reaction. For instance, during the alarm reaction, the cells of the adrenal cortex discharged their secretory granules into the blood-stream and thus became depleted of storage material; in the stage of resistance, on the other hand, the cortex became particularly rich in secretory granules. Whereas 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 used, this acquired adaptation was lost again. The animal entered into a third phase, the "stage of exhaustion," whose symptomatology strikingly resembled that of the alarm reaction.^{4, 5}

The "G.A.S."

All these observations suggested that an additional all-embracing name for the entire syndrome was required. Since the response was generalized throughout the body and clearly related to adaptation, we called it the "General Adaptation Syndrome" (G.A.S.), emphasizing its evolution in three stages:

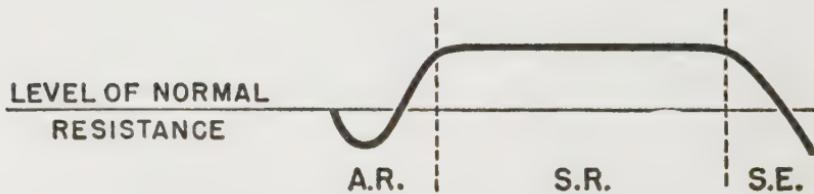
⁴ SELYE, H.: Stress. Montreal: Acta, Inc., Med. Publ., 1950.

⁵ SELYE, H.: The Story of the Adaptation Syndrome. Montreal: Acta, Inc., Med. Publ., 1952.

1. — The alarm reaction
2. — The stage of resistance
3. — The stage of exhaustion.

For example, if an animal is continuously exposed to some stressor (say, cold), the adrenal cortex first discharges all its fat granules which contain the cortical hormones (alarm reaction), then it becomes laden with an unusually large number of fat droplets (stage of resistance) and finally it loses them again (stage of exhaustion). As far as we can see, the same triphasic course is followed by most, if not all, of the manifestations of the G.A.S.

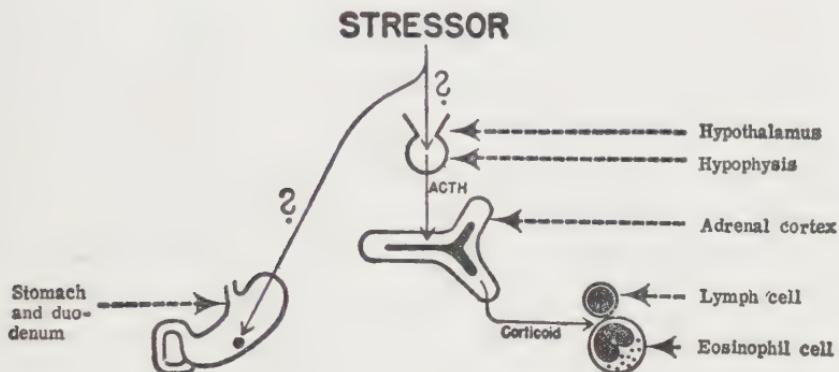
The next figure illustrates this graphically, using general resistance to injury as an indicator.



In the acute phase of the alarm reaction (A.R.), general resistance to the stressor with which the G.A.S. had been elicited, falls below normal. Then, as adaptation is acquired, in the stage of resistance (S.R.), the capacity to resist rises considerably above normal. But eventually, in the stage of exhaustion (S.E.), resistance drops below normal again.

STRESS AND THE ADAPTATION SYNDROME

The following illustration summarizes the state of our knowledge in 1937:



Through some unknown "first mediator", a stressor affecting any part of the body stimulates the pituitary to secrete ACTH which in turn induces the adrenal cortex to secrete corticoids. These cause acute involution of the lymphatic organs (lymph nodes, thymus) and disappearance from the blood of lymphatic and eosinophil cells. This sequence was proven by experiments showing that the chain reaction can be inhibited at the level of the hypophysis or adrenal by removing these glands and can be restored by administering extracts made from them.

Thus, it became clear that many of the most striking effects of stress are mediated through the "pituitary-adrenocortical axis." Later it was shown that the immediate stimulus for ACTH secretion is the production in the adjacent brain region, the hypothalamus, of some "ACTH-releasing factor."

However, the nature of the "first mediator" which presumably stimulates the hypothalamus to release this nerve hormone is still unknown.

The mechanism through which stress produces gastrointestinal ulcers is also poorly understood, but—unlike the other changes mentioned—it is not strictly dependent upon the pituitary-adrenal axis, since it occurs also in animals exposed to stress after removal of their hypophysis or adrenal gland. Nervous stimuli appear to play a prominent role in the production of these "stress ulcers" although a high blood-corticoid level sensitizes for their development.

Only the future will tell us just how much good the adaptation syndrome has done for the understanding of disease, the relief of human suffering 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 fact that the G.A.S. was found by naked-eye inspection, without complex modern instruments and techniques or even the wisdom and experience that would have been necessary to use them.

Don't Miss the Forest for One Tree

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 remember 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 still 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 the latest analytic hardware—and to hire an assistant who knows how to use it.

Third Lecture

The “Diseases of Adaptation.” Corticoids Produce Hyalinosis, a “Collagen Disease.” Corticoid Hypertension. Heart Accidents. Anaphylactoid Inflammation. Hormone Anesthesia. Pseudopregnancy of Lactation. Antihormones. Cystic Transformation of Parathyroids.

I have told the story of the adaptation syndrome in some detail because the problems it posed intrigued me all my life and because it is probably one of my main reasons for pleading the cause of supramolecular biology. But I have others, and although these will have to be dealt with more succinctly, I would like to say at least a few words about them. It could hardly be mere coincidence that most of my subsequent encounters with new phenomena were also quite unplanned and —like the G. A. S.—based on observation by simple inspection.

The “Diseases of Adaptation”

Soon after the description of the stress syndrome, we came to the conclusion that many maladies are really more “diseases of adaptation”, that is derailments of the G.A.S., than the results of the direct damaging actions of pathogens.

In keeping with this hypothesis, we wanted to see what would happen if an animal were given excessive doses of various "adaptive hormones", that is, substances such as adrenocortical hormones which are produced in excess by the body during the G.A.S. We expected changes similar to those characteristic of the alarm reaction since these are associated with increased adrenocortical function. We knew by then that during the alarm reaction, tissues exposed to irritants cannot develop an adequate inflammatory response. Therefore, it was logical to suspect that here, the adaptive hormones might be responsible for the suppression of inflammation.

Corticoids Produce Hyalinosis, a "Collagen Disease"

In 1940, careful plans were laid to test this hypothesis but, much to our surprise, the only cortical hormone then available in adequate amounts, desoxycorticosterone, far from inhibiting inflammation, actually promoted it. Especially in animals receiving dietary supplements of NaCl, it produced what we call "hyalinosis". This syndrome is characterized by a hyalinizing myocarditis (reminiscent of the cardiac inflammation found in rheumatic fever), periarteritis nodosa (an inflammation of the arteries), nephrosclerosis (with inflammatory changes in the kidney) and a considerable increase in the inflammatory response to all kinds of tissue irritation. In essence then, we produced a generalized predisposition for inflammation, not unlike that seen in the "collagen diseases" of man. [Plate II.]

This finding was quite the opposite of what we had expected; that is probably why I overlooked it at first, although it was right there under my nose, ready to be discovered many times over before its significance finally registered. Again and again in desoxycorticosterone-overdosed rats, I saw the characteristic white specks on the heart and kidney, I saw and even palpated the typical nodules of periarteritis nodosa in the mesentery, but mistook them for abscesses due to some kind of incidental infection. I concluded only that our tests were spoiled.

Since desoxycorticosterone was hard to come by at the time, it took us two years to repeat these experiments often enough until finally we just had to assume a causal relationship between treatment and syndrome. Only then did we perform the histologic studies which revealed the almost ubiquitous presence of the hyaline deposits after which the syndrome was named. By then, it required no special acumen to realize that this hyalinosis is essentially different from—and in a way even the opposite of—the changes produced by adrenocortical extracts. The latter, as we had surmised, did in fact prove to inhibit inflammation, just as exposure to stress did.

Need for the Term "Corticoids"

These were the findings which induced me to recommend the term "corticoids" to replace Hartman's "cortin" for what he thought was a single life-maintaining hormone. Now, we had learned to distinguish between two groups: 1. The pro-

inflammatory, or mineralocorticoids such as desoxycorticosterone and the subsequently discovered aldosterone. These facilitate the production of inflammatory changes and act mainly on mineral metabolism. 2. The anti-inflammatory, or glucocorticoids such as those of our crude cortical extracts, and the subsequently discovered cortisone group. These inhibit inflammation and act primarily on sugar metabolism.

Corticoid Hypertension

Since in man, nephrosclerosis is usually associated with hypertension, we measured the blood pressure of our desoxycorticosterone-treated rats and found it greatly augmented. This was the first experimental proof showing that corticoids can produce hypertension with sclerotic changes in the blood vessels. But after all this, we were still far from having shown a relationship between stress and the often fatal heart accident of cardiac infarction. It was not until 1957 that another accidental observation gave us the first hint of it.

Heart Accidents

In the course of experiments designed to clarify the mechanism of hyalinosis, and particularly of hormonally-induced hypertensive nephrosclerosis, we tested several recently synthesized halogenated corticoids. All these "halocorticoids" proved to possess both gluco- and mineralocorticoid activities and to produce hyalinosis when given in combination with various sodium salts, especially NaCl. How-

ever, one group of rats was treated with halocorticoids plus sodium phosphate and they all died before any visible renal change could have developed. On that day, we had very many rats to dissect and—contrary to our custom—we did not examine the other tissues, since we were now looking for nephrosclerosis. As soon as the kidneys were found to be normal, these animals landed in the garbage can; the experiment had obviously failed to show what we wanted to see.

Then I began to wonder just why these rats had died and retrieved them for a more thorough autopsy. This proved to be most rewarding: the hearts of all of them exhibited large whitish patches of necrosis (that is, localized tissue death), quite similar to those seen in patients who die of cardiac infarction. [Plate III.] We now had a simple and reliable test object for the production of cardiac necrosis. This unplanned observation, made by simple inspection, was the starting point for several years of planned research, much of which depended upon complex techniques; yet, to my mind, the decisive factor was to have retrieved those first rats from the garbage can and taken a good look at what we had not at first been looking for. Our test furnished the material for two extensive monographs on the experimental production and prevention of heart diseases by chemical means.^{6, 7} The main results were the following:

1. The appearance of cardiac necrosis is associated with a

⁶ SELYE, H.: *The Chemical Prevention of Cardiac Necroses*. New York: The Ronald Press Co., 1958.

⁷ SELYE, H.: *The Pluricausal Cardiopathies*. Springfield: Charles C Thomas Publ., 1961.

sharp drop in the potassium content of the heart and can be prevented by the oral administration of potassium supplements.

2. In themselves inactive, small doses of halocorticoids (with or without dietary supplements of sodium) so prepare or "condition" the heart that it responds with usually fatal necroses to diverse stressors (e.g., forced muscular exercise, hemorrhage, cold). Thus, chemical agents (corticoids, sodium) can selectively predispose one organ, here the heart, to the damaging action of stress.

3. Animals pretreated with a stressor (e.g., forced muscular exercise) before and during the period of humoral conditioning become resistant to this cardiotoxic action of stress. Hence, subsequent exposure to stressors after conditioning fails to elicit the cardiac necroses which would otherwise occur.

4. This resistance is not due merely to the development of a specific adaptation to the agent used to produce stress, since pretreatment with one agent (e.g., forced muscular exercise) protects the heart against the subsequent application of not only the same agent but also that of unrelated stressors (e.g., trauma). Evidently here, we were dealing with the phenomenon of true "cross-resistance", inurement to one agent causing resistance to another agent. For example, pre-treatment with muscular work offered protection not merely because after a period of training exercise was no longer stressful; the well-trained rat became resistant to stress no matter how produced.

Despite all this work, the fundamental questions concerning the biochemical mechanism through which our agents produce or prevent cardiac necrosis have not been solved. They will probably never be solved to a point where no problems remain. It is evident that we shall get much further by planned experimentation with appropriate techniques, for example those of electron microscopy and analytical chemistry. But even our primitive experiments have taught us much that may be applicable to clinical problems.

Clinical Application

For example, the experimental necroses produced by our techniques are not preceded by thrombotic occlusion of the coronary vessels. This observation suggested that necrosis may be the cause rather than the consequence of coronary thrombosis. Subsequently, it was found by several other investigators that—contrary to earlier views—this is often true in man also. Patients who die immediately after a cardiac accident, frequently have no thrombotic occlusion of their coronary vessels, while those who survive longer almost invariably show evidence of it. Presumably, here, the vascular thrombi develop secondarily in necrotic tissue.

The use of potassium as a prophylactic against coronary infarction in man is still in the experimental stage, but so far the results are very encouraging. If the efficacy of this procedure is confirmed, its practical value will not be diminished by our ignorance of the ultimate underlying mechanism; no

more than the value of penicillin is diminished because we do not understand exactly just how it acts.

You will remember that, depending upon the circumstances, stress can both produce and prevent cardiac necrosis. This finding clarifies the apparently paradoxical but well established observation that in man, physical exercise can also either produce or prevent cardiac infarcts, depending upon the circumstances. Moderate habitual exercise keeps the body fit and protects, while unaccustomed severe exercise can be fatal, especially to individuals "conditioned" by arteriosclerosis, heavy smoking, obesity or heredity.

Anaphylactoid Inflammation

Another phenomenon accidentally discovered by simple inspection is the "anaphylactoid inflammation." In 1937, the year after the first paper on the G.A.S. was published, we were interested in determining the relative stressor action of various compounds injected intraperitoneally. One of these was egg-white.⁸ I cannot remember the scientific reasons for selecting this particular substance, but we were testing hundreds of compounds at the time and I was not particularly choosy. Besides, I do recall that during this busy period, I used to get to the lab very early in the morning and make my breakfast there. To me, ready availability of materials has always been a great inducement for research and every morning, when I opened the ice-box, there were those eggs . . .

⁸ SELYE, H.: Studies on adaptation. *Endocrinology*, 21, 169 (1937).

Anyhow, whatever my reasons may have been, I injected the egg-white intraperitoneally to a few rats and found that within fifteen minutes or so all of them sat up on their hind quarters and started furiously rubbing their noses. The snout region became swollen and blood-shot; they looked for all the world as if they had a severe attack of hay fever. However, their paws and the anogenital region were also swollen and hyperemic; apparently we were dealing with a selective reaction of the peripheral or acral parts reminiscent of the selective growth in these regions seen in the disease known as acromegaly. Histologically, the change proved to result from a hyperacute serous inflammation. The phenomenon resembled the angioneurotic edema or Quincke's disease that tends to develop in predisposed people as a manifestation of allergy to certain foods and other agents. In a way, the reaction also reminded me of anaphylaxis, but evidently, it required no previous sensitization to the eliciting agent, since it seemed quite unlikely that anyone would have injected my rats with egg-white before I put my needle to them. [Plate IV.]

At this point, I recalled the classic observation of "anaphylactoid shock" made by my teacher, Biedl, in collaboration with Professor R. Kraus of Berlin. They found that in guinea pigs, an anaphylaxis-like shock can be provoked by peptone without previous sensitization. Our acral inflammation was essentially different, but since it also resembled allergy and required no earlier sensitization, I called it (in honor of Biedl) the "anaphylactoid inflammatory reaction." For the

sake of brevity, this is now usually contracted to anaphylactoid reaction or anaphylactoid inflammation.

Again the Adrenals and Inflammation

At that time, we were particularly interested in demonstrating the importance of the pituitary-adrenal axis for resistance to various agents; hence, I injected egg-white into adrenalectomized rats. In these, anaphylactoid inflammation proved to be unusually severe and often fatal. Furthermore, severe stress (conducive to marked adrenocortical enlargement) protected the normal but not the adrenalectomized rat against this response.

Of course, in 1937, purified anti-inflammatory corticoids were not yet available, but these were the findings that led us to postulate their existence and to suggest that the adrenal cortex may be an important regulator of inflammation in general. This view received strong support a few years later when—as I have said before—we found that desoxycorticosterone can produce inflammatory changes such as myocarditis and periarteritis nodosa, with an increase in the so-called inflammatory potential (the ability of connective tissue to respond to irritants). However, the very idea that the adrenal cortex should have anything to do with inflammation seemed so outlandish at the time that no one took it seriously until many years later, when the first antiphlogistic corticoid became available for clinical testing and proved to suppress a variety of inflammatory diseases.

The Lessons Taught by Anaphylactoid Inflammation

When first seen, anaphylactoid inflammation had only been produced by egg-white and only in rats. This finding posed a problem but it would have remained a pure laboratory curiosity—as so many other accidental findings—had it not attracted the attention of the Problem Solvers. However, it promised to be a very reproducible and simple test object (although we did not know for what) and hence, many scientists throughout the world began to analyze its mechanism and implications. Since its discovery in 1937, it has been the topic of nearly a thousand publications by physiologists, biochemists and clinicians, many of whom used much more complicated techniques than we usually employ.⁹ This work helped us to learn quite a bit, for example:

1. Anaphylactoid inflammation is associated with, and perhaps even due to, a discharge of mast-cell granules which contain histamine and serotonin. Mast cells, histamine and serotonin are particularly plentiful in the acral regions of the rat where the anaphylactoid inflammation develops, and the reaction can be inhibited by pretreatment with antihistamines and antiserotonin.
2. Egg-white is a mast-cell discharger which liberates histamine, serotonin and granules from the cytoplasm of mast cells.
3. Not only egg-white, but a number of other mast-cell dischargers (e.g., dextran, dextrin, polymyxin, compound

⁹ SELYE, H.: *The Mast Cells*. Washington: Butterworth, 1965.

48/80, stilbamidine) produce a typical anaphylactoid inflammation in the rat.

4. Pretreatment with any of these mast-cell dischargers protects the rat against the production of an anaphylactoid inflammation by subsequent treatment with the same or any other mast-cell discharger. Presumably, the response cannot occur when the cells are already depleted of their active materials.

5. Not only the rat but several other species, including man, can respond to certain agents with a typical anaphylactoid inflammation.

6. In rats sensitized for calciphylaxis or calcergy (to be defined later), mast-cell dischargers produce a calcifying anaphylactoid reaction. This is characterized by a massive calcification of the acral regions which normally respond only with serous inflammation.

7. In rats sensitized for the thrombohemorrhagic phenomenon or "THP" (also to be defined later), treatment with a mast-cell discharger can produce thromboses and hemorrhages in the acral parts. This reaction is reminiscent of allergic purpura as it occurs in man.

8. In animals "conditioned" with egg-white, or similar mast-cell dischargers, resistance against potentially tissue-damaging agents is greatly diminished, and an acute conditioned necrosis (ACN) results. This predisposition to necrosis can be duplicated by certain mast-cell products (histamine, serotonin) and—just as the anaphylactoid inflammation

itself—it can be prevented by pretreatment with mast-cell dischargers, antihistamines and antiserotoninins.

9. Anaphylactoid inflammation proved to be useful for the bioassay of pro- and anti-inflammatory substances.

These are but a few of the most salient facts brought to light by using anaphylactoid inflammation as a test object. They helped us to learn a good deal about the mechanism of the response and its use as a model for the study of various fundamental questions relating to the pathogenesis and therapy of disease. But of course the basic mechanism of anaphylactoid inflammation still remains, and will always remain unsolved.

Hormone Anesthesia

My next finding was not only accidental but I was not even the one who provoked the accident. In 1941, I was working on the effect upon the sex organs of the recently synthesized ovarian hormone, progesterone. For the purpose of this study, I injected rats subcutaneously with this compound daily, anticipating changes in the sex organs. After a few weeks, I handed the work over to a technician who had just joined our lab and, much to my surprise, the next day she reported that all the animals had died. Since I had given the same amount of progesterone for many days before without any trouble, I thought that she must have made some mistake in preparing her solution and merely told her to repeat the experiment more carefully. Next day, the girl came to see me greatly perturbed: despite every precaution, the animals died

after the first injection. I could not imagine what might have gone wrong, so I asked her to inject another group of rats, this time in my presence.

It turned out that, being unacquainted with our techniques, she had injected the hormone intraperitoneally because in her previous job (in a bacteriological lab) this was the customary procedure. I did not think that the route of administration would make much difference, but while I was telling her so, all the rats fell asleep, just as if they had received a strong anesthetic, and eventually they died. Now, this was very odd. Progesterone had never been shown to have any toxic effects and no steroid hormone—indeed no hormone of any kind—had ever produced anesthesia. So I repeated the experiment, using smaller doses of progesterone. The animals again fell asleep, but now they woke up within a couple of hours and were then perfectly all right.¹⁰

Here we were dealing with a true hormonal anesthesia, with sleep induced by a natural product of an endocrine gland. Apparently, this phenomenon had been missed before because, following the usual subcutaneous injection, the absorption of progesterone is too slow to reach anesthetically acting blood levels. However, when the inexperienced technician injected the compound her way, it was rapidly absorbed from the large peritoneal surface. She had simply not noticed anesthesia because after the first injection there was

¹⁰ SELYE, H.: Studies concerning the correlation between anesthetic potency, hormonal activity and chemical structure among steroid compounds. *Anesth. Analg. Curr. Res.*, 21, 42 (1942).

no reason for her to watch the animals until injection time next day, and by then they were already dead. Even if she had examined them soon after injection, it is doubtful whether she would have ascribed their immobility before death to a true anesthesia. After I had described these observations, several experienced authors challenged my interpretation, attributing the immobility of the animals merely to "shock." Yet, now we know that steroid hormones produce anesthesia not only in animals but also in man. Indeed, hydroxydione, a close derivative of progesterone, is in clinical use at present as the anesthetic of choice for certain surgical operations.

Odds and Ends

Among the odds and ends of my research activities, I could cite many more to plead the cause of simple techniques. They were useful even during the problem-solving stage, at least for the decisive initial steps.

What Keeps up Milk Secretion?

It has long been known, for example, that lactation stops if the milk is not removed from the mammary glands. The mother's breast dries up if she loses her baby; so does the udder of a cow if milking is discontinued. Over the years, many theories were put forward to explain this phenomenon, but none could be supported by objective evidence. Some physiologists thought that the pressure of accumulating milk causes atrophy of the breast, while others believed that con-

tinuous nervous stimulation through suckling or milking is indispensable for the maintenance of secretion. Of course, when the young are separated from their mother, both the removal of the milk and the nervous stimulus of suckling stop. Tying off the duct would not help to clarify this problem either, because the young would die of starvation. Theoretically, denervation of the gland would be the perfect test, but technically this is impossible because the nerves of the mammary gland enter through so many pathways that complete denervation is not feasible.

Intrigued by the seemingly enormous technical difficulties, we proceeded as follows: in one group of lactating rats we tied off all the milk ducts, while another group acted as foster mothers. During the day each litter was allowed to be with its own mother, but since the experimental rats gave no milk, we changed the litters each night, the young of the foster mothers being placed with the rats that could give no milk, and vice versa. Thus both litters were sufficiently nourished since they had access to milk twelve hours a day, and the stimulus of nursing was constantly maintained in both groups. Indeed, in the experimental animals, the stimulus was excessive because the baby rats became very hungry and suckled all the more voraciously when they were offered dry nipples.

This simple trick solved our problem perfectly and the results were quite clear: the stimulus of suckling was in itself sufficient to maintain lactation, even when the milk was not removed. As long as the mothers were supplied with vigorous

young, milk secretion continued to a point where the glands actually burst under the pressure and discharged their milk into the surrounding tissue.

The "Suckling Reflex" and Pseudopregnancy

With this same technique we could also show that our "suckling reflex" not only maintains lactation, but also keeps the pituitary and ovary in the functional state necessary for milk secretion. Consequently the sexual cycle is suppressed and in many respects the animals behave as if they were pregnant. This condition is now known as the "pseudopregnancy of lactation." The cessation of menstruation during the initial stages of lactation in women depends upon a similar mechanism.

Subsequently, a much more complex methodology had to be used (by others) to identify the nervous pathways through which the stimulus of nursing is transmitted to the pituitary, which so alters its hormone secretion as to cause the observed milk secretion and the associated interruption of the sexual cycle.

Antihormones

I have played a very secondary role in the discovery of the antihormones by my chief, J. B. Collip, but this too was an observation involving no complex methodology. It was already known when we started, that during chronic treatment with gonadotrophic sex hormones, the gonads (ovaries, testes) are at first greatly stimulated but then undergo

atrophy. Was this due to some kind of exhaustion of the over-stimulated gonadal tissue, or to the production of some "anti-hormone" comparable to classical blood-borne immune bodies?

To clarify this problem, we injected one set of female rats chronically with gonadotrophic hormone until their ovaries became very atrophic. Then we removed samples of their blood and injected it together with gonadotrophic hormone into a new set of rats, while controls were given gonadotrophic hormone in combination with the blood of unpre-treated animals. Fresh recipients given gonadotrophic hormone with the blood of normal rats showed the expected gonadal stimulation; rats given this hormone together with immune blood failed to respond. Obviously, the development of gonadal irresponsiveness following prolonged treatment with gonadotrophic hormone was due to some blood-borne "antihormone." Much more refined methods were subsequently used (by others) to characterize the chemical nature of these antihormones, and indeed, this work has still not been completed.

Parathyroid Cyst Formation

In my fifth lecture I shall report in detail upon the curious phenomenon of calciphylaxis which is obtained, for example, by conjoint treatment with vitamin-D and various metal salts. The salient feature of this reaction being soft-tissue calcification, it seemed logical to assume that among the metal salts those of calcium would be most active. I embarked on experi-

ments to demonstrate this with bored reluctance because I felt that there was not much point in proving the self-evident. However, the "predictable" thing did not happen: curiously, salts of calcium, unlike those of many other metals, did not produce soft-tissue calcification under our conditions. What happened was quite unexpected: the normally solid parathyroid glands of rats treated with vitamin-D plus calcium salts became enormously enlarged through the formation of cystic cavities. Presumably, under these circumstances, the glands continue to produce their secretion but are unable to discharge it normally into the blood.¹¹ [Plate V.]

This finding—like most of the others just mentioned—raised more problems than it answered: Does the fluid that accumulates between the glandular cells actually contain parathyroid hormones? If so, what biochemical mechanisms could permit continued secretion, at the same time blocking discharge into the blood? Are the parathyroid cysts that occasionally occur in man (and that have hitherto been viewed as congenital malformations) related to the experimentally induced cysts which are evidently not malformations?

Pretty good Problem Solvers will be needed to answer these and the many other questions raised by this chance observation. Meanwhile, all we know is that cyst formation can be induced in the parathyroids. Yet, without this information, none of these questions could have been asked.

¹¹ SELYE, H., ROJO ORTEGA, J. M. and TUCHWEBER, B.: Dietary production of parathyroid cysts. *J. Nutr.*, 84, 97 (1964).

DISEASES OF ADAPTATION, ETC.

I have mentioned these minor odds and ends of research only as further illustrations in support of the view that in the most diverse fields of biology accidental findings made with simple techniques must precede research on a molecular level. In my next two lectures I would like to get back to the mainline of investigations on the body's response to stress and show you how these led us to a general hypothesis of disease. With its help we shall try to formulate precise questions, not only in terms of molecular but even of supramolecular biology—still using only the simplest experimental techniques.

Fourth Lecture

Renal Hypertension. The "Endocrine Kidney." The "Granuloma Pouch." Topical Stress and the Local Adaptation Syndrome (L.A.S.). How Could Stress Produce Specific Changes? Pluricausal Local Lesions. Tissue Scaffoldings. Bone Induction in the Heart.

Renal Hypertension

Today, I shall need your concentrated attention for we shall be discussing a very complex problem, that of renal hypertension. In our laboratory, we became particularly interested in this topic following the observation that, in association with the syndrome of hyalinosis, mineralocorticoids produce nephrosclerosis with hypertension. Which comes first, hypertension or nephrosclerosis? Ever since Goldblatt devised his clamp to reduce blood flow through the renal artery, it was known that hypertension can result from a diminution of renal blood pressure. In our desoxycorticosterone-overdosed rats, hypertension was associated with obstructive lesions in the afferent arterioles of the renal glomeruli. These we assumed might act as innumerable micro-“Goldblatt clamps” obstructing the entry of blood into the

renal corpuscles. Could the entire syndrome of hyalinosis—including the myocarditis, the periarteritis nodosa and the increased inflammatory potential—be the consequence of such a primary action upon the kidney?

The hypothesis was attractive because Goldblatt and several others had previously found that in dogs, hypertension produced by the clamp is often accompanied by extrarenal manifestations of vascular damage. Yet, if mineralocorticoids produce generalized blood-vessel lesions as a consequence of a primary action upon the afferent arterioles, how could they act on this particular segment of the vascular tree selectively in the first place?

In order to explore these problems on a large scale, we thought it would be helpful to devise a simple and reliable technique for the production of renal hypertension in the rat, the species in which the original desoxycorticosterone experiments were performed. With this in mind, we went ahead and tried to put clamps on the renal arteries of rats but these vessels are so small that the method proved to be neither simple nor reliable.

The "Endocrine Kidney"

Yet, we badly needed a perfected modification of the arterial clamp technique for another reason also. The rise in blood pressure, induced by compression of the renal artery, was always ascribed to the increased production of some hormonal substance by the kidney. However, the operation also caused a variable, though never complete, disturbance

in urine formation; hence, it was impossible to determine whether the hypertension was due to an increased renal secretion or a decreased urinary elimination of a hypertensive substance.

What we wanted was a technique which would eliminate only one of these two main renal functions. But how could this be accomplished? If you tie the duct, urine secretion ceases, but the whole kidney is eventually destroyed by the pressure of the accumulating fluid. If you tie the artery completely, the kidney also dies, and if you tie it partially, as Goldblatt did, both kidney functions are altered.

How to Obtain a Given Degree of Vessel Constriction

Of course, it would have been helpful if we could have compressed the renal artery exactly to the point where the pressure in the kidney would no longer be sufficient for urine secretion (which largely depends on blood pressure), but would still be adequate for hormone secretion (which would presumably be increased when pressure was diminished). But how could we possibly hope to accomplish all this in rats (suitable for large-scale experimentation) in which the smallness of the renal artery makes even the ordinary Goldblatt operation virtually unfeasible!

While wondering about all this during the dissection of a rat, we happened to notice that, in this species, the two renal arteries originate 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-gauged degree of constrict-

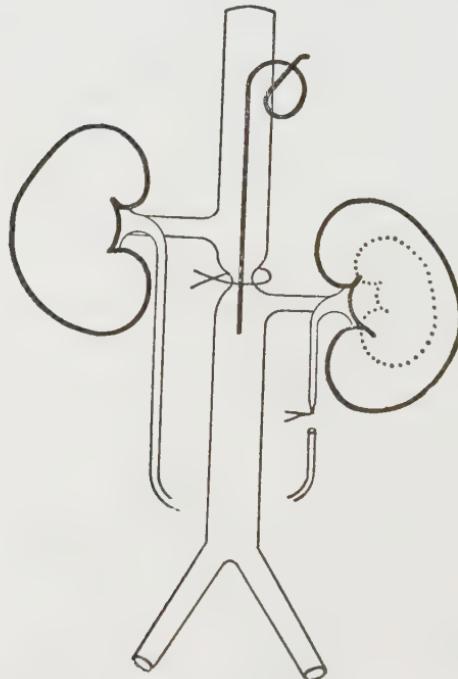
tion. A clamp placed here would diminish the pressure in the left kidney (whose artery originates at a relatively low level), while the right kidney would continue to secrete urine and prevent death from uremia.

We had to find a way to constrict the aorta to the same degree in all cases. In the rat, even this main vessel is rather narrow for such fine manipulations, but the difficulty was circumvented with the aid of a simple piece of wire (the stylet of a hypodermic injection needle). One end of it was curved back so that it could easily be held between two fingers and placed in front of the aorta, parallel to its main axis, between the two renal arteries. Then, a nylon thread (which neither shrinks nor swells) was passed around aorta and wire, embracing both. This firmly tied loop stopped the circulation. Now, we only had to remove the wire to establish a bore accurately corresponding to the caliber of our stylet. Thus, we solved the problem of obtaining an exactly reproducible degree of constriction, but of course, this was not necessarily the desired degree. How could we decrease the pressure in the left kidney just enough to stop urine secretion without damaging the organ? At first, we thought we would have to adjust the aorta ligature in each rat while measuring the pressure in the renal vessels, but this would have been technically quite impossible.

Two Ways to Solve the Problem

Fortunately, a simple trick helped us to circumvent the need for measuring the pressure, while assuring us of obtain-

ing exactly the desired degree of constriction. We argued that, for a rat of any given size, there must exist a caliber of wire corresponding to the bore to which the aorta should be constricted to produce the desired effect. So, the only task remaining was to find a wire thickness suitable for any one rat.



Schematic illustration of "endocrine kidney operation." A loop of thread embraces aorta and curved wire between origins of two renal arteries. Duct of lower kidney is cut. Dotted line shows size to which the organ will shrink as a consequence of endocrine transformation.

This is how we solved our problem: By that time, I had done a good deal of work with the piece of wire used in the initial experiments and had become rather attached to it; so, instead of laboriously trying to find a caliber of wire to suit a given rat, I determined the size of animal which happened to fit my wire.

How to Gauge the Success of the Operation

I reasoned that if I took rats of different weights (ranging between say, 40 and 200 grams) and constricted their aortas 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 be just right. The success of the operation should then be readily detectable if we also sectioned and tied off the duct of the left kidney, the one in the low pressure territory. If the pressure fell exactly to the right level, there should be no accumulation of urine in the tied-off stump of the duct, and the kidney should not become necrotic. If the pressure did not fall sufficiently, there should be urine accumulation and if it fell too much, there should be renal necrosis.

All these assumptions were confirmed by actual observation. The blood pressure rose markedly only in animals with the perfect degree of constriction. In these, hyalinosis with vascular lesions (similar to those produced by mineralocorticoids) developed throughout the organism, including the untouched contralateral right kidney; only the left kidney (in

which the blood pressure had been diminished by our operation) showed no such changes.¹²

Thus, the accidental observation that, in the rat, the renal arteries leave the aorta at different levels, followed by the planned experimentation just described, helped us to solve one problem, namely that a kidney secreting no urine can still induce hypertension and hyalinosis. Since neither unilateral nephrectomy nor renal denervation succeeded in duplicating this effect, it must have been due to a chemical principle of renal origin.

Creation of a "Solid" Kidney

As soon as we arrived at this stage, a new problem presented itself as a consequence of another unexpected observation. The kidney with the restricted blood supply—unlike its contralateral partner—was not only free of nephrosclerosis and vascular changes, but it shrank to a fraction of its original size. Histologic examination showed it to be completely transformed into a solid organ exhibiting the typical structure of an endocrine gland. The fact that it could produce hyalinosis at a distance added functional proof of its endocrine activity. In essence, we had produced a purely “endocrine kidney” by diminishing the renal blood pressure exactly to the critical level which permits (and indeed in-

¹² SELYE, H. and STONE, H.: Pathogenesis of the cardiovascular and renal changes which usually accompany malignant hypertension. *J. Urol. (Baltimore)*, 56, 399 (1946).

creases) hormone secretion without causing degeneration or necrosis of the organ.

These findings raised many problems concerning the relationships between the endocrine and urine-secretory functions of renal tissue; hence, numerous investigators employed the endocrine-kidney operation for the study of the structural and biochemical changes associated with these activities.

The “Granuloma Pouch”

Another by-product of our work on the G.A.S. was the development of the “granuloma pouch” technique. In our studies on the effect of stress and stress hormones upon inflammation, we badly needed some quantitative and reliable technique for the analysis of the inflammatory process itself. Usually, for such studies in animals, inflammation is produced by rubbing some irritating material on the skin, instilling it into the eyes, or injecting it subcutaneously. But under these conditions, the causative irritant (microbes, chemicals) becomes intimately intermixed with the fluid (exudate) and cellular (granuloma) parts of the inflammatory tissue itself; furthermore, the outlines of the whole focus are irregular and unpredictable, so that quantitative analysis of the constituents is virtually impossible. Because of these same disadvantages, the inflammatory reactions produced by systemic treatment—including the anaphylactoid inflammation—were also unsuitable for our purpose.

The Objectives

What we really needed was an experimental model of inflammation, readily reproducible in animals and possessing the following features:

1. The model must not permit the causative irritant to escape; otherwise it would be impossible to establish the quantitative relationships between irritant and response.
2. It must have a predictable, regular shape and size, so that it may be accurately measured.
3. The two major components of inflammation, the cellular barricade and the inflammatory fluid, must not be intermixed (as are the solid and fluid parts of a wet sponge), so that they may be separately measured.
4. The structure must have walls of even thickness, so that its functional value as a barrier may be measured (for example, by injecting microbes or corrosive chemicals into the cavity and determining how much the pouch wall can stand before it perforates). An irregular wall with variable weak spots could not be relied upon for such tests.

This was quite an order; we spent many years unsuccessfully trying to devise such a test. I always felt that some kind of mold could do it: for instance, a glass bead or a small ball of metal which would force connective tissue growing around it to take on a regular, spherical shape. But it would have to be a very bland and elastic foreign body and, indeed, one which would eventually disappear, leaving a cavity for fluid accumulation. All the molds I tried were hard and caused the

surrounding skin to perforate wherever the rats pressed against them; besides, there still remained the problem of removing the mold after the barricade had formed. The idea of such a test was intriguing, but it seemed quite impractical until a lucky accident finally showed the way.

A Lucky Accident

In patients suffering from consumption, it is often useful to inject air (or some other gas) into the chest cavity in order to collapse a diseased lung and give it a rest to promote healing. On the other hand, since any kind of stress is particularly bad for tuberculous patients, I was interested in finding out exactly how stressful the air injection itself would be. To determine this, I injected air into the chest cavity of rats with the intention of later measuring their adrenal response as a stress indicator. While I was doing this, a group of visiting Brazilian physicians were shown into my lab. As I turned to greet them, my needle slipped out of the rat's chest cavity and all the air went under the skin of the back; there, it formed a perfectly regular, roughly egg-shaped, connective-tissue sac. This was it! Why not use air as a mold with which to force connective tissue to form a sac of predictable size and shape? Air is very elastic, and being gradually absorbed, it need not be removed to permit fluid accumulation in the pouch. I deliberately made such air-sacs and injected an irritant (usually croton oil) into the cavity in order to transform the connective-tissue lining into an inflammatory barricade.

This proved to be a very practical procedure: the lining

formed a granuloma pouch and the cavity filled up with inflammatory fluid. After the rat was sacrificed, this fluid could be measured accurately by aspirating it into a graduated syringe, and the connective-tissue barricade could be dissected and weighed separately. In fact, if the rats were shaved, the progress of inflammation could be followed day by day by transilluminating the sac with an electric flashlight and measuring the height of the fluid-column. Even function tests to determine the effectiveness of the barricade could be performed quite easily by injecting microbes, enzymes, or corrosive chemicals into the cavity and determining the maximum concentration tolerated without causing perforation.

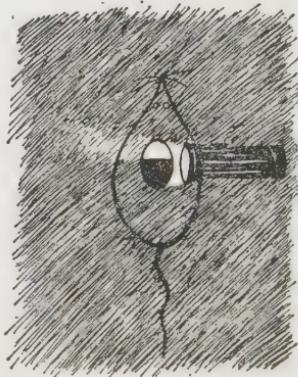
[Plate VI.]

This is what the pouch looks like on a rat

walking about
in daylight



or held vertically
for transillumination
in the dark



This "granuloma pouch test" proved very helpful in the analysis of the effect of stress upon inflammation. It is commonly employed by the pharmaceutical industry for the testing of pro- and anti-inflammatory drugs. It is also used extensively in studies on the biochemistry of inflammatory fluid and the growth of microbes or transplantable cancers in "a living test tube" of connective tissue.¹³

The L.A.S.

The granuloma pouch could be elicited by many agents; in fact, almost any compound introduced into a subcutaneous air sac transformed the wall into a granuloma and led to the exudation of fluid into the cavity. Long-acting, chronic irritants, which cannot readily be absorbed or inactivated (e.g., croton oil, carrageenin, kaolin), were more effective than substances that are rapidly removed or destroyed (e.g., hypertonic saline solutions, formaldehyde, acids or alkalies), but in essence, this was certainly a nonspecific local response to damage as such, the topical counterpart of the G.A.S. This Local Adaptation Syndrome or "L.A.S." was also quite specific in its manifestations but nonspecific in its etiology: the structural changes were very much the same no matter which tissue irritant was employed. The inflammatory response varied in intensity—depending upon the strength of the irritant—but it always consisted of granuloma and exudate.

¹³ SELYE, H.: On the mechanism through which hydrocortisone affects the resistance of tissues to injury. J. Amer. med. Ass., 152, 1207 (1953).

It is true that various tissue irritants produced qualitatively somewhat different granuloma pouches: the exudate could be hemorrhagic, purulent or serous, the pouch wall predominantly fibrous or rich in histiocytes, but we interpreted this as mere modifications of a stereotyped basic pattern by superimposed specific effects of individual pathogens.

L.A.S. vs. G.A.S.

This same variability exists also in the G.A.S. in which—as we have seen—the nonspecific changes are almost always complicated by specific actions of the stressors used. For example, cold causes fever, heat, sweating, insulin hypoglycemia, adrenalin hyperglycemia and mercury calcifying nephrosis; these changes are superimposed upon the alarm reaction that can be evoked by any of these agents. In the G.A.S. as in the L.A.S., the stereotyped effect of stress is “contaminated” by specific actions of the stressor which blur the picture. In many respects—though, certainly not in all as we shall see—the L.A.S. corresponds to inflammation, a generic term which has always been accepted for a variety of sub-forms (e.g., serous, purulent, hemorrhagic, histiocytic).

The L.A.S. also resembles the G.A.S. in many other respects. For example, upon chronic intense irritation it goes through three stages (primarily characterized by acute inflammation, granuloma formation and necrosis) corresponding to a local alarm reaction, a stage of resistance and a stage of exhaustion. As in the G.A.S., the second stage is associated with a considerable rise in resistance since well-developed

granuloma pouches can tolerate enormous amounts of irritants without undergoing necrosis. The close relationship between G.A.S. and L.A.S. is further emphasized by our previously mentioned observation showing that systemic stress (particularly through the adaptive hormones produced during the alarm reaction) is one of the most potent regulators of the L.A.S., whereas excessive tissue damage with local stress can produce a G.A.S. Under ordinary conditions this tissue damage is accompanied by inflammation, while the resulting G.A.S. is associated with an increased production of anti-inflammatory hormones. Consequently, a feedback mechanism goes into effect in which the L.A.S. produces a G.A.S. which (primarily through the production of anti-inflammatory hormones) tends to inhibit the L.A.S., at least as regards its predominant inflammatory characteristics.

How Could Stress Produce Specific Changes?

Of course, such common phenomena as nonspecific tissue reactions to injury have not passed unnoticed throughout the centuries. It has long been known that the most diverse chemical and physical irritants can produce edema, hyperemia, suppuration, hemorrhage, necrosis, cell degeneration or connective-tissue proliferation. Indeed, it has been postulated that even such specific structural changes as calcification, bone formation or the induction of malignant neoplasms may occur as a consequence of nonspecific tissue injury. But why do they not occur whenever tissues are irritated by any stimulus of sufficient strength?

Pluricausal Local Lesions

The fact that after appropriate conditioning, almost any stressor can produce selective necrosis in the heart first drew our attention to what I subsequently called the "pluricausal diseases." Apparently certain maladies—like musical chords—occur only when two or more agents act at the same time. We shall have much to say about this later but meanwhile I want to point out that pluricausality cannot be proven unless we find techniques permitting us to show that given changes are regularly produced by combinations of agents, none of which acts separately. It would be unwarranted to suggest on mere theoretic grounds that local irritants produce this or that type of tissue response by a combination of nonspecific (local stressor) and specific actions. The synthetic nature of their effects must be proven by eliciting the response through combined treatment with the supposed ingredients. We shall show later how this became possible with other "pluricausal changes." I merely wanted to mention the problem here since it first presented itself in this context.

Meanwhile, we wondered whether the tissue irritants which, in addition to ordinary inflammation, produce one or the other specific response do so because their molecules contain two pathogenic factors, one nonspecific, the other specific. Without destroying the molecules, we could not separate these factors. However, it did seem possible to show the composite nature of a specific reaction by actually synthetizing it through conjoint treatment with several pathogenic agents.

It might well be that pure stress—for instance that produced by different shapes of a chemically totally inert foreign object—would produce essentially distinct qualitative changes, depending merely upon the regional distribution of the same mechanical stressor. For example, could the subcutaneous implantation of variously shaped objects made from chemically inert pyrex glass induce the formation of qualitatively distinct tissues? If so, these responses would be pluricausal even though produced by a single object, since they would depend not merely upon the intensity of stress but upon coordinated “chords” of it, appropriately arranged combinations of pressure (and/or suction) upon the “keyboard” of the treated area.

Tissue Scaffoldings

I was bemused by this daydream, but that is all it was. There seemed little chance of figuring out a way to test it. Then I remembered that, during the preliminary stages of the granuloma pouch work, I had used all kinds of solid objects as “molds” to direct tissue growth. At that time, I had occasionally observed very peculiarly shaped living tissue-structures growing in and around the implanted material which they appeared to use as a kind of scaffold. We now repeated these experiments and found that even objects (we called them “tissue scaffoldings”) made of chemically inert pyrex can in fact induce the growth of different cell types, depending merely upon their size and shape.

For example, long tubes open at both ends stimulated the

IN VIVO

formation of a thin but perfectly vascularized tendon-like connective-tissue cord going through the axis of the cylinder from one end to the other. "Y" or "X" shaped tubes respectively produced bifurcating and cross-shaped connective-tissue cords.

On the other hand, in unilaterally closed tubes, the air in the lumen was gradually replaced by an invading adipose tissue, a veritable fingerlike lipoma.

In short cylinders, the central cord often developed into a tubular bone with typical circumferential lamellae.¹⁴ These structures resembled the long-bones of the rat, the center being filled with both fatty and hemopoietic bone marrow whereas near their ends, we found growth-cartilage plates in the process of endochondral ossification. When this type of broad but short tube was left in place for about a year, it invariably induced cancers (fibrosarcomas or osteochondro-fibrosarcomas). Curiously, with rare exceptions, these originated not in actual contact with the glass but in the connective-tissue "basal plates" which (as a parchment stretched over either end of a drum) closed the ends of the tubes.¹⁵

Of course, even in a case like this, when a single pathogen (here the glass tube) produces a lesion, the latter could still depend on several factors. For example, the large "tissue scaffolding" most readily conducive to cancer formation also

¹⁴ SELYE, H., LEMIRE, Y. and BAJUSZ, E.: Induction of bone, cartilage and hemopoietic tissue by subcutaneously implanted tissue diaphragms. *Wilhelm Roux' Arch. Entwickl.-Mechanik Organis.*, 151, 572 (1960).

¹⁵ SELYE, H., GABBIANI, G. and TUCHWEBER, B.: Factors influencing the development of mechanically induced experimental neoplasms. *Europ. J. Cancerol.*, 1, 80 (1962).

stimulates the production of much fluid; this exudate fills the cavity enclosed by the tube and comes into contact with a large surface of tissue at its broad "basal plates." It is conceivable that the stagnant exudate could act as a favorable culture medium for viruses normally present (but dormant) in the rat. Such germs might become pathogenic only when they find a suitable milieu for growth, and if they were carcinogenic, the resulting tumors would indeed be pluricausal in that their development would depend on: 1. the presence of viruses in the body, and 2. the formation of a sheltered cavity filled with a suitable culture medium.

Significantly, none of these glass objects produced any specific kind of growth when they were prevented from forming a fluid-filled cavity by being broken up into pieces before implantation. Flat plates of glass likewise induced only a surrounding fibrous capsule. [Plate VII.]

In the course of work with tissue scaffoldings we were particularly intrigued by the induction of the singular long-bone-like structures, but unlike all the other forms of tissue transformation (metaplasia), this one was very inconstant. We had to find a more reliable method, but for years all our carefully planned efforts were fruitless until another incidental observation came to our rescue.

Bone Induction in the Heart

In certain work on stress and heart disease, we wanted to reduce the cardiac muscle radically to see whether this would increase the stress-susceptibility of the remainder. To elimi-

nate exactly gauged amounts of myocardium, we devised a technique by which a greater or lesser apical portion of the heart could be tied off by a simple ligature placed around both ventricles. Thus, up to one third of the ventricles could be tied off without causing death. Indeed, much to our surprise this apparently drastic intervention did not even produce serious impairment in the animal's well-being or stress resistance, so we discarded this technique as one of no use for our purpose. Then something rather unpredictable turned up.

We had kept twelve rats from this experiment to show as curiosities to visitors, but after two months we decided that there was really nothing unusual about them and they were killed. As expected, we found at autopsy that the tied-off portion of the heart had become necrotic; however, unexpectedly the section immediately above the ligature was not only distended (reconstituting the original ventricular size) but completely transformed into typical flat bone. It consisted of a cup-shaped double bone plate with spongy spicules, the bone marrow between them. On histologic cross sections, the structure was almost indistinguishable from the rat's skullcap.^{16, 17} [Plate VIII.]

Some authors argued that in the case of bone formation in our tissue scaffoldings, contact with the vertebrae may

¹⁶ SELYE, H., GRASSO, S. and GENTILE, G.: Ossifikatsia cerdtsa, vyzvannaya khirurgicheskim vmeshatelstvom. (Cardiac ossification induced by a surgical intervention.) Eksp. Khir. No. 6, p. 22 (1961).

¹⁷ SELYE, H., MAHAJAN, S. and MAHAJAN, R. S.: Histogenesis of experimentally induced myositis ossificans in the heart. Amer. Heart J., 73, 195 (1967).

have been involved, since the glass rings were implanted into the connective tissue of the back. However, in the rats with the cardiac ligature there was no possible chance of direct bone induction by adjacent osseous tissue.

A good deal of work is now in progress on the various forms of metaplasia that can be induced by tissue scaffoldings or by means of the cardiac ligature technique. There is some reason to suspect that in the scaffoldings as well as in the heart, constant pressure upon connective tissue may play a role. Mechanical factors are certainly important in the modelling of already formed bone and they might conceivably even result in new bone induction, but it would be premature to formulate theories, for this problem has not even begun to be solved.

Fifth Lecture

Pathogen vs. Soil. Experimental Diatheses. Calciphylaxis. Calcergy. The Thrombohemorrhagic Phenomenon (THP). The Acute Conditioned Necrosis (ACN). Emergence of a General Hypothesis. Monocausal and Pluri-causal Diseases. How Could Different Pathogens Produce Identical Lesions or the Same Agent Produce Different Lesions? Degrees of Specificity. Summary and Outlook of the General Hypothesis. Pathosynthesis. Classification of Receptors. A Glimpse of Subatomic Biology.

Pathogen vs. Soil

By now, we became increasingly intrigued by the interactions between a potential pathogen and the soil upon which it acts. We had seen that: 1. Whether or not stress produces a cardiac infarct can be predictably determined by previous conditioning with certain chemical substances. 2. Whether or not connective tissue reacts with inflammation depends largely upon the balance between pro- and anti-inflammatory corticoids. 3. The most diverse types of metaplasia can be elicited at will by the appropriate distribution of pressure (local stress) over a connective-tissue territory on the back or a scar on the cardiac apex. Could certain pluri-

causal lesions depend upon the co-ordinated excitation of "elementary tissue receptors" by "elementary pathogenic stimuli"? In theory, a single molecule may contain several biologically active units, e.g., one for the production of stress and another for the induction of bone formation or carcinogenesis. But how could we hope to break up individual molecules into their suspected elementary pathogenic functional groups when the latter might not even be distinct parts but merely distinct physical or chemical properties (e.g., electric charges of atoms in a single molecule)?

For these reasons it is better to speak of "elementary qualities" rather than "particles" or subatomic loci. To use an illustrative analogy, grains differing in size, weight, magnetic force, color or temperature, can be identified in a mixture by appropriate means (sieves, centrifuges, magnets, color filters or thermometers). Once isolated, they can even be manipulated as blocks for the planned synthesis of qualitatively distinct structures, although each grain is homogeneous and devoid of any characteristic regional differences or loci that could be compared to functional groups in a molecule.

Experimental Diatheses

In this attempt at separation, planning did not get us very far, but chance helped. It showed us how to produce "experimental diatheses," that is, predispositions for a specific reaction form. Here, one kind of agent sensitizes tissues so that they respond very selectively with a simple ("elementary")

reaction to a second category of agents whose only evident feature is that they share the same appropriate ("elementary") stimulus. In other words, here the induction of a diathesis helps to single out one class of tissue receptors, making them available to bioassay by exposure to a certain class of stimuli. In a sense, this technique permits the functional isolation of a "pure strain" of receptors and a "pure strain" of stimuli which could never have been spatially isolated since they are only functional parts, "elementary qualities," within a complex matrix.¹⁸

Let us now see to what extent this hypothesis is corroborated by solid facts learned from our study of the experimental diatheses, particularly:

1. Calciphylaxis
2. Calcergy
3. The Thrombohemorrhagic Phenomenon (THP)
4. Acute Conditioned Necrosis (ACN)

All these lesions are pluricausal in that they depend upon the co-ordinated action of a "conditioning factor" (or "sensitizer") which induces a latent predisposition to a specific reaction form (e.g., calcification, thrombosis, necrosis) and a "challenger" which unmasks this predisposition by making the disease manifest and determining its location.

We began to think in terms of experimental diatheses in the course of our work on inflammation. Here, the balance between pro- and anti-inflammatory corticoids can be regarded as a conditioning factor for this type of response,

¹⁸ SELYE, H.: Pluricausal Diseases. *Exp. Med. Surg.*, 24, 191 (1966).

whereas the tissue irritant makes this tendency manifest and determines the area in which inflammation will occur. However, the first really typical instance of an experimental diathesis conducive to a pluricausal disease was again a chance observation made while we were looking for something totally different.

During studies on the infarct-proneness of the heart, induced by certain corticoids, we remembered that vitamin-D derivatives are chemically related to the steroid hormones; hence, we wanted to know whether dihydrotachysterol (DHT), a vitamin-D congener, could imitate the corticoids in sensitizing the heart for the production of necroses. This it didn't do.

Calciphylaxis

However, one day, as we were making our daily rounds through the Institute, one of my assistants called attention to the fact that many of the DHT-treated rats had a scaly skin disease; he suggested that we kill them because they might infect the rest of the colony. I plucked out a patch of hair to see the skin better, but the scaliness was not too bad and we decided to keep them for a while, hoping they would recover. Next day, the plucked region had become quite white and subsequently it hardened, giving the impression of a mineralized carapace. Histochemical studies then soon confirmed our impression that the mild trauma of plucking had produced massive calcification, presumably because the rats were conditioned for it by the DHT pretreatment. This immediately

struck me as a noteworthy phenomenon, perhaps because I myself was subconsciously conditioned for it by previous experience.

Flashback to Student Days

I remembered that in 1927, while still a medical student, I embarked upon my research career by purchasing a few elderly rats from the janitor of our pathology department in order to poison them with irradiated ergosterol, a substance which had just become available at that time. Overdosage with this synthetic vitamin-D preparation produced widespread metastatic calcification in adult rats (particularly in the cardio-vascular system, kidneys, lung and intestine), but only minor changes in the skeleton. However, the young of rats so treated during pregnancy or lactation responded to vitamin-D (received through the milk or placenta) with an altogether different syndrome. In them, the usual soft-tissue calcification was negligible, but multiple spontaneous fractures occurred as a consequence of bone absorption; simultaneously the skin—especially the scalp—lost its elasticity and adhered to the subjacent tissue so that the animal became “hidebound.” These facts were duly (though somewhat haltingly) reported to the Society of German Physicians in Prague on October 26, 1928, in what happened to be my first lecture. Since I was looking for bone lesions, I attached little importance to the skin and did not even examine it for histochemical evidence of calcification.

In 1932, working as a postgraduate student at Johns Hop-

kins University in Baltimore, I noted that parathyroid extract can produce a similar skin hardening in the rat, but this time I did perform histochemical studies and found that the affected regions were heavily calcified and sclerotic. They resembled the calcifying type of scleroderma.

Scleroderma

Not until 25 years later did we succeed in reproducing this scleroderma-like change in rats treated with DHT. However, even then, the cutaneous lesions produced either by parathyroid extract or by DHT could not serve as practical models of disease because they were invariably accompanied by high mortality and developed only inconstantly, only in newborn rats, and only on the scalp or neck, not wherever we wanted to induce them. In retrospect, it seems probable that my failure to obtain consistent results in these early experiments was due to the fact that cutaneous lesions developed only where I accidentally traumatized the skin while holding the rats by the nape of the neck for injection. Newborn animals might have been especially sensitive merely because their hairless, tender skin is particularly subject to injury during handling. Be this as it may, now (with the aid of plucking) we had a reliable technique permitting the consistent production of cutaneous calcinosis at any desired point of skin surface in rats of different age groups without having to give near-lethal doses of parathyroid extract or DHT.

The perfection of this simple test was a decisive point in

our studies: with its help, we made more progress during the next six months than we had during the preceding 32 years. The way was now open for a systematic analysis of the particular qualities a local challenger must have to produce cutaneous calcinosis in the suitably sensitized animal. It turned out that a variety of chemical agents can replace plucking as a challenger, and if such compounds are injected intravenously, many of them elicit selective local calcification in certain internal organs for which they have a special affinity.

We now know that in calciphylaxis, sensitization is possible with various agents whose only common characteristic appears to be that they cause hypercalcemia. Here, parathyroid hormone or vitamin-D derivatives act as sensitizers in that they condition the organism so that subsequent treatment with challengers will elicit localized tissue calcification. The most potent challengers are traumatic injuries or injection of mast-cell dischargers, mast-cell products and certain metals.

Topical vs. Systemic Calciphylaxis

For example, after pretreatment with a conditioning dose of parathyroid hormone, subsequent topical challenge of connective tissue with CrCl_3 or ferric dextran produces local calcification (topical calciphylaxis). Under similar circumstances intravenous challenge with CrCl_3 induces calcium precipitation in the parathyroids, ferric dextran in the pancreas, serotonin in the salivary glands, etc. (systemic calci-

phylaxis). In other words, the hypercalcemic agent acts as a general tissue sensitizer for a particular (here calcifying) type of response, but challengers are necessary to make this tendency manifest and to localize the reaction in certain regions.¹⁹ [Plate IX.]

With regard to their participation in experimental pluri-causal diseases, metallic salts can be roughly classified into four groups. Group I (e.g., FeCl_2 , CrCl_3) comprises the calciphylactic challengers while—as we shall see—the other groups play important roles in calcergy and the THP.

Calcery

Now just a few words about calcergy, a phenomenon which we discovered (again accidentally) as a by-product of our work on calciphylaxis.

We speak of local calcergy when topical calcification is produced, without sensitization, in tissues adjacent to an injected foreign substance. This phenomenon is elicited by a single pathogen. It represents a “monocausal disease” and hence it does not concern us here. Let us mention, however, that most of the topical “calcergens” are metals of Group II (e.g., KMnO_4 , LaCl_3).

Systemic calcergy is obtained by the intravenous injection of metallic compounds of Group III (e.g., lead salts) followed by topical or systemic challenge with mast-cell dischargers or mast-cell products.

¹⁹ SELYE, H.: Calciphylaxis. Chicago: The University of Chicago Press, 1962.

The local tissue lesions of topical calciphylaxis, topical calcergy and systemic calcergy with topical challenge, are virtually indistinguishable: they consist mainly of hydroxylapatite deposition in the directly treated connective tissue. By contrast, after sensitization for calciphylaxis or for systemic calcergy, systemic challenge produces circumscribed calcium depositions in distant organs such as the salivary glands, pancreas, uterus, carotid body, parathyroids or the autonomic nervous system.^{20, 21} [Plate X.]

The "THP"

While attempting to produce systemic calcergy by intravenous injection of various metals plus compounds suspected of being appropriate challengers, we hit upon many combinations which proved ineffective in eliciting calcification, but they induced thrombosis with hemorrhage in the challenged area. Thus, we stumbled upon the Thrombohemorrhagic Phenomenon (THP). Here, sensitization is obtained by metallic compounds of Group IV (e.g., ScCl_3 , InCl_3) or sulphated polysaccharides (e.g., carageenin, agar), the most effective challengers being mast-cell dischargers, 5-HT, epinephrine, norepinephrine, vasopressin derivatives and exposure to cold.

In the THP as in calciphylaxis, we distinguish a topical and

²⁰ SELYE, H., GABBIANI, G. and SERAFIMOV, N.: Histochemical studies on the role of the mast cell in calcergy. *J. Histochem. Cytochem.*, **12**, 563 (1964).

²¹ SELYE, H., GABBIANI, G. and TUCHWEBER, B.: Neurotropic calcergy. *Neurology (Minneapolis)*, **14**, 1084 (1964).

a systemic variant: the topical THP is elicited (in properly sensitized animals) by the local injection of a challenger into connective tissue; the systemic THP is induced by intravenous challenge, in organs particularly sensitive to the challenger used.²² [Plate XI.]

As we have seen, in this entire series of experiments, each accidental observation was followed by a period of development to elucidate the conditions under which it occurs and, while we were trying to do this, we found something unpredicted and indeed unpredictable. Almost invariably, this new phenomenon, though clearly in view, just did not register at first because we were not looking for it, or it did register but merely as a regrettable failure to find what we were looking for. Only after it presented itself several times did we finally notice it in the peripheral field of our vision, sufficiently to attract our attention.

The “ACN”

Similar considerations apply to the Acute Conditioned Necrosis (ACN). We stumbled upon this phenomenon in the course of certain experiments on the THP in which we used serotonin to influence the thrombohemorrhagic changes which occur in the brain of animals receiving large amounts of hypertonic saline, urea or glucose. It is known that subcutaneous treatment with such solutions produces an acute

²² SELYE, H.: Thrombohemorrhagic Phenomena. Springfield: Charles C Thomas Publ., 1966.

shrinkage of the brain when given in doses quite well tolerated by the tissues at the site of injection. However, when animals so treated were concurrently given an intravenous or intraperitoneal injection of serotonin, the skin underwent acute necrosis over the whole subcutaneous region infiltrated with the hypertonic solution. As always in such instances, our immediate reaction was that the experiment had failed: evidently the action of serotonin on these brain lesions could not be examined because the animals had lost a large portion of their skin surface and developed enormous gaping ulcers. It was only an afterthought—presumably triggered by a flashback to earlier experience with other pluricausal lesions—that here, we may have an excellent model for the induction of a necrotizing diathesis.

This hope proved to be well founded. Subsequent systematic studies showed that sensitization for the ACN is best obtained by mast-cell dischargers (compound 48/80, polymyxin, egg-white), mast-cell products (histamine, serotonin) and vasoconstrictors (epinephrine, norepinephrine, vasopressin derivatives). Moreover, we found that not only hypertonic solutions but various other inflammatory irritants can act as challengers for this type of response at dose levels not normally conducive to necroses.²³ [Plate XII.]

Now that we have briefly outlined the most important observations supporting the concept of the pluricausal diseases, we might perhaps say a few words about the background, present status and outlook of this hypothesis.

²³ SELYE, H.: Mast Cells and Necrosis. *Science*, 152, 1371 (1966).

The General Hypothesis

As we have seen, all the ingredients were found quite accidentally and usually by error, so to speak, in the course of work designed to substantiate other hypotheses which proved to be false in most cases. It is highly probable that the concept I wish to outline now will have the same fate but "our facts must be correct; our hypotheses need not be if they are fruitful."²⁴ Indeed, once completely verified, a theory has no more fertilizing value; only as long as we doubt its correctness can it inspire experiments that may lead to new facts. The discovery of each new problem must be followed by a period of planned research designed to solve it. So let us now briefly consider the theory which we use to plan our current experiments.

Monocausal Diseases

The concept that every well-characterizable specific disease entity must have its own particular cause gained acceptance mainly during the nineteenth century. The emergence of modern bacteriology under the influence of Semmelweis, Pasteur, Koch and their contemporaries, furnished countless examples in support of this view as applied to the microbial diseases. It became evident that the characteristic syndrome of any one infectious malady—such as tuberculosis, cholera, typhoid or diphtheria—could be elicited only by its own specific kind of germ.

Soon afterwards, research in the fields of nutrition and

²⁴ SELYE, H.: *The Stress of Life*. New York: McGraw-Hill, 1956.

endocrinology showed that the same principle is applicable here also. Such previously mysterious diseases as scurvy, pellagra or rickets were each traced to the lack of one specific vitamin, while the most diverse endocrine derangements were found to result either from a lack or an excess of particular hormones, each compound being responsible for one kind of derangement only. These data were readily acceptable, since they agreed with earlier observations in toxicology: it had long been known that poisoning with lead, arsenic or certain plant extracts induces specific syndromes, each characteristic of the particular poison used.

In the face of all this well-documented evidence, it seemed that we must henceforth abandon the vague notions of our predecessors, who thought that diverse diseases can result from a single cause and, conversely, that one and the same malady can be produced by different pathogens. The very idea that any one disease, say tuberculosis, might be due—in different patients—to malnutrition, heredity, excessive physical work or emotional shock, appeared to be as unscientific as the superstitions of antiquity which attributed the most diverse maladies to the “evil eye” or the jealousy of the gods. Yet, there remained the disturbing fact that certain individuals are uncommonly resistant or susceptible to certain diseases; indeed, these “individual variations in disease proneness” can often be traced to, or even purposely modified by, identifiable factors.

Of course very few lesions are truly moncausal in the sense that their development is the inevitable obligatory con-

sequence of a particular pathogen. As pertinent examples we might mention paralysis after spinal cord transection, blindness after enucleation of the eyeballs, burns after exposure to sufficiently high temperature, hemorrhage after transection of the aorta, sterility following ovariectomy, or renal necrosis after thrombosis of the main renal artery. Here, the respective lesions represent the obligatory consequences of the agents mentioned because there are no collateral mechanisms that could assure homeostasis, thus compensating for the loss. Many more maladies are predominantly moncausal in that they can be produced only by one particular agent, yet the soil factor is also important since they occur only in susceptible individuals (e.g., tuberculosis by the mycobacterium of tuberculosis, lead poisoning by lead, scurvy by lack of vitamin C). Here, the degree of susceptibility may vary between broad limits depending upon conditioning factors just as any irritant can produce much, little, or no inflammation, depending upon the balance between pro- and anti-inflammatory hormones in the body.

The typical pluricausal diseases are not dependent upon any particular pathogen; they have no specific single cause but are the consequences of pathogenic constellations. To this group belong peptic ulcers, accidental thymus involution, many forms of collagen disease, nephrosclerosis, thrombohemorrhagic diseases, atopic dermatitis, various neuroses and many others. In fact, the possibility of a pluricausal pathogenesis must be considered in the case of all "idiopathic" maladies.

Pluricausal Diseases

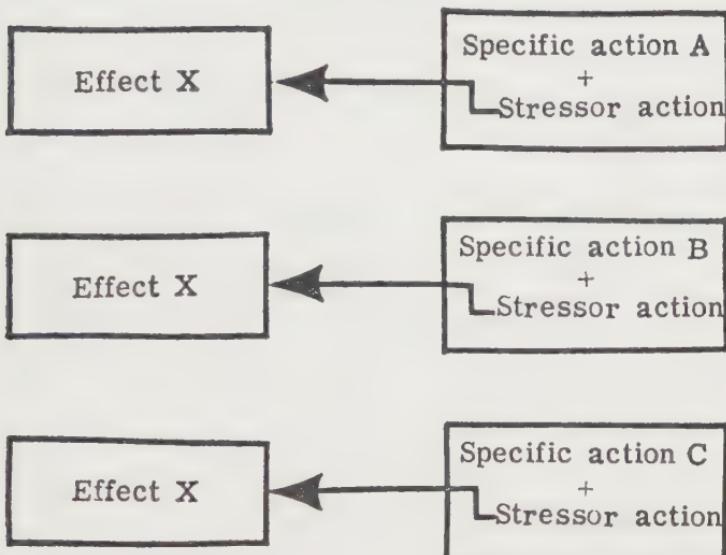
To do this we must attempt to analyze the soil factor by objective and, wherever possible, quantitative experimental techniques. As we have seen, up to now, one of the most striking contributions to this field has been to show, on many disease models, that a variety of conditioning (or sensitizing) factors can so prepare the organism that it will respond to different challengers with a stereotyped reaction whose character can be predicted.

The most frequent objections to the concept of pluricausal diseases in general and stress-induced "diseases of adaptation" in particular arose from the difficulty of understanding how different pathogens could produce identical lesions or, *vice versa*, how the same pathogen could elicit essentially different derangements. These apparently paradoxical facts can only be explained by the assumption that pathogenic constellations rather than individual pathogens are required to produce certain changes. As a rule, the final link which completes a pathogenic set of circumstances (and, hence, makes the disease manifest) impresses us as the decisive factor but, actually, it is no more essential than the others.

How Could Different Pathogens Produce Identical Lesions?

The diagram on p. 113 visualizes how different complex pathogens can produce identical lesions, a problem often

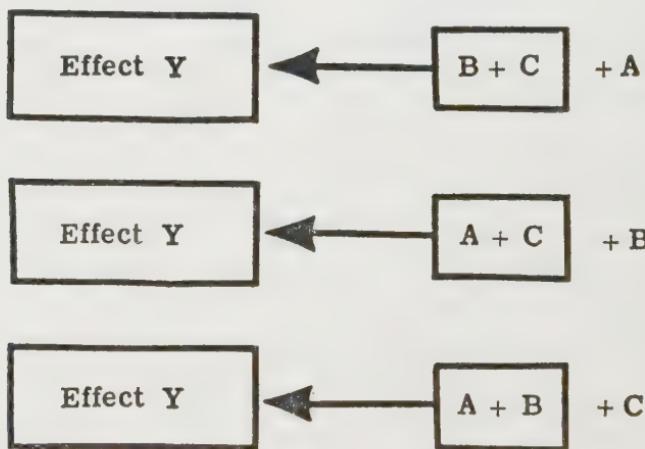
encountered in the "diseases of adaptation" in which exposure to stress is the decisive factor.



Here, three totally unrelated agents A, B and C produced the same effect X. However, if we analyze the situation more closely, it becomes apparent that the pathogenic properties of these agents are complex and the common effect does not depend upon their distinct specific actions but upon their common stressor effect. If A stands for cold, its specific effects will be cutaneous vasoconstriction, shivering, etc. If B represents insulin it will cause hypoglycemia, and if C is adrenaline it will elicit hyperglycemia. But the fact that all these agents produce the characteristic manifestations of an alarm reaction is not due to these distinctive actions but to the stressor properties which they have in common.

In such instances the elucidation of the pathogenic mechanism depends upon the correct recognition of the decisive common element. This is not always a simple matter. [There is an old story about a man who, after getting drunk on whisky and soda, rum and soda, and gin and soda, concluded that he must henceforth avoid soda water in order to remain sober.]

So much for stereotyped actions of complex agents. However, after specific conditioning for one or the other type of lesion, even different pharmacologically simple agents can produce the same effect. This is illustrated by the next diagram.



Here, *A*, *B* and *C* represent simple pharmacologically "pure" agents which possess only one specific effect. Yet, it is evident that if an individual is conditioned by pretreatment

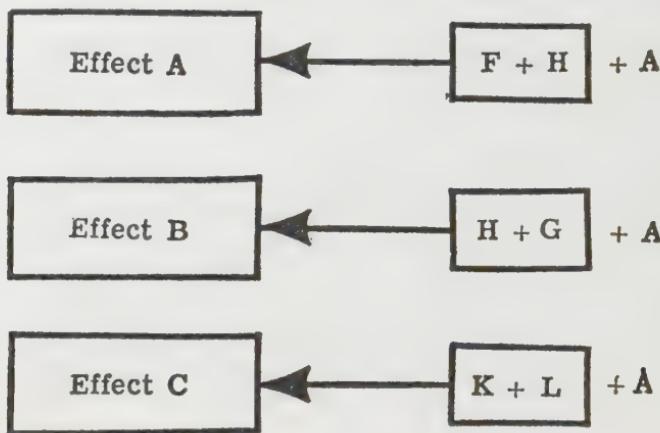
with $B + C$, $A + C$ or $A + B$ respectively, an effect dependent upon the conjoint action of all three factors can be elicited in the first case only by A , in the second by B , and in the third by C .

For example, mastocalciphylaxis can be produced only by conjoint treatment with a calciphylactic sensitizer (e.g., dihydrotachysterol), a mast-cell discharger (e.g., dextran), and a metal (e.g., FeCl_3). Hence, in an individual treated with any two of these agents, only the missing third one will be able to complete the required pathogenic constellation.

How Can the Same Agent Produce Different Lesions?

It follows furthermore that, in the case of diseases dependent upon the combined action of several factors, different lesions may be caused by the same agent if the latter happens to be the only missing link necessary to complete the requisite pathogenic combination. Thus, in the diagram on p. 116, agent A can elicit effect A , B or C (depending upon other agents with which the organism is previously conditioned) providing that in the first case $F + H + A$, in the second $H + G + A$, and in the third $K + L + A$ are required to create the corresponding pathogenic constellations.

It has often been claimed that, if the maladies which we describe as "diseases of adaptation" (e.g., "stress ulcers," cardiac infarcts, nephrosclerosis or hypertension) were really due to stress, they should all occur simultaneously in any one individual exposed to a stressor. On the basis of what we have just said this is evidently not true.



Degrees of Specificity

These considerations suggested that it is not sufficient to distinguish between specific and nonspecific lesions; there are different degrees of specificity. Some changes are produced by many, others only by few agents and it was thought that a classification of pathogens on this basis may be fruitful. As the years went by, more and more evidence accumulated in support of the view that there are "elementary pathogenic stimuli" which act with considerable specificity on certain "elementary biologic receptors," and that by proper combinations of the simplest pathogens, it is possible to construct similes of the complex syndromes that constitute naturally occurring diseases.

Systemic stress affecting the entire organism is by definition the most nonspecific form of reaction. However, as we

have said before (p. 91), inflammation, necrosis, thrombosis and certain degenerative lesions can also be produced by many, though not by all, pathogens; hence, they represent a second level in the degree of nonspecificity. Finally there are responses, such as certain immune reactions to antigens, which are almost completely specific.

The larger the number of receptors that respond to an agent, the more nonspecific is its effect, and even apparently simple pathogens (e.g., individual types of microbes, simple molecules, atoms) are biologically complex if they act on several distinct types of receptors. We found no manifest relationship between simplicity of structure and simplicity of biologic effect, the latter being due presumably to the sum of many chemical and physical characteristics. In view of this lack of correlation, the only practical way of identifying and classifying elementary pathogenic stimuli is by bioassay. In other words, agents which can selectively produce individual elementary tissue reactions (e.g., inflammation, necrosis or calcification) are themselves considered to be elementary stimuli. This basis of classification is acceptable, though only until the reaction produced can be broken down into still smaller elements of morbid response. As we shall see, most biologic responses are chain reactions in which activation of any one link is necessarily transmitted to its neighbor until the response has run its natural course, just as in chemical chain reactions the products of any one process initiate the next step. Even the simplest biologic responses still consist of

numerous chemical interactions, yet they can be considered as units because they are "atomic" in the original sense of the word: they cannot be broken down into still simpler reactive units; in other words, no agent can produce these reactions partially.

Summary and Outlook of the General Hypothesis

It is difficult to be articulate about the tenets and goals of a hypothesis at a time when there is still so little to substantiate it; but this is when a clear formulation of whatever we have is most badly needed to bridge that bewildering gap between intuition and intellect. In this and the preceding lectures, I have described many well-established facts. That was easy. But I also tried to weld them together. That was difficult because the parts just do not fit into a single harmonious pattern as yet. Still, the essence of science is generalization; without some map of the salient landmarks, we cannot prospect further in any field. So then let us try to summarize by drawing an outline, even though we know it to be incomplete and suspect it of being faulty on many points. You may say it is too early now, but now is when we need it—so here it is:

Identical nonspecific lesions can be elicited by several combinations of in-themselves inactive and essentially different pathogens: 1) "sensitizers" which induce a latent predisposition for a specific reaction form (e.g., inflammation, necrosis, calcification, thrombosis and hemorrhage); 2) "challengers"

which unmask this predisposition by making the disease manifest and determining its location.

Our working hypothesis postulates that selective conditioning can functionally isolate one type of receptor at a time for identification. Thereby it permits the pharmacologic exploration of many normally masked receptors with bioassay techniques which furnish results quite as objective and measurable as those in common use for the study of normally unmasked receptors (e.g., α - and β -adrenergic or cholinergic receptors).

The technical advantages of this "receptor isolation" may be likened to those of isolating pure strains of bacteria or cells, organelles (mitochondria, lysosomes) or chemical elements. Receptor isolation is not a physical purification but a functional separation from irrelevancies, and hence, even more closely comparable to the functional isolation, by planned breeding, of individual determinants of heredity.

Elements of Disease

If you glance through a textbook of pathology, you get the impression that there are hundreds, if not thousands, of distinct diseases; yet, when you come to look at the underlying microscopic changes, the number of qualitatively different tissues is not so great. Cells can respond to pathogens only in a limited number of ways; they can grow or shrink, they can store or discharge materials, they can move and they can die. The virtually infinite variety of diseases afflicting man

may well be mosaics, "configurational wholes" resulting from different combinations of such elementary pathologic responses. After all, the names of all diseases can be written with the handful of letters in our alphabet; everything in and around us is made up of only about a hundred natural elements; the recipe that tells a germ-cell to make a mouse or a man is transmitted in a genetic code of only four letters.

In the history of every science, the definition of constituent elements proved to be a decisive breakthrough. It was always of the greatest heuristic value to learn how vastly different things are made up of a few standard ingredients: objects of atoms, atoms of subatomic particles, tissues of cells, inheritance of genes, the spectrum of primary colors and so on. Is it not possible that eventually we may also be able to identify the elements of disease?

We already know some: surely inflammation, necrosis and phagocytosis are stereotyped forms of reaction which participate in numerous disease processes. The manifest power of many pathogens to produce such reactions is easy to demonstrate: we merely have to put the agents in contact with tissues to obtain the characteristic response. But apparently many pathogenic capacities of stimuli are contaminated by others, or they remain latent under ordinary circumstances; to bring them out in pure form we need the techniques of special conditioning.

It is as though certain normally masked tissue receptors were exposed or activated through conditioning so that they may be reached even by pathogenic stimuli too weak to be-

come evident under ordinary circumstances. Apparently, a truly selective conditioning agent exposes only one type of receptor. Thereby it produces a specific diathesis in which exposure to a certain kind of challenger always elicits only that variety of lesion for which the organism has been specifically sensitized (e.g., inflammation, necrosis, calcification, thrombohemorrhagic phenomenon). However, the same type of change can be produced by combinations of different agents as long as these are selected from the appropriate classes of sensitizers and challengers. What we have called the "elementary pathogenic stimuli" (for calcification, necrosis, etc.) can thus be demonstrated by objective bioassays even when they are normally not evident.

Classification of Pluricausal Diseases

Now let us try to define, in more precise terms, just how conditioning plus challenge could produce pluricausal diseases. Up to now, three principal categories have been identified:

1. *The "leakage type."* Here the conditioner is blood-borne and the challenger merely causes it to leak out of the vessels at a given point; thereby the lesion becomes evident and its localization determined. The simplest model for this type of response is the leakage of intravenously injected dyes or microorganisms at sites of damage. As we shall see presently, in certain instances, the extravasated blood-borne conditioner can act as an induced receptor which secondarily attracts other pathogenic agents.

2. *The "metabolic type."* Here the conditioner causes a metabolic derangement which renders the challenger toxic. This is the basis of many well-known toxic drug interactions which can arise in the intestine or other absorptive sites, in transit or at receptor sites. For example, monoamine oxidase inhibitors can cause extraordinary side effects in patients whose diet contains catecholamines. The combination of Brie cheese (containing tyramine) and the drug tranylcypromine has caused severe hypertensive reactions because of similar reasons. When alcohol is taken after Antabuse (Disulfiram) acetaldehyde intoxication develops because the metabolism of alcohol is blocked at the acetaldehyde stage. This effect has been used to combat alcoholism. Many of the conditioning drugs that belong to this class act by enhancing the enzymatic breakdown (in hepatic microsomes) of other drugs, and if toxic metabolites are formed, the result will be a truly pluricausal change.

3. *Mixtures of types 1 and 2.* For example, in tuberculin reactions and various forms of allergy, a blood-borne antibody conditions for topical challenge by an antigen.

"Pathosynthesis"

The most potent tool we have for the experimental analysis of such complex problems of pathogenesis is "pathosynthesis." This consists in the experimental production, by the conjoint application of comparatively simple elementary pathogens, of lesions having a predictable histologic struc-

ture and organ distribution. The usual approach to the study of pathogenesis is restricted to the search for individual and often still highly complex pathogens responsible for the multifaceted spontaneous diseases. It is hoped that patho-synthesis will assist us in elucidating the mechanism of some among those seemingly mysterious maladies which, having no identifiable individual cause, are now labelled as "idiopathic."

Microsyndromes

The simplest prototypes of pathologic reactions (inflammation, necrosis, calcification, thrombosis and hemorrhage), still involve many structural elements, but functionally, they represent "elementary pathologic syndromes" in that their constituent parts are inseparably interconnected. That these stereotyped building blocks of spontaneous diseases are really nonspecific with regard to their etiology can be demonstrated only by bioassay: the identification of chemically and pharmacologically distinct agents which (in addition to their specific actions) share the property of evoking the manifestations of one such response.

Flashback to "Actions" and "Reactons"

This entire concept took a precise form only recently, as I was reviewing the principal facts revealed by our work on the "experimental diatheses" in preparation for these lectures. However, in retrospect I realize that its roots go back ten

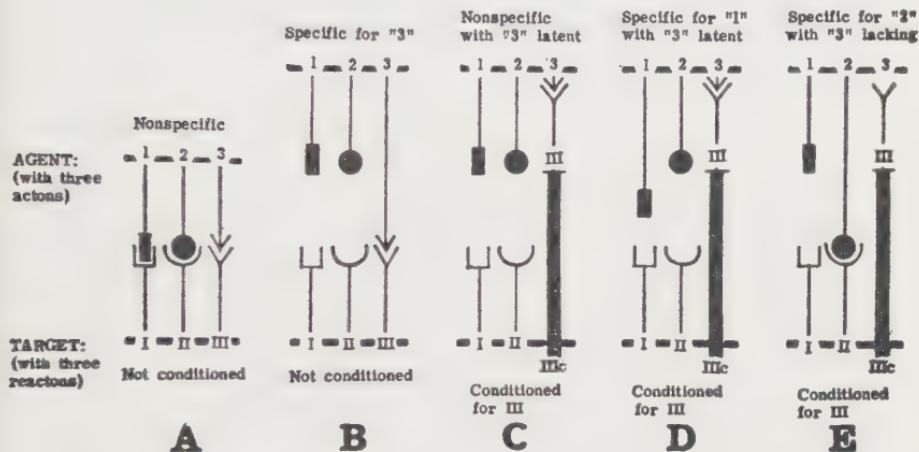
years when, in "The Stress of Life,"²⁴ I began to question the cell as the ultimate unit of life. At that time, I concluded that:

"The cell is undoubtedly a building block, a structural unit, of life. It has a visible membrane which separates it from its surroundings and emphasizes the distinctness of this element in space. But it is not the elementary unit of biologic function. We have seen that within the cell there are smaller organizations which must also be regarded as units, in that they can still function independently of each other. In analogy with the larger biologic units (such as the *nephrons* of the kidney, the *neurons* of the nervous system), I have called these *reactons*. The reacton is defined as *the smallest biologic target which can still respond selectively to stimulation*. The limits of these units are not visible under the microscope; in fact, they may not have any sharp, structural limits. But, irrespective of their position, they can function in unison, since certain agents act selectively on one type of reaction in many cells and intercellular substances throughout the body. Here the functional organization into reacton units is more important than the structural subdivision into cells."

On the basis of what we have said today, the "reacton" corresponds to the "elementary receptor" capable of developing "elementary syndromes" through the activation of any one of its interdependent parts, the links of the simplest biologic chain reactions. Accordingly, we may refer to the "elementary stimuli" capable of activating such links as "actons."

²⁴ SELYE, H.: *The Stress of Life*. New York: McGraw-Hill, 1956. (p. 233).

The acton-reacton interplay and its modification by conditioning agents may be schematically illustrated as follows:



The drawing attempts to visualize five typical agent-target interactions (A-E). For simplicity's sake each agent is represented as having only three elementary stimuli or actons (1. Quadrangle 2. Circle 3. Arrow) while the targets are provided with three corresponding elementary receptors or reactons (I-III).

A: A nonconditioned target is exposed to a nonspecific agent, that is one in which all actons are approximately of equal strength. A nonspecific response results.

B: An agent in which acton "3" is manifest produces a "3/III" type of elementary specific response even in the nonconditioned target.

C: A nonspecific agent in which acton "3" is underdeveloped (and hence normally latent) nevertheless elicits the "3/III" type of response if it acts on a target in which the conditioner IIIc especially exposes reacton "III."

D: The same result is obtained even if the agent has a mod-

erately overdeveloped acton "I" which would produce a specific response at "I" if the target were not conditioned at "III."

E: If the agent has no acton "3," even a target conditioned at "III" will fail to react with the "3/III" type of response, irrespective of whether or not the agent has one preponderant acton (as is the case here at "2").

Classification of Receptors

At this point, it may be well to specify just what is meant by "receptors." Pharmacologists tend to use the term rather vaguely for any subcellular structure that can receive a stimulus and respond to it. Morphologists speak of "target organs" in dealing with larger structures, for example, the thyroids or adrenals which react selectively to the corresponding trophic hormones of the pituitary. This distinction is not always clear-cut since even entire organs respond as a consequence of the reactivity of subcellular receptors within them. It is important, however, to distinguish between innate and induced receptors.

Innate receptors are highly specific preformed structures responding in a predetermined manner to highly specific agents (e.g., α -adrenergic receptors to epinephrine) whose effect can in turn be blocked by highly specific drugs (e.g., α -adrenergic blocking agents).

Here, the situation may be compared to a telephone system in which the receivers are preformed structures responding only in a predetermined manner and only to specific stimuli (sound).

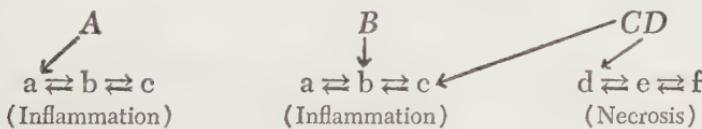
Induced receptors are by definition, not preformed and

they can respond to diverse (nonspecific) agents, but only after specific conditioning. The simplest examples are systemic calcergy and mastocalciphylaxis in which intravenously injected lead or iron can set up a calcium trap wherever a nonspecific agent causes capillary leakage of these metals into tissue.

This situation can be compared to a system of pipes which, upon nonspecific damage causing them to leak at any point, will liberate water, steam, dyes, gas or oil, depending upon the material put into them. If the liberated substance subsequently reacts with some other compound it can be regarded as an induced receptor for the action of the latter.

Whatever the shortcomings of this type of speculation, it seems reasonable to assume that in our prototypes of pluricausal lesions, different conditioners can predispose different elementary tissue receptors to stimulation by various challengers. Furthermore, as long as the same interdependent receptor groups are sensitized, challenge of their different links by different compounds will lead to the same result.

This concept may be illustrated as follows:



Indivisibility of Microsyndromes

Here, *A*, *B* and *CD* represent three elementary stimuli while *a-f* represent interdependent individual biochemical

links in three chain reactions conductive to elementary syndromes. Supposing $a - b - c$ stands for inflammation and $d - e - f$ for necrosis, then the whole process of inflammation can be elicited by A , B or CD (although these stimuli act primarily on a , b and c respectively), because no matter which link is activated primarily, the others will also become involved. Here the situation is somewhat comparable to that of a paper ribbon which, no matter where it is lighted, will burn from end to end.

Our schema also illustrates that if an agent CD has two actons, it can activate two elementary syndromes; one (representing inflammation) through its action on c , the other (representing necrosis) through its action on d .

Presumably, each of these microsyndromes is biologically indivisible precisely because it consists of metabolically inter-dependent reactions which must always run their entire course. For the same reason, chemically different pathogens can elicit the same microsyndrome by acting on its different links, and the same chemical compound may possess several hidden and/or manifest pathogenic potencies owing to the complexity of its structure.

A Glimpse of Subatomic Biology

We postulate that even individual atoms contain several types of actons if they demonstrably possess different combinations of qualitatively distinct potencies, for example, one for the quality of the response, the other for its localization in one or the other region. Thus, when injected subcutaneously

in the rat, both lead and holmium salts cause topical calcification (local calcergy); however, when administered intravenously, lead chloride, unlike holmium chloride, sensitizes for calcification at sites of subcutaneous challenge with mast-cell dischargers, while holmium unlike lead causes massive calcification of the spleen.

Time will tell to what extent this hypothesis can be substantiated by further experimentation. Now, all we can say is that meanwhile it served us well as a guide to facts which we could not have found otherwise. But we are not bound to remain loyal to the concept of actons and reactons; we shall desert it without the slightest scruples as soon as we find an interpretation more compatible with the facts.

In any case, here, we are at the subatomic level of biology. We are beginning to explore with simple techniques entities even more minute than the subjects of supramolecular biology that could be studied only through the most sophisticated modern approach of quantum mechanics.²⁵ It is ironical that I should have to end up here in my defense of the old-fashioned coarse methods recommended for the exploration of broad correlations and the gross phenomena of life!

²⁵ SZENT-GYÖRGYI, A.: Introduction to a Submolecular Biology. New York: Academic Press, 1960.

Sixth Lecture

The Mechanism of Problem Finding. Discovery vs. Development. Intuition vs. Planning. Unpredictable vs. Predictable Results. Synthesis vs. Analysis. Peripheral vs. Tubular Vision. Simple vs. Complex Techniques. Apprenticeship vs. Formal Courses. The Four Steps in Research. The Incurable Ambivalence.

The Mechanism of Problem Finding

The preceding lectures gave us a chance to explore the psychologic factors at work in problem finding. We have analyzed many examples, some because of their momentous importance, others merely because I happened to have experienced them myself. At first, it seemed to me irreverent—perhaps even in bad taste—to mention my own experimental ventures and speculations in such distinguished company, but I gave you my reasons for doing so, and I think they are valid. When intoxicated by the joy of finding a new natural phenomenon, we give little attention to the mental processes that led us to it, and few investigators bother to take note of them. I have always been interested in the psychology of research, and self-observation has helped me to appraise it

more realistically than I could have on the basis of data published by others. Besides, I hoped that by giving you a concise summary of what I regard as the highlights of our work, even those who disagree with my views on psychology and supramolecular biology would not feel that attending these lectures was a complete waste of time.

Now that we have a fair number of concrete examples to illustrate what we mean by problem finding and problem solving, let us attempt to analyze the nature of both by confronting some of their salient characteristics. Those of the Problem Finders will be listed first, not because they are more important, but simply because the definition of a problem must necessarily precede its solution.

Discovery vs. Development

Discovery is the realization that something new exists. In biology the novelty may be a structural element in living matter (a new organ, tissue, cell, subcellular particle or chemical), some unexpected correlation between parts of the body, or a hitherto unobserved physiologic reaction or disease. As used here, the word "discovery" necessarily means the finding of something unpredictable, but it does not necessarily imply importance. To be important, a discovery must be not only unexpected, but also generalizable, that is, applicable to many situations. Only this gives it real scope.

Development, in our sense, is the further exploration of an already discovered fact. This work may be equally or even more important than the original observation that posed the

problem. For example, in itself, the discovery of the mast cells by Ehrlich a century ago, did not help us to learn anything about physiology or pathology; the new cell type was just a microscopic curiosity. Then came many years of carefully planned exploration. With techniques of ever-increasing complexity, it could be shown that these cells contain heparin, histamine and serotonin, participate in various anaphylactic and anaphylactoid reactions, facilitate the localization of blood-borne particles and play a decisive role in regulating tissue resistance to injury. The mast-cell problem is still far from being solved, but then, how could we have even begun to solve it without knowing that it exists?

Intuition vs. Planning

In problem finding, the principal requirement is inspiration, perhaps with a certain amount of opportunism, a tendency to follow the line of least resistance rather than the steadfast pursuit of what we set out to find. On the other hand, problem solving is based on careful planning and persistence on a steady course until the aim is reached. It requires patience and the courage to resist all temptations to start on something new in the hope of quick returns. Here perspiration is often more effective than inspiration.

Yet, even in problem solving, it is rarely possible to be guided merely by the laws of logic. As the great physiologist, Claude Bernard, put it:

"When philosophers, such as Bacon or other more modern thinkers, wanted to offer a general systematization of precepts

for scientific research, they may have seemed seductive to people who see the sciences only from afar; but such undertakings are of no value to already trained scientists, nor to those who intend to dedicate themselves to science; in fact, they confuse them by implying a false simplicity of things; in addition, they encumber the mind by a mass of vague and inapplicable precepts which must be rapidly forgotten if one wants to enter into science and become a true experimenter."

The same thought was expressed even more poignantly by Jean de Maistre, when he said:

"Those who have made the most discoveries in science are those who knew Bacon least, while those who have read and pondered him, like Bacon himself, have not succeeded well."

Even the construction of hypotheses is much less dependent upon logical reasoning than most people think. No hypothesis can be arrived at by logical reasoning alone since it must be based on insufficient evidence, or else it is not a hypothesis at all but a factual conclusion. Indeed, the more a lack of facts forces a hypothesis to depend upon imagination, the more ingenious it is.

Of course, the evaluation of results can be accomplished only by reasoning. During the last few decades, even mathematical techniques, particularly biological statistics, proved to be of value in this respect. We must beware, however, of the more ambitious attempt of mathematical biology to express, in the form of equations, vital phenomena in which most of the variables are unknown. Such efforts could succeed only when the unknowns are unimportant, but we can rarely be

sure that this is so. In any event, it is only to the mathematician that an equation is more meaningful than say, a blood-pressure curve or the histologic picture of a neoplasm. Even when a biologic phenomenon can be expressed mathematically, this accomplishes little more than the translation of the same set of data from the language of the biologist to that of the mathematician. Legal English is more precise than the kind we use every day, but no one would bother to express the laws of life in this overly accurate and careful form. The removal of all ambiguities and shadings would merely give the impression of more precision than actually exists. As a rule, the same can be said of attempts to translate the laws of life with all their exceptions and imprecisions into the precise language of mathematics.

No matter how distasteful this may be to many scientists, we must accept the fact that intellect is not always the safest approach to exploration and the acquisition of knowledge. The homing pigeon's "knowledge" of geography, the bat's "understanding" of radar are very effective though not intellectual; it is not through the logical rules of grammar that a child learns his native tongue.

Unpredictable vs. Predictable Results

This is merely another aspect of what we have just said. The results of intuition are obviously unpredictable; no one can plan to find a new problem. Therefore, this type of activity can never become a full-time job and even the most

typical Problem Finder will try to keep busy solving one problem, at least to some extent, while he is hoping for some lead to find another.

The results of problem solving are much more predictable; they furnish a steady occupation because they can be largely planned in advance. It would have been impossible for Fleming to predict his discovery of penicillin, but once the antibiotic activity of penicillium became known, it was easy to plan the agenda. It was safe to foretell that most probably, sooner or later, the active principle would be concentrated, extracted, purified and eventually synthesized, as has been the case with most other biologic principles. Through a flash of intuition, many a Problem Finder has made one and only one important discovery in his life, but most competent Problem Solvers have succeeded in applying their logic and technical skill to numerous problems.

This predictability is very reassuring, but it is not a guarantee of outstanding success. Those who try to solve a problem must first be sure that it is worth solving. To undertake a task just because it has never been done before (a very common motive, especially among beginners) is insufficient reason. Of course, if you use the latest and most powerful electron microscope to study the preputial glands of the African elephant, you are virtually sure of a "scoop;" probably throughout the history of the life sciences no one has ever embarked on this project before. But is this really a justification for your efforts?

If you think that this is an unlikely example, note the following titles gathered from current scientific journals:

"Effects of nembutal anesthesia on progesterone-4-¹⁴C metabolism in the adrenal gland of the Mongolian Gerbil."

"Nuclear magnetic resonance of chocolate."

"Gas-liquid chromatography of light hydrocarbon gases evolved from french fried potatoes, grown in Iowa."

"Blood-sugar changes in the rabbit following intravenous injection of dust samples from the streets of Milan."

Even without any preparatory search through the literature, the authors of these communications could be reasonably sure of contributing genuine "firsts."

Synthesis vs. Analysis

Apart from the simple observation of facts and the recognition of their importance, the greatest contribution of the typical Problem Finder is synthesis, the intuitive perception of correlations between apparently unrelated facts. In a modest way this is what we attempted to do in our work on the G.A.S. and on pluricausal diseases. Here, most of the basic facts were known long ago; the only new contribution was to find the connections between them. Innumerable early workers had seen adrenal enlargement after this or that intoxication, gastric ulcers after burns, "accidental thymus involution" in children with acute infections, or loss of weight in patients suffering from cancer. In retrospect, all these were manifestations of stress; but in themselves they did not suggest a stereotyped triphasic adaptive reaction in which the

pituitary-adrenocortical system plays a decisive role. Very much the same thing could be said about the pluricausal disease concept.

On the other hand, the principal task of the Problem Solver is necessarily analysis. Once he has selected his subject he tries to break it down by chemical or physical means. He has to get at the finest structural details of his target with the most powerful microscope in order to arrive at its constitution and the mechanisms that make it work. The synthesist wants to know what happens if you put things together; the analyst wants to know the parts into which a thing can be broken down.

Peripheral vs. Tubular Vision

When we look at the point where we expect a change, we can easily miss the dim outlines of even the most important things that turn up elsewhere. When we focus our eyes or mind on any one target, its correlations with its surroundings cannot be appraised. The Problem Finder must have peripheral vision. In order to use it well, he dare not get too close to any one point for fear he will lose sight of its position within the whole and deprive himself of accidentally coming upon even more important things than those he was looking for. That is why his investigation must always remain more superficial than that of the Problem Solver. The latter is actually aided by tubular vision, by the power to block out all irrelevancies and focus on the finest details within the target he has singled out for analysis. But did you not notice

that the experienced histologist always looks at a slide first with the naked eye to see the general outlines before he uses increasingly higher magnifications?

You could never learn what a mouse is like by carefully examining each of its cells separately under the electron microscope any more than you could appreciate the beauty of a cathedral through the chemical analysis of each stone that went into its construction. It would be very useful to know the exact structure of parathyroid hormone, but the chemist would not even have an inducement to start work along these lines had it not been shown first, by simple removal of the parathyroids and the injection of impure parathyroid extracts, that the gland is of vital importance.

Simple vs. Complex Techniques

The Problem Finder likes to use the simplest techniques because they lend themselves particularly to the scanning of broad horizons. They usually show the whole rather than only detail, and, as a rule, they can be quickly learned and quickly performed. Conversely, the Problem Solver prefers sophisticated methods, even if they are much more time-taking and difficult to learn, because only they can get down to the finest constituent elements in which he is interested.

Incidentally, it was characteristic of almost all the great biologists that they developed their own primitive technology. They could not have learned it from courses or books because their subject was new. Lavoisier had to make his own balances, thermometers and calorimeters. Pasteur

proved to be an extraordinarily resourceful inventor of simple bacteriologic techniques, many of which are still in use today. The birth of a new science requires the midwifery of a new technology. Neither Lavoisier nor Pasteur were physicians; the former was a physicist, the latter a chemist; yet, by applying simple techniques of their own sciences to the problems of life, they managed to clarify aspects of medicine no contemporary physician would have dreamed of.

Many vs. Few Endpoints

The Problem Finder likes to use simple techniques whenever possible, not only because with them he can do many tests in little time, but because most of them reveal many endpoints simultaneously and thereby show correlations which are missed as we zero-in on one individual target. In the analysis and exploitation of accidental findings, the logical planning of each new experiment must await the conclusions to be drawn from its predecessor. The average time for the induction of cancers with tissue scaffoldings is one year, whereas an alarm reaction, an acute conditioned necrosis, a thrombohemorrhagic phenomenon, calciphylaxis or calcergy can be detected in a day. It is easy to see why I could make much more progress in studies requiring such short-time tests than in the work on carcinogenic tissue scaffoldings.

For the same reason—all other things being equal—I prefer clinical observation, naked-eye inspection or, at most, light-microscopic examination, to the more specialized electron-microscopic studies or chemical determinations of individual

compounds in living matter. The latter reveal only single or few targets and this interferes with the discovery of unexpected correlations between different points. A blood-sugar determination can reveal only sugar, and only in the blood. This information may be indispensable and all that is needed at a certain stage of a project designed to solve a particular problem; however, this degree of selectivity diminishes the possibility of making chance observations. The light microscopists can see at a glance, within a single field, thousands of details in shape, color and the position of targets relative to each other. In other words, a single histologic slide is a test with innumerable endpoints.

It would be ridiculous to conclude from all this that analytical chemistry is not as good an approach to the study of life as morphology—the choice must depend on what we want to find—but simple statistics will tell you that, of the two, morphology offers a greater chance to those whose curiosity extends beyond the largely predictable. I, for one, always like to gamble on serendipity, the chance of finding a good thing without work while desperately searching for some trifling, if not nonexistent, detail.

Apprenticeship vs. Formal Courses

The Problem Finder's ways are best assimilated by apprenticeship, by working side by side with someone experienced in the art. The Problem Solver, on the other hand, requires much more of the formal training given through organized courses and laboratory work. This is understandable because

the former depends more on instinctive habits of thought, the latter upon the logically designed application of erudition and method.

It has often been said that the Problem Finder's art is not teachable at all, because it depends so much on innate talent. Of course, you cannot teach the totally ungifted, but those who have some talent can certainly develop it better under apprenticeship than without any guidance. The widespread belief that problem finding cannot be taught probably has its root in the fact that it is not teachable in the usual way through books and ordinary organized classroom techniques. It presupposes the day by day close association of teacher and pupil at work. Most subconscious activities must be learned this way, by following an example. To become great in the arts you must have innate talent; you can learn little from books and courses, but work under a great artist certainly helps. The same is true even of subconsciously guided physical activities: athletics, dancing, driving. Even if Einstein had spent his entire life studying the mechanics of an automobile, he could not have driven it through traffic as competently as if he had practiced a few days under the supervision of a simple taxi driver.

Dubious vs. Evident Practical Applications

The future of a totally new discovery can never be appraised as well as that of a project consisting of the application of known principles to the exploitation of a known fact.

But this should not discourage the prospective Problem Finder. As Charles Richet said:

"Young man, I say, if you want to discover a new truth, do not worry about its practical applications. Don't ask yourself how medicine, commerce or industry will profit by it; for, if you do, you will find nothing. You want to solve the problem that you consider important: embark on its solution without worrying about the consequences. Approach the question from its simplest side. Do not let the injunctions of journalists, hygienists, engineers, pharmacists, or physicians stop you. Let them talk. Go straight at your problem by the shortest route. Leave to the practitioners the cumbersome task of conclusions and industrial complications. *Veritas lucet ipsa per se*. Truth is self-sufficient."... "Where would we be if Galvani, instead of touching the legs of his frogs with iron and copper, had wanted to construct a telephone? Soubeiran, in discovering trichlorinated methane, which he called chloroform, did not at all try to find an anesthetic, no more than Röntgen had looked for ways to facilitate surgical operations."

General Practice vs. Specialization in Research

Those who have a very general biologic culture have a better chance of finding entirely new problems than those who specialize. Yet, after completion of their formal university courses, few among today's scientists maintain a working familiarity with many fields. Nowadays, you rarely meet a mature scientist who has retained at least the recent medical graduate's general knowledge of, say histology, physiology, biochemistry, pharmacology, clinical medicine and surgery. Most of them try to specialize and become experts in one

field. This is undoubtedly the sound attitude for the vast majority whose primary interest is the solution of well-defined problems. But we shall always need at least a few general practitioners of medical research, men whose minds are open to the many things that come their way. We shall depend upon them in research just as we shall always require general practitioners of clinical medicine who can look at the patient as a whole and at least determine to which kind of specialist he ought to be sent.

Because of the unpredictability of his results, the Problem Finder must have strong faith in his own talents; to him, sincere modesty about his capacities is a severe handicap. He needs optimism and self-confidence to carry him over the long arid periods during which nothing worthwhile comes up for weeks—sometimes years. He also needs the courage of strong convictions right at the start of his career for his decision not to follow the fashion of extreme specialization. Nowadays, as soon as a beginner enters post-graduate school, most of his teachers will not even mention other possibilities. It will be taken for granted that if he came for advanced training, that means specialization. In the all-important initial interviews, his professors will only try to find out whether they should channel him towards molecular biology, electron microscopy, immunochemistry, electrophysiology or some other métier. It will probably not even occur to them that the candidate may not be the type who should be channelled towards any established trade.

It is characteristic of our *Zeitgeist*, the spirit of our times,

that only recently, one of my most talented young assistants frankly admitted to me that he must learn a speciality for diplomatic reasons. He said that the general practice of medical research is what suits him best, but he feels that he simply has to become an expert in some sophisticated technology, because the prejudice against nonspecialization is so strong that otherwise his career at the University would be jeopardized. I am afraid he was right. Most chiefs get an assistant to carry out some special task in their department but few of them think of training pupils to become chiefs themselves, leaders capable of correlating and inspiring the manifold activities of a modern research team.

Surprise vs. Fulfillment

Perhaps one of the most striking ways of visualizing the essential difference between planned and unplanned research is our own instinctive reaction to success. When we are faced with an unplanned discovery, we are tempted to exclaim: "How in the world did you think of it?" When we learn about a particularly well-designed systematic study which, through the application of complex methods, has led to the solution of a tough problem, we say: "Well done!" or "An extremely competent job!" Nobody will describe the discovery of penicillin as a fine job competently executed, but the synthesis of penicillin must certainly be so described.

Transitional Types

Of course there are few, if any, pure Problem Finders or Problem Solvers; the difference between scientists is one of degree. Even the purest Problem Finder will make some effort to analyze what he has found and even the purest Problem Solver will, in the course of his planned work, usually encounter something unexpected. Yet, the distinction is not merely theoretical, especially to beginners, because it is healthy for them to know that there are two ways to success. They must realize that they do have a choice, and that depending upon it, they will require different types of training. They must also realize that whichever path they select, they have nothing to be ashamed or proud of for the two ways are equally important facets of the same endeavor.

In fact, intuitive problem finding and planned problem solving are often inextricably intermixed. Otto Löwi has told me that the idea for his most important experiment on the chemical transmission of nerve impulses came to him one night when he suddenly awoke from profound sleep. He immediately realized the transcendent importance of his intuitive flash and jotted it down on a piece of paper, but next morning, though aware of having had an inspiration, he could not read his scribble. Try as he would, he was unable to remember what the hunch was until the following night, when he again awoke with the same flash of insight. This time, he tried to arouse himself sufficiently to take legible notes, and next day he performed the famous experiment which won

him the Nobel Prize. He showed that if two frog hearts are connected and perfused with the same solution, stimulating the nerve of one heart causes a change in cardiac rhythm which is transmitted to the other heart by the perfusing fluid.

This extremely simple and elegant experimental arrangement, conceived so easily by the subconscious mind, opened an entire new field of research. The possibility of chemical mediation of nervous activity had been suspected before by many scientists (including Löwi himself), but no one could think of a good way to prove it. While Löwi's simple experiment solved one problem by showing that nervous stimuli can be chemically transmitted, it raised many others as to the intimate mechanisms involved. Incidentally, this technique is so logical that it could have been planned, in fact, I always thought it had been, until I learned from Löwi himself that it was not.

The Four Steps in Research

Research usually progresses in four steps, but it is rare for any one scientist to carry a problem through all of them singlehanded:

1. *Seeing.* We may see something new without taking any notice of it. In this case, we are like the man who walks along the street, deep in thought; he sees other pedestrians just enough not to run into them, but he could pass his own brother without recognizing him. This way I saw the triad of the alarm reaction and the phenomenon of calciphylaxis many times before even deciding to take a closer look.

2. *Noticing.* At this point we realize that we have hit upon something noteworthy, but we cannot yet formulate it with sufficient precision to define just what the actual problem is. I guess this was the point we had reached in our work on stress when we realized that our toxic extracts contained no new hormone, but we were still groping about in vain to define what we should be looking for if not a new hormone.

3. *Problem finding.* Then the problem crystallizes and suggests a course of action. In stress research, for example, this happened when we decided to disentangle the mechanism through which a trauma to the leg or scalding of the skin can produce adrenocortical stimulation, thymicolymphatic atrophy and gastric ulcers. This suggested experiments designed to interrupt the pathways (nervous, humoral) through which stimuli are transmitted from one part of the body to another. But we still had no precise idea of just how to go about this.

4. *Problem solving.* Even this last step may entail no complex methodology; for example, the demonstration that stress is mediated through the pituitary, required only the perfecting of the hypophysectomy technique and the preparation of crude pituitary extracts. However, depending on how deep we want to go, problem solving may necessitate all the sophisticated machinery of molecular biology. "Transitional types" of investigators can carry a problem through several of these stages, whereas the pure Problem Solver will usually limit himself to step four. We cannot say that we have really found a problem unless we succeed in developing it at least

enough to show its impact so that Problem Solvers will become interested and take over.

All these steps are indispensable for success, and those who lack the competence or the patience to investigate each problem in depth must surround themselves with a team of colleagues trained in different fields. This is not easy, for people who work side by side in the same Institute tend to develop similar interests. I have been fortunate in this respect because, through lecture tours in many countries and through the visits of many foreign scientists who came to learn our techniques, we managed to establish a rather international team. We have electron microscopists, biochemists and clinicians who can work closely together, overcoming the usual barriers of geographic distance, specialization, language—and even political convictions. Still, to me the greatest thrill will always be *to notice for the first time what everybody has always seen*.

General Summary

I have arrived at the end of my tale and we might as well follow tradition by closing with a summary.

Throughout my life, I have been guided by a precept which is now inscribed over the entrance of our Institute:

*“Ni le prestige de ton sujet
Et la puissance de tes instruments
Ni l'étendue de tes connaissances
Et la précision de tes plans*

THE MECHANISM OF PROBLEM FINDING

*Ne pourront jamais remplacer
L'originalité de ta pensée
Et l'acuité de ton observation."*

Neither the prestige of your subject and
The power of your instruments
Nor the extent of your learnedness and
The precision of your planning
Can substitute for
The originality of your approach and
The keenness of your observation.

The primary purpose of these lectures was to own up to this credo which served me well, for its old message has almost been forgotten. Indeed, sometimes I fear it is in danger of falling into disrepute.

This is a crucial time in the history of science, especially in biology and medicine. Preoccupation with detail and the complex machinery necessary to appraise detail, threatens to kill the art of observation by our natural senses and the gift of the broad-scale co-ordination of highlights. Some people say that the old-fashioned way of doing research has been made obsolete by modern technology. It has been claimed that all those aspects of life that can be seen with the eyes and elucidated by simple experiments have already been described. I have tempted to illustrate by many examples—some from the literature, others from my own experience—that this is not so.

Of course, the application of chemistry and physics, the mathematical analysis of biologic phenomena and the con-

struction of complex instruments have much to offer—no one doubts this; it is the leading principle taught at our universities, it is the most effective path to the solution of the most complex problems, it needs no protagonist. But in order to solve a problem, you must first come to realize that it exists, and in trying to find it, neither logical reasoning nor powerful instruments can help as much as an instinctive awareness, a sense for the importance of some among the many things that everybody can see. That is why I wanted to be the advocate of the naturalist, of the simple observer and correlator of the old school in biology that appears to be threatened with extinction.

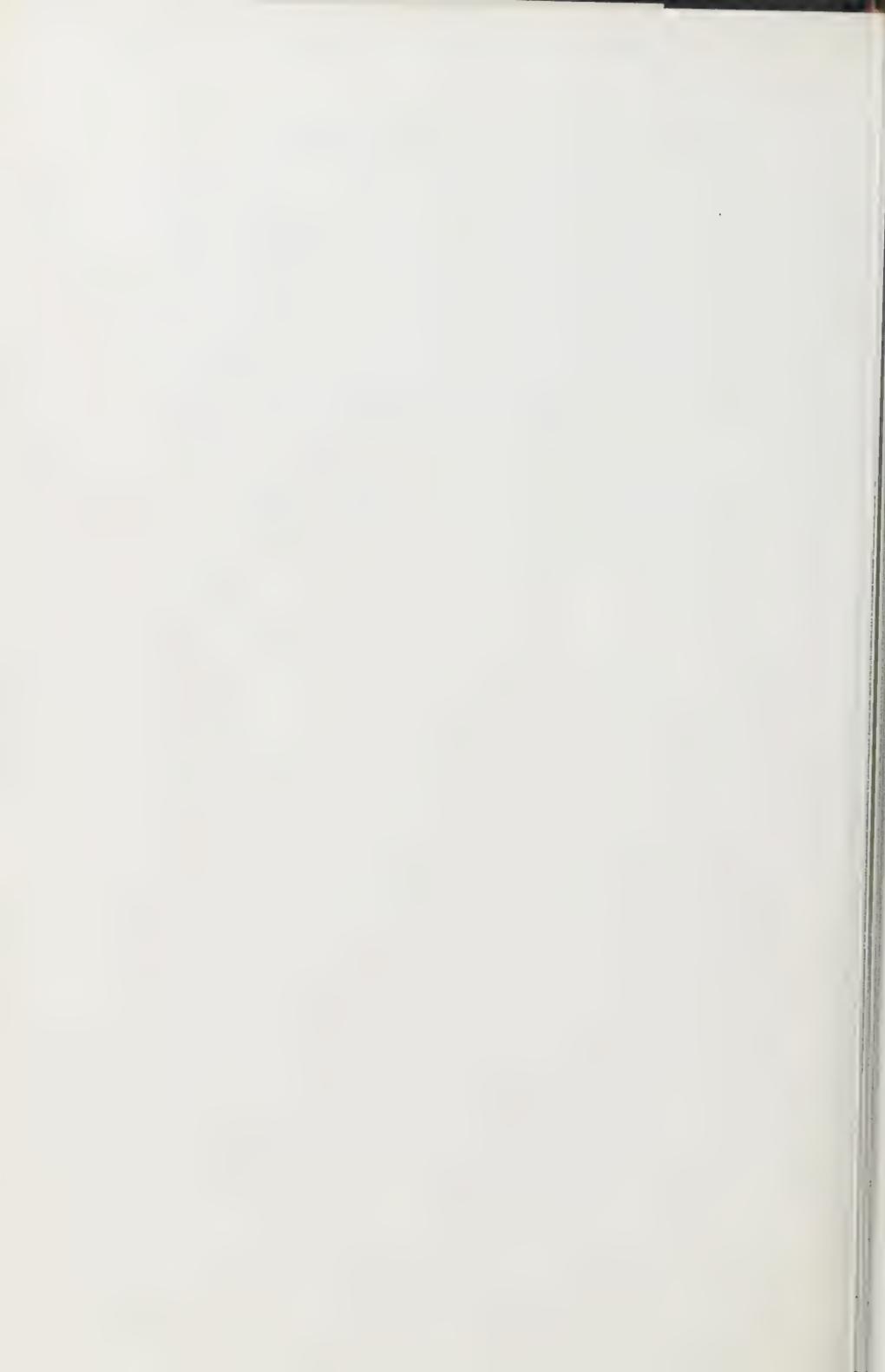
The Incurable Ambivalence

It is not easy for me to fulfill this task because my profound admiration for the Problem Solvers makes my position ambiguous. Since I have said so much in favor of instinct as compared with carefully planned efforts, it may be fitting to illustrate the ambivalence of my feelings by telling you about one instinctive reaction that may perhaps explain the central problem better than this whole lengthy, carefully planned series of lectures:

Among contemporary Problem Solvers, I always had the greatest admiration for Professor Humberto Fernández-Morán, the distinguished electron-microscopist of the University of Chicago. He is both a physician and a physicist who not only uses, but actually builds the most perfected high-power electron microscopes. I have read many of his

remarkable publications, but since I had never met him, I could not resist the temptation to phone him last time I was in Chicago and he kindly invited me to his home for dinner to be followed by a visit to his famous laboratories.

My interest in his research and his colorful personality was further increased by our dinner conversation and it reached a climax at about midnight in his lab when I began to realize the grandeur of his scientific contribution. There was the latest model of his famous diamond knife with which he could physically cut glycogen molecules into smaller sugars. There, I could actually see individual molecules of hemocyanin under his most powerful electron microscope. He explained to me that this was merely the beginning because now he was working on a still more powerful electron microscope which will show objects clearly at a magnification of two million times. I was deeply moved by what I saw and speechless with admiration. But then suddenly my iconoclastic subconscious broke out to the surface and flashed the terrifying thought through my obsolete mind: "Imagine this great genius using all his enormous intellect and knowledge to build an instrument with which to restrict his visual field two million times!"



Atlas

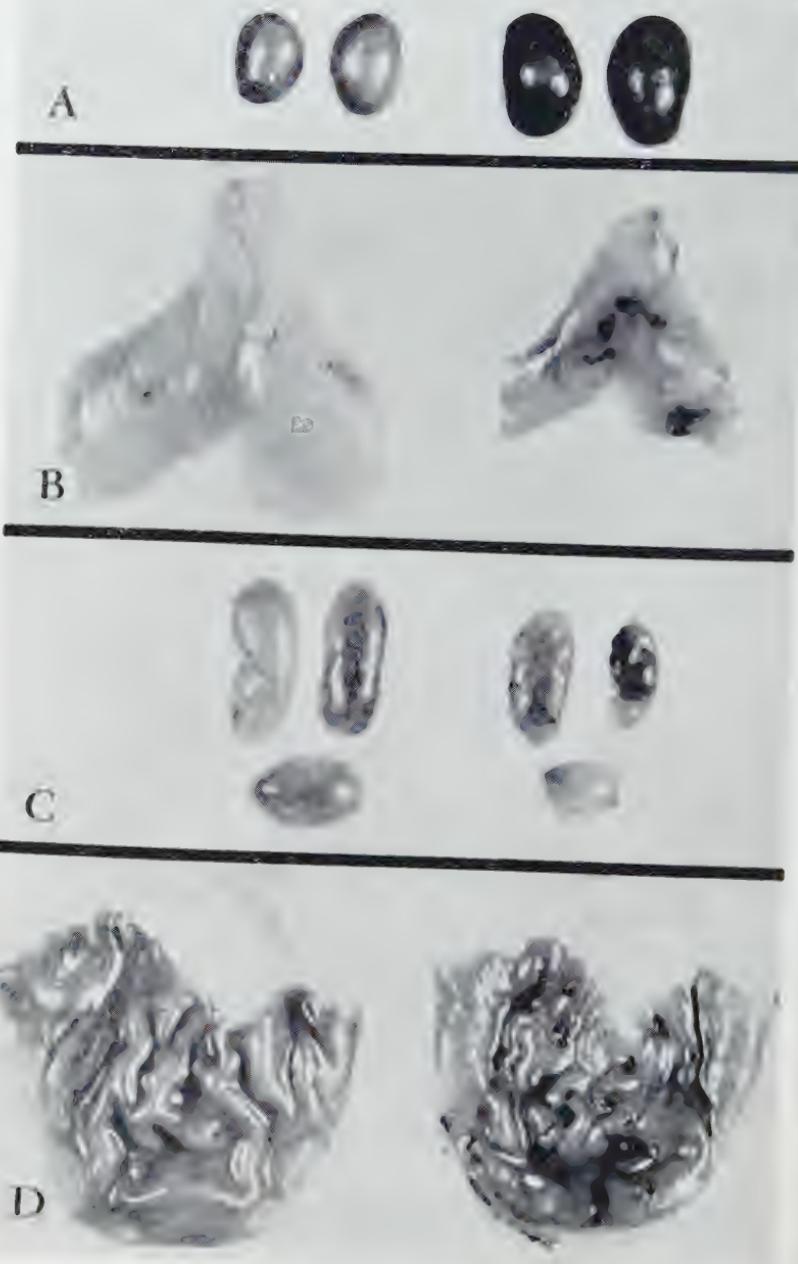


PLATE I

PLATE I. *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 stress of being immobilized
on a board for 24 hours. Note the marked enlargement with loss of whitish
lipids 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). [Selye, H.:
The Story of the Adaptation Syndrome. Montreal: Acta Inc., Med. Publ.,
1952.]

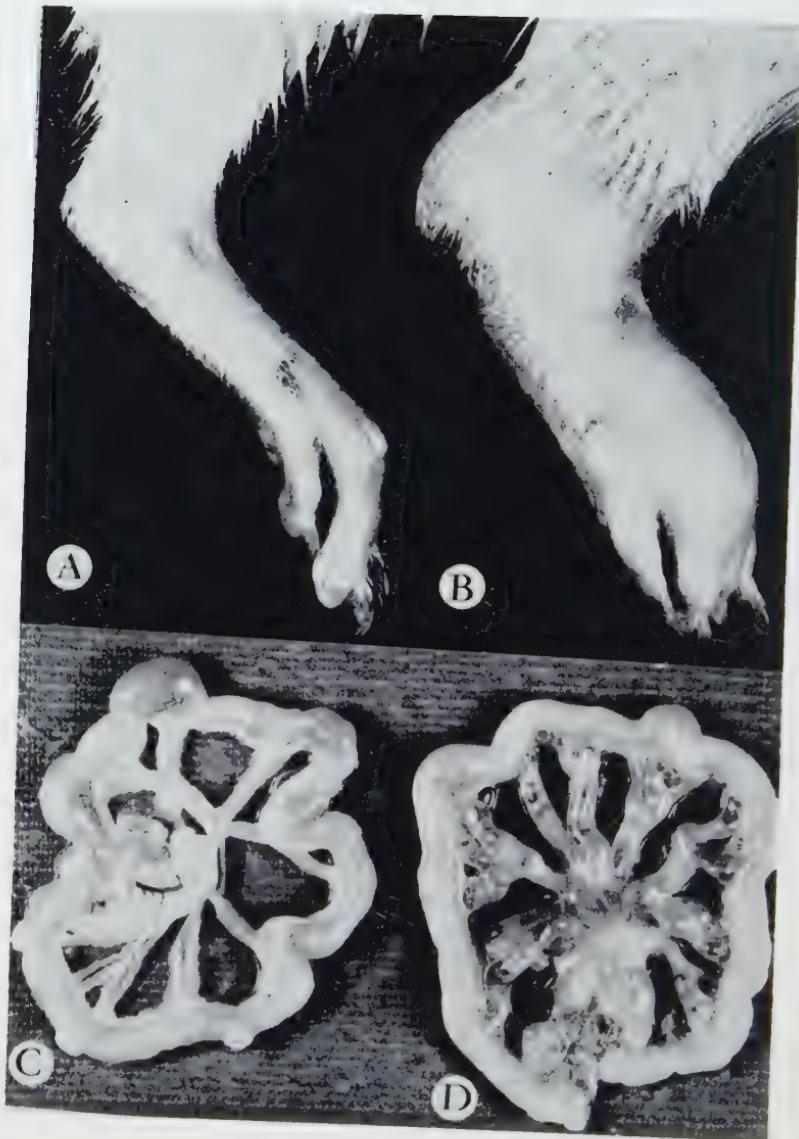


PLATE II

PLATE II. *Inflammation.*— *A*:ACTH-pretreated rat. *B*:Unpretreated control. Both animals were given repeated injections of the same amount of formaldehyde into the paw. The controls developed severe chronic arthritis, whereas the ACTH-pretreated animals showed only a negligible response. *C*:Normal mesenteric vessels of control animal. *D*:Intense periarteritis nodosa in rat given a proinflammatory corticoid. [Selye, H.: Stress. Montreal: Acta Inc., Med. Publ., 1950.]

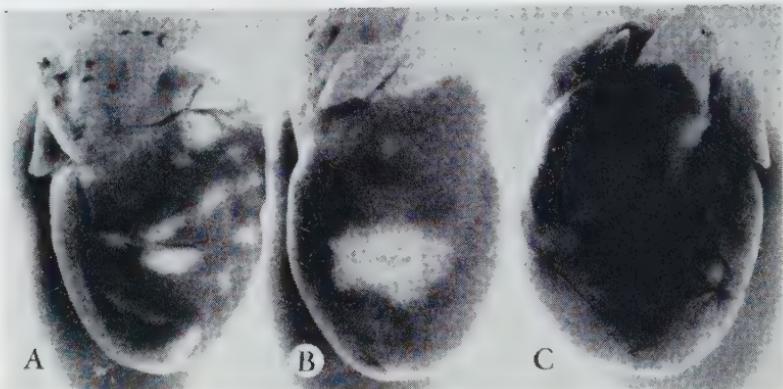


PLATE III. *Chemical production and prevention of cardiac infarcts.*—
A and B: Multiple infarct-like myocardial necroses in two rats treated with corticoids and sodium salts. C: Normal heart of rat which, in addition to the above treatment, was given potassium chloride. [Selye, H. and Renaud, S., *Exp. med. Surg.*, 15, 335 (1957).]

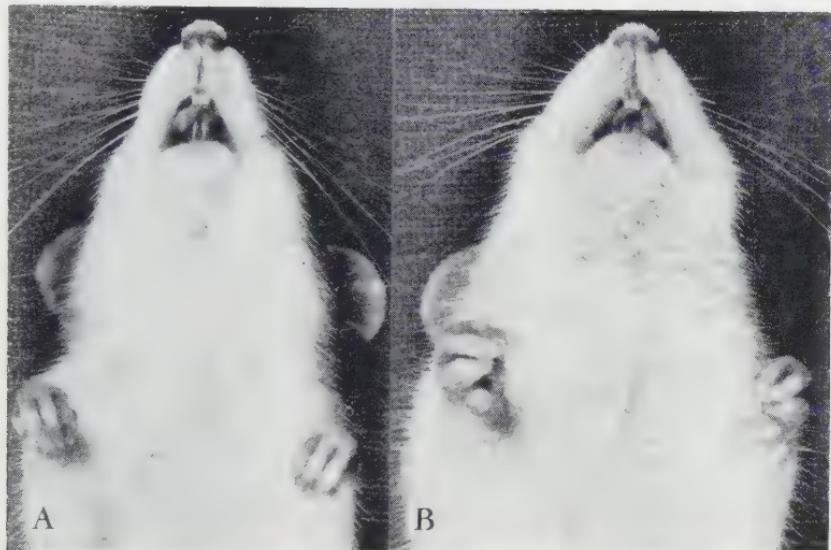


PLATE IV. *Anaphylactoid Inflammation*.— A:Normal control rat.
B:Anaphylactoid inflammation of the snout and paws in a rat given a single peritoneal injection of egg white.

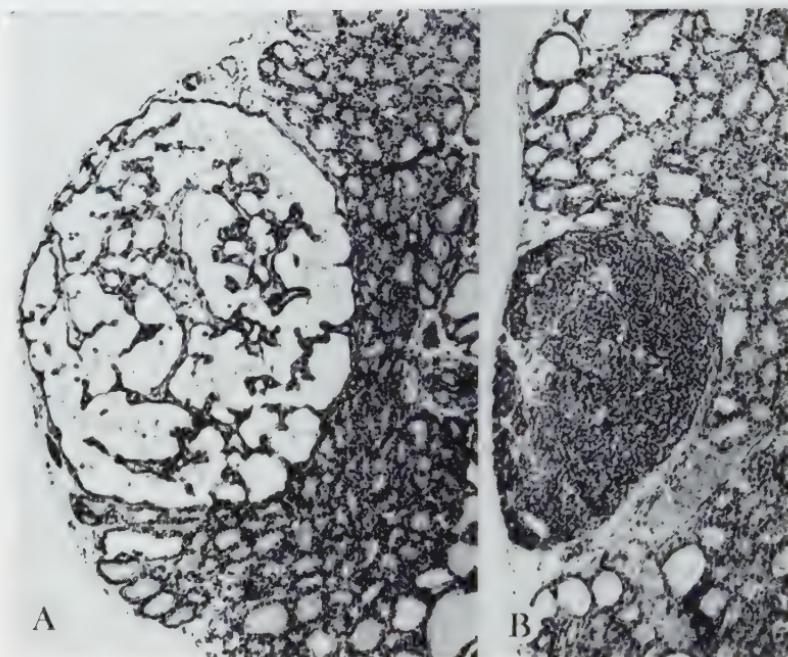


PLATE V. *Cystic parathyroids*.— A:Advanced cystic degeneration of the parathyroid (shown attached to the darker thyroid) in a rat which received large amounts of the vitamin-D derivative dihydrotachysterol (DHT) plus calcium acetate. The cysts have become so voluminous that they perforated into each other. B:Essentially normal parathyroid of a control rat which received an ineffective small dose of DHT plus calcium acetate. The normal solid structure of the parathyroid is preserved. [Selye, H., Rojo Ortega, J. M. and Tuchweber, B.: J. Nutr., 84, 97 (1964).]

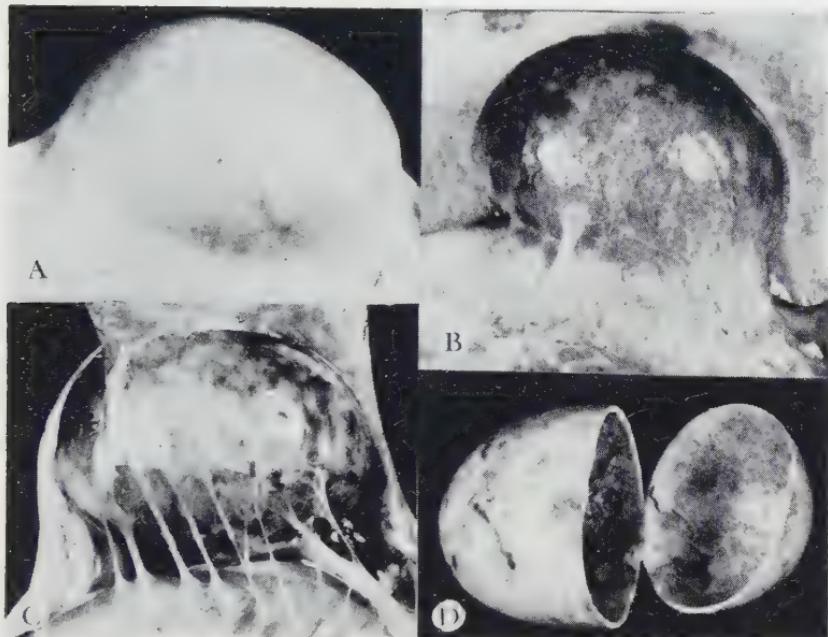


PLATE VI. *The granuloma pouch*.— A:A fully formed granuloma pouch viewed through the intact skin of the back. B:Here, the covering skin was dissected and turned back, exposing the cutaneous muscle. C:The skin muscle has also been dissected and lifted up to show its relation to the actual egg-shaped inflammatory, granuloma membrane beneath it. The nerves and vessels of the pouch are clearly visible, as cords emerging between the ribs. D:After fixation, the granuloma pouch is opened to show its even thickness and the great regularity of the external and internal surfaces. [Selye, H.: J. Amer. med. Ass., 152, 1207 (1953).]



PLATE VII



PLATE VII. *Tissue scaffolding*.— A:Postoperative aspect of the rat while still under anesthesia, after implantation of the tissue scaffolding. To the right of the animal, two additional glass-ring scaffoldings viewed from side and top. B:A typical bony structure removed from the axis of a tissue scaffolding after sixty days. Note the broad base (bottom) from which a strong (in this case bifurcating) tubular bone emerges upward like a spine. C:In a larger tissue scaffolding, sarcoma developed in both basal plates and invaded the central cord. [Selye, H., Lemire, Y. and Bajusz, E.: Wilhelm Roux' Arch. Entwickl.-Mechanik Organis., 151, 572 (1960); and Selye, H., Gabbiani, G. and Tuchweber, B.: Europ. J. Cancerol., 1, 80 (1962).]



PLATE VIII. *Bone formation in the heart*.— A:Ligature around tip of heart. B:Extensive subendocardial bone-plate formation. C:The plate consists of two tables separated by blood-forming bone marrow tissue. [Selye, H., Grasso, S. and Gentile, G.: Eksp. Khir. No. 6, p. 22 (1961).]

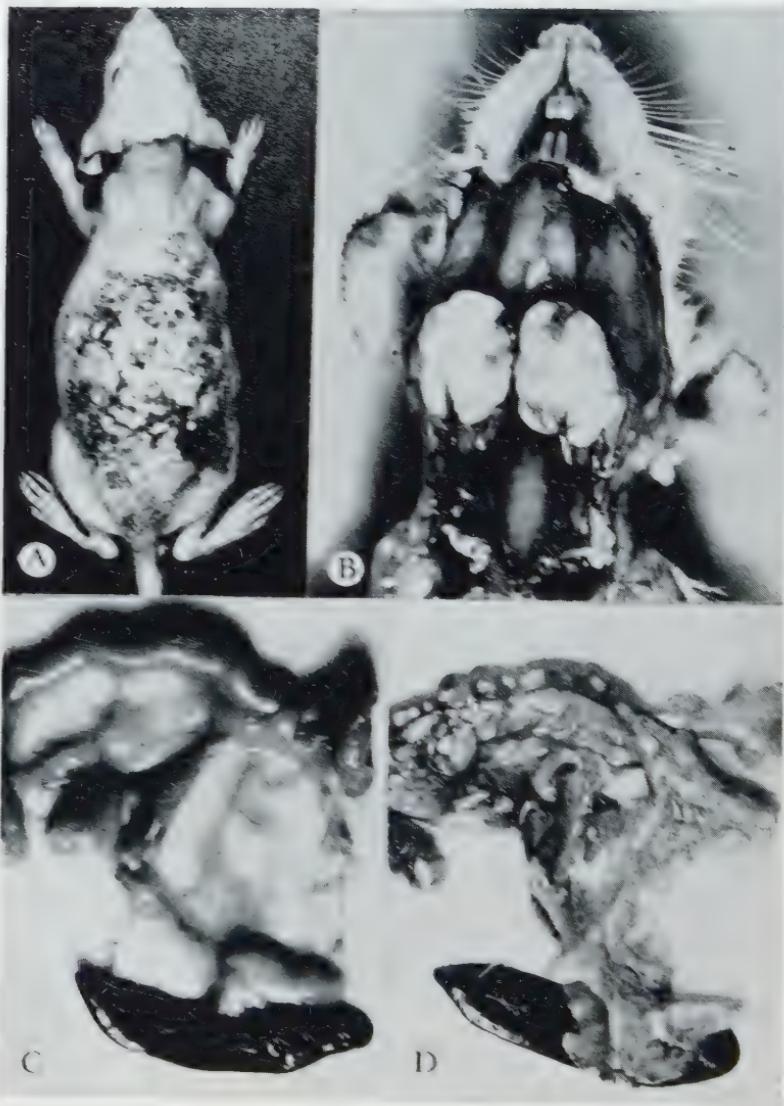


PLATE IX

PLATE IX. *Calciphylaxis*.— The animals shown in this plate have been sensitized for calciphylaxis by the oral administration of the vitamin-D derivative DHT. A: Subcutaneous challenge with iron causes extensive topical calcium impregnation of the skin. B: Systemic challenge with serotonin results in calcification of the salivary glands. C: Normal, almost transparent, pancreas (between duodenum and spleen) of a conditioned but not challenged control. D: Massive calcification of the entire pancreas following intravenous challenge with iron. [Selye, H.: *Exp. med. Surg.*, 24, 191 (1966).]

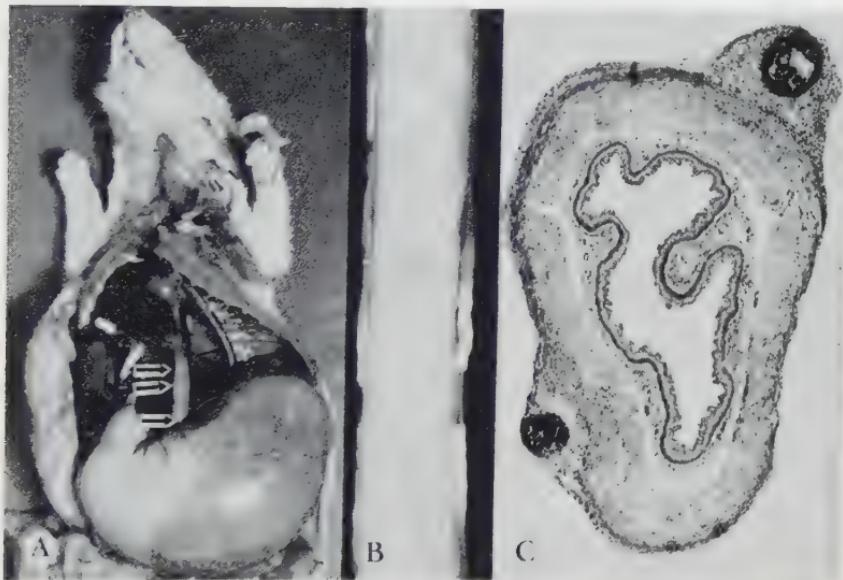


PLATE X. *Systemic calcergy*.— Rat sensitized for systemic calcergy by intravenous injection of lead acetate and challenged with histamine given hypodermically. A: Paralytic dilation of stomach due to destruction of vagus nerves. White calcified nodules (arrows) detectable in left vagus as it descends along esophagus flanked by two vagus nerves whose course is interrupted by heavy white calcium deposits. B: Calcification of vagus nerves (flanking esophagus) seen at loupe magnification. C: Horizontal section through esophagus with heavy calcification (black) in both vagi. [Selye, H., Gabbiani, G. and Tuchweber, B.: *Neurology*, 14, 1084 (1964).]

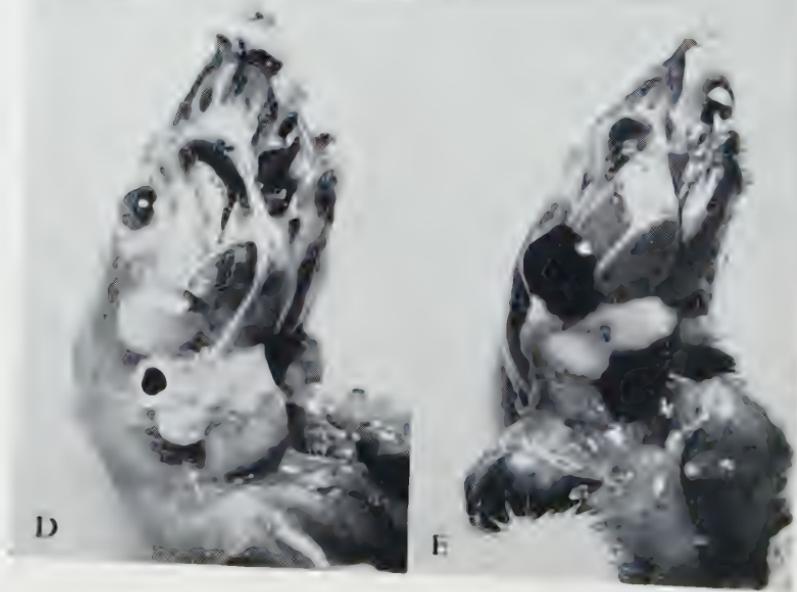
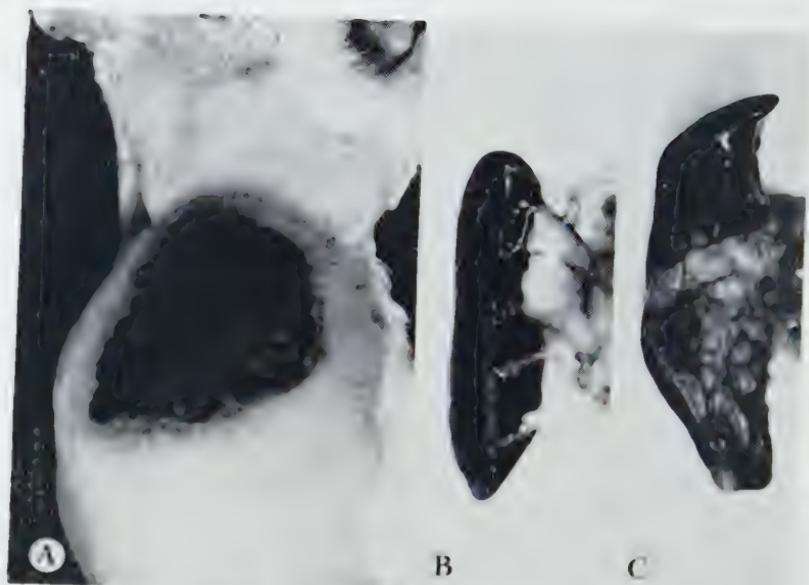


PLATE XI

PLATE XI. *The thrombohemorrhagic phenomenon (THP).*— All animals were sensitized by appropriate metals or by carrageenin given intravenously. *A*:Hypodermic norepinephrine produces extensive local hemorrhage and thromboses in the skin. *B*:Sensitization alone causes no change in the pancreas (shown here adjacent to the spleen). *C*:After sensitization, hypodermic challenge with norepinephrine induces hemorrhagic pancreatitis. *D*:Similar sensitization without challenge leaves the external lacrimal and submaxillary salivary glands unchanged. *E*:After sensitization, hypodermic challenge with serotonin causes severe hemorrhage and thrombosis in both these organs. [Selye, H.: *Exp. med. Surg.*, 24, 191 (1966).]



PLATE XIII. *Acute conditioned necrosis (ACN).*— A:Animal sensitized with dextrin intravenously and challenged with hypertonic NaCl subcutaneously on the back. Extensive liquefaction necrosis of the challenged area. B:Normal skin at the site of the same challenging injection in a rat in which the conditioning by dextrin was abolished by the antiserotonin and antihistamine compound cyproheptadine. [Selye, H. and Rohan, P.: Pflügers Archiv, 291, 1 (1966).]

Glossary of Technical Terms and Abbreviations

In order to bring this lecture series within reach of readers who have had no medical training, this glossary gives at least brief dictionary definitions even of common biologic terms. A more detailed discussion, especially of novel concepts, will be found in the text at the pages indicated in parentheses.

ACN. See *acute conditioned necrosis*.

ACTH. See adrenocorticotrophic hormone.

acton. The simplest identifiable biologic stimulus. It is assumed that even individual molecules may possess several actons, each of which is capable of acting selectively on individual reactons within a biologic target.

acute conditioned necrosis (ACN). Necrosis or tissue death produced by various irritants after appropriate conditioning (sensitization) of tissues, for example with vasopressor compounds, mast-cell dischargers, or mast-cell products.

adaptive hormones. Hormones produced for adaptation to stress.
(See p. 59.)

adrenaline. See epinephrine.

adrenals. Endocrine glands which lie (one on each side) just above the kidneys and consist of an outer cortex (which produces corticoids) and an inner medulla (which secretes epinephrine and related hormones).

GLOSSARY

adrenocorticotropic hormone (ACTH). A pituitary hormone which stimulates the growth and function of the adrenal cortex. (See p. 40.)

alarm reaction (A.R.). The first stage of the adaptation syndrome.

In the G.A.S. it affects the body as a whole; in the L.A.S. it is limited to a part. Correspondingly, we speak of a general and of a local alarm reaction. (See p. 52.)

aldosterone. One of the proinflammatory corticoids. (See p. 61.)

anaphylactoid reaction. A response which resembles anaphylaxis but develops without any previous sensitization by an antigen.

It is called "anaphylactoid inflammation" when it manifests itself primarily by inflammatory changes. (See p. 65.)

anaphylaxis. A hypersensitivity reaction which develops following the injection of an antigen into a sensitized organism.

antagonist. An agent which acts against another agent.

antibiotics. Antibacterial substances, most of which are prepared from molds or fungi (e.g., penicillin, streptomycin).

antibodies. Substances produced in response to infection or to inoculation with antigens. They play an important part in immunity and hypersensitivity.

anti-inflammatory corticoids. Adrenocortical hormones which inhibit inflammation, for example, cortisone or cortisol. They have a marked effect upon glucose metabolism and are therefore also known as *glucocorticoids*. (See p. 61.)

atrophy. Shrinkage of an organ. See involution.

bioassay. Determination of the potency of a substance by comparing its effect on a living organism with that of a standardized preparation.

calcergy. Direct calcification. It is induced by an agent upon contact with tissue and requires no special sensitization.

calciphylaxis. A biologic mechanism through which the organism can send large amounts of calcium and phosphate selectively to certain regions.

GLOSSARY

collagen. An insoluble fibrous protein which is the chief constituent of connective-tissue fibrils.

conditioning factors. Substances or circumstances which influence the response to an agent. (See p. 111.)

connective tissue. A tissue consisting of cells and fine fibers; it is a kind of living cement which connects and reinforces all other tissues. Inflammation develops mainly in connective tissue. (See p. 67.)

corticoids. Hormones of the adrenal cortex. It is customary to subdivide them into the anti-inflammatory glucocorticoids and the proinflammatory mineralocorticoids. (See pp. 59, 60.)

cortisone. One of the anti-inflammatory corticoids. (See p. 61.)

cyst. A sac or vesicle within tissue which has a distinct wall and contains fluid.

desoxycorticosterone. One of the pro-inflammatory corticoids. (See pp. 59-61.)

DHT. An abbreviation for dihydrotachysterol.

dihydrotachysterol. A compound closely related to vitamin D.

diseases of adaptation. Maladies which are principally due to imperfections of the G.A.S., as for instance, to an excessive or insufficient amount, or an improper mixture, of adaptive hormones. (See p. 58.)

ecology. The totality of the relationships between organisms and their environment.

-ectomy. A suffix indicating extirpation, or surgical removal, of an organ (e.g., adrenalectomy = adrenal removal).

edema. A swelling of tissues owing to imbibition with water.

electrolyte. A substance which in solution is capable of conducting the electric current. Water-soluble salts belong to this group.

endocrine kidney. A kidney that has been so modified by surgical operation that it ceases to produce urine but continues to elaborate hormonally active substances. (See p. 79.)

GLOSSARY

endocrines. Ductless glands which secrete their products, the hormones, directly into the blood. (See p. 79.)

epinephrine. One of the hormones of the adrenal medulla. (See p. 108.)

extract. A preparation obtained by mixing tissue, e.g., liver, ovary, etc., or constituents of a drug, with solvents (water, alcohol, etc.) and then separating the soluble from the insoluble material. (See p. 40.)

formalin. An irritating aqueous solution of formaldehyde. (See p. 43.)

G.A.S. Abbreviation for general adaptation syndrome.

general adaptation syndrome. The manifestations of stress in the whole body, as they develop in time. The general adaptation syndrome evolves in three distinct stages: alarm reaction, stage of resistance, stage of exhaustion. (See pp. 34, 53.)

glucocorticoids. See *anti-inflammatory corticoids*.

gonadotrophic hormones. Pituitary hormones which stimulate the growth and function of the gonads (ovary, testis).

granuloma. Inflamed connective tissue.

granuloma pouch. A pouch formed by inflamed connective tissue. It is used as an experimental model of inflammation and is produced in animals by the subcutaneous injection of air and an inflammatory irritant. (See p. 85.)

growth hormone. See somatotrophic hormone.

histology. The study of the minute microscopic structure of tissues.

hormones. Chemical substances released into the blood by the endocrine glands to stimulate and coordinate distant organs. Bodily growth, metabolism, resistance to stress, and sexual functions are largely regulated by hormones. (See p. 40.)

5-HT. See *serotonin*.

hypercalcemia. An increase of the blood calcium level above normal.

GLOSSARY

hypophysectomy. Removal of the hypophysis, or pituitary.

hypophysis. Synonym for pituitary.

inflammation. The typical reaction of tissue (particularly of connective tissue) to injury. Its main purpose is to barricade off and to destroy the injurious agent by which it was elicited. (See p. 67.)

insulin. The antidiabetic hormone produced by the pancreas.

intuition. Knowledge obtained without recourse to conscious reasoning. Immediate apprehension or cognition, as contrasted with speculative or mediate knowing. A hunch.

involution. Natural shrinkage or decline of an organ. See *atrophy*.

L.A.S. Abbreviation for local adaptation syndrome.

local adaptation syndrome. The manifestations of stress in a limited part of the body as they develop in time. The local adaptation syndrome evolves in three stages, characterized mainly by inflammation, degeneration, or death of cell-groups in the directly affected part. (See p. 89.)

lymphatic tissues. Tissues containing mainly lymph cells, for example, the thymus, the lymph nodes. (See p. 55.)

lymph nodes. Nodular organs, consisting of lymphatic tissue, in the groin, under the armpits, along the neck, and in various other parts of the body. (See p. 55.)

mast cell. A hormone-producing cell irregularly distributed throughout the connective tissue. It contains granules which produce hormones and can bind certain substances such as calcium.

mast-cell dischargers. Compounds which cause the mast cells to release their products into the surrounding tissue.

metabolism. The transformation within the body of foodstuff into tissue and energy.

metaplasia. The transformation of one type of tissue into another.

mineralocorticoids. See *pro-inflammatory corticoids*.

morphology. The branch of biology that deals with the form and structure of tissues, comprising anatomy and histology.

GLOSSARY

necrosis. Localized tissue death within a surviving organism.

nephritis. Inflammation of the kidney.

nephrosclerosis. A kidney disease often causing hypertension.
(See p. 61.)

nonspecific. A *nonspecifically formed* change is one which affects all or most parts of a system without selectivity. It is the opposite of a specifically formed change, which affects only one or, at least, few units within a system. A *nonspecifically caused* change is one which can be produced by many or all agents.
(See p. 50.)

parathyroids. Small endocrine glands, closely attached to the thyroid, which regulate calcium and phosphate metabolism.

pathogen. A disease-producing agent.

pathology. The study of disease.

periarteritis nodosa. A form of arterial inflammation.

pituitary. A little endocrine gland embedded in the bones of the skull just below the brain; also known as *hypophysis*. (See p. 39.)

pro-inflammatory corticoids. Adrenocortical hormones which stimulate inflammation, as for example, aldosterone, desoxycorticosterone. They have a marked effect upon mineral metabolism, and are therefore also known as *mineralocorticoids*. (See pp. 60, 61.)

reaction. In biology, the response of the body, or one of its parts, to stimulation.

reacton. The smallest identifiable biologic target. It is the primary subcellular unit in living matter, which still exhibits the property of responding selectively to stimulation. (See p. 123.)

rheumatic fever. An acute and often recurring disease, most common in children and young adults. It is characterized by fever with inflammation of the joints and the heart valves. (See p. 59.)

scleroderma. A skin disease characterized by connective-tissue proliferation and often accompanied by calcium deposition.

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sclerosis. A pathological hardening, usually produced by overgrowth of fibrous tissue, sometimes with calcification (as in arteriosclerosis).

serotonin. Also known as 5-hydroxytryptamine or 5-HT. A tissue hormone causing vasoconstriction.

somatic. Pertaining to the body.

somatotrophic hormone (STH). A pituitary substance which stimulates the growth of the body in general and of inflamed connective tissue in particular. Also known as *growth hormone*. (See p. 39.)

specific. A *specifically formed* change is one which affects one or few units within a system, with great selectivity. A *specifically caused* change is one which can be produced only by one or few agents. The term *specific* has no meaning unless we indicate whether it refers to the change itself or to its causation. (See p. 50.)

stage of exhaustion. The final stage of the adaptation syndrome. It may be general or local, depending upon whether the whole body or only a region has been exposed to stress. (See p. 53.)

stage of resistance. The second stage of the adaptation syndrome. It may be general or local, depending upon whether the whole body or only a region has been exposed to stress. (See p. 52.)

steroids. Compounds having a polycyclic structure like that of the sterols, vitamin-D derivatives and certain hormones (e.g., cortisone).

STH. Abbreviation for somatotrophic hormone. The growth hormone.

stimulus. In biology, anything that elicits a reaction in the body.

stress. The sum of all nonspecific changes caused by function, damage, or the rate of wear and tear in the body. In simple terms: the common results of exposure to anything. For example, the bodily changes produced, whether a person is exposed to nervous tension, physical injury, infection, cold, heat, x-rays or anything else. This is what is left when we abstract

GLOSSARY

from the specific changes that are produced only by one or few among these agents.

stressor. That which produces stress. (See p. 55.)

syndrome. A group of symptoms and signs which appear together.

target area. The region upon which a biologic agent acts.

THP. See *thrombohemorrhagic phenomenon.*

thrombohemorrhagic phenomenon (THP). A change characterized by thrombosis and hemorrhage.

thrombosis. Clot formation in a blood vessel during life.

thymicolumphatic. A generic designation for the thymus, the lymph nodes and related structures.

thymus. A large lymphatic organ in the chest. (See p. 55.)

tissue. An aggregate of cells and intercellular substances forming one of the structural materials of the body. Each type of tissue (nervous, muscular, connective) has a different specific structure.

triad. A syndrome consisting of three manifestations. (See p. 40.)

ulcer. Erosion and inflammation on a surface.

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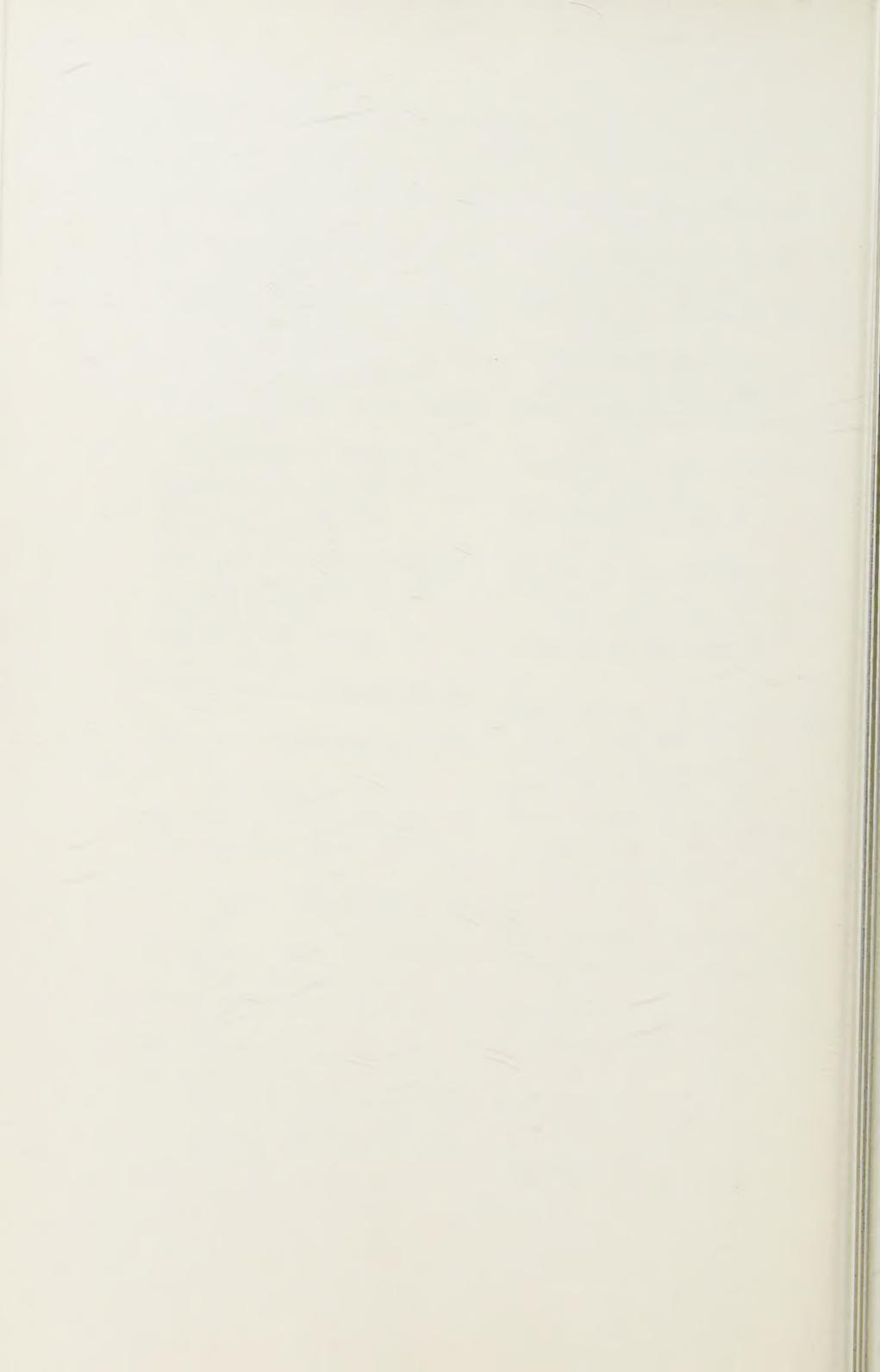
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ABOUT
DR. HANS SELYE

* * *

The publication of this first edition of *IN VIVO* in Canada's Centennial Year coincides with Selye's 60th birthday and the 40th anniversary of his first scientific publication. His famous concept of "biologic stress" has opened countless new avenues in medicine; in addition it has led to yet another even more general concept, namely that of the "pluricausal diseases".

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* * *

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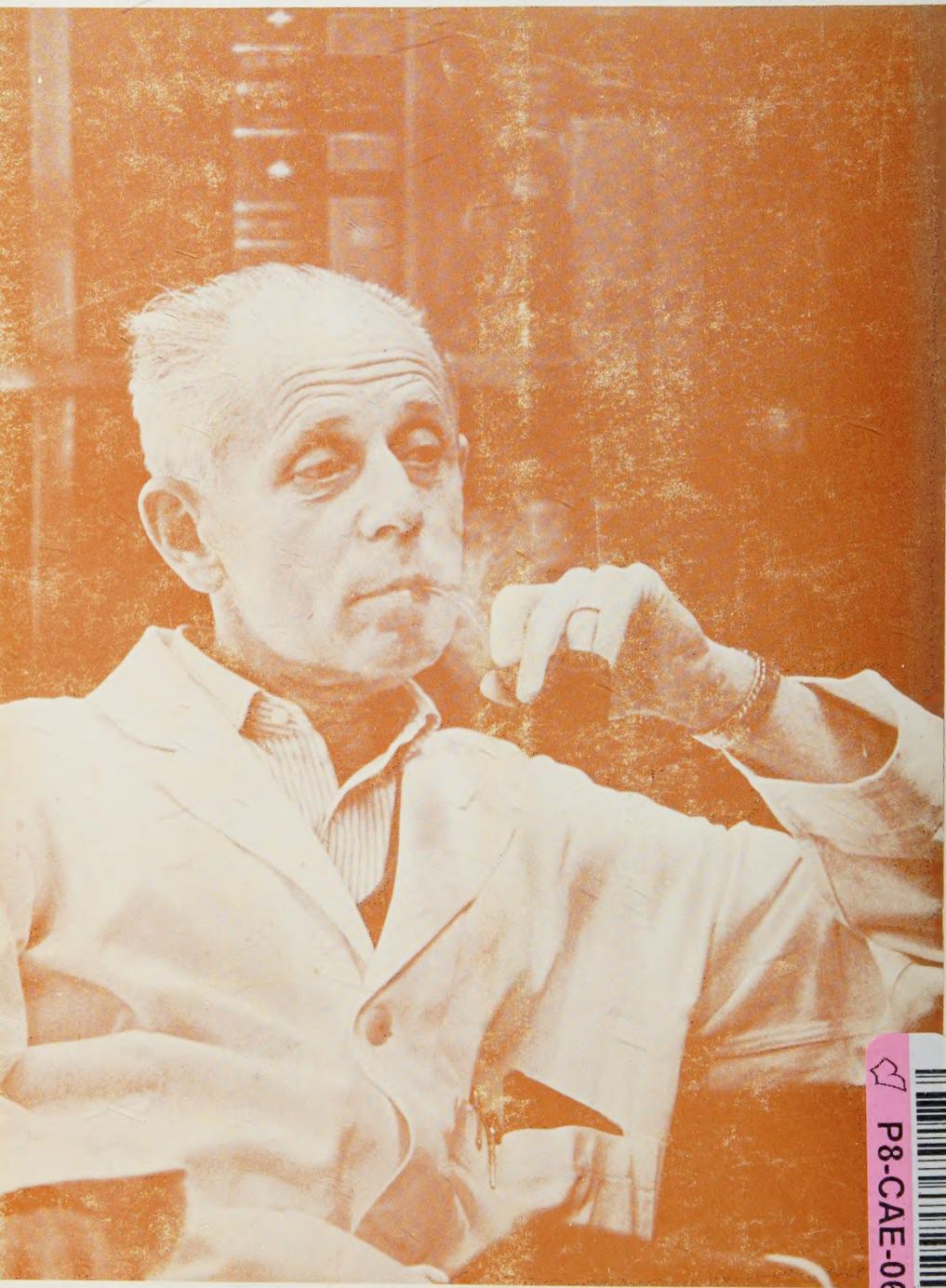
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