CLINICAL ENDOCRINOLOGY

Second Edition

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WITH 274 ILLUSTRATIONS, 6 IN FULL COLOR

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Preface to the Second Edition

THIS VOLUME is an expression of appreciation for the cordial reception accorded the first edition. The expansion of knowledge in several areas of endocrinology during the past few years necessitated extensive revision of virtually all sections and complete rewriting of certain chapters. New material is presented on the following topics, among others: new developments in the field of thyroid pathology and therapy (triiodothyronine; hypothyroidism and cretinism due to abnormal hormone synthesis) and in the field of adrenal pathology and therapy (aldosterone; aldosteronism; classification, diagnosis, and treatment of virilizing adrenal hyperplasia; use of synthetic modified adrenocortical steroids), use of long-acting progesterone derivatives, classification and diagnosis of testicular failure, and others.

No significant changes have been made in the organization of the text or in the manner of presentation, except for the inclusion of brief comments on the involvement of endocrine glands and the therapeutic use of hormones in "nonendocrine" disorders.

As previously, the bibliography has been selected with the primary aim of referring the reader to recent, stimulating, and comprehensive discussions and not necessarily to the original publication on any topic. Critical reviews are included wherever possible.

We are deeply indebted to many colleagues, students, and other friends for invaluable suggestions and helpful criticism and to the publishers for their unfailing cooperation.

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Preface to the First Edition

WITHIN A RELATIVELY BRIEF PERIOD, clinical endocrinology has developed from a rather disreputable—although precocious—stepchild of medicine into a highly respected and dignified member of the family of medical specialties. This remarkable metamorphosis is one of the most striking examples of the beneficial influence on clinical medicine of the application of the experimental method. It illustrates clearly the practical value of integrated studies by workers trained in the different disciplines of physiology, anatomy, biochemistry, organic chemistry, biology, pathology, and clinical medicine. In few other fields have studies in such a variety of species of experimental animals been so productive of benefit to man. In few other fields have such intensive co-operative enterprises been conducted in the clinic, with such brilliant results. Almost a century ago, Claude Bernard stated that when medicine becomes scientific it must be founded on physiology, and that progress in scientific medicine would depend on application of the experimental method. The current status of clinical endocrinology testifies to the validity of these predictions.

Our present knowledge of endocrine physiology permits a rational and, frequently, a purely objective approach to the diagnosis and treatment of endocrine disorders. Satisfactory methods are now available for quantitative determination of many hormones in blood and urine. Rather precise information is available concerning the functional interrelationships of endocrine glands and the metabolic effects of various hormones and of aberrations of endocrine function. Studies in these directions constitute an ideal basis for accurate and often quantitative functional diagnosis. In order to take full advantage of available diagnostic procedures and to appreciate clearly specific therapeutic indications and contraindications, one must have a thorough understanding of endocrine physiology. One need mention only the remarkable recent advances in the diagnosis and treatment of disorders of the adrenals and thyroid to substantiate this statement.

It is our conviction, therefore, that clinical endocrine disorders can be understood fully only when seen as problems in pathologic physiology. This book has been written from that point of view. It represents a synthesis of the experiences and interests of the authors in physiology, clinical endocrinology, and biochemistry.

The integrated approach to endocrinology reflects our experience in presenting the subject to undergraduate and graduate students and practitioners over many years. The response of these students stimulated the preparation of this book.

Each gland is discussed in the time-honored sequence of the medical curriculum: embryology, anatomy, histology, physiology, pathology, pathologic physiology, diagnosis, and treatment. The undergraduate student will thus find here a text which he can read in consecutive order.

The practicing physician, on the other hand, primarily interested in accurate diagnosis and proper treatment, will find not only the best approaches to diagnosis and advice as to effective therapy, but also a concise explanation of the rationale underlying the diagnostic procedures and therapeutic recommendations. The index has been prepared with the aim of enabling the reader to secure this information readily.

The practical needs of clinicians have been kept paramount throughout the book. Treatment is taken up specifically in every chapter for every syndrome discussed. The illustrations are largely original and largely photographs of patients with typical diseases rather than rare or bizarre conditions. Differential diagnosis has been emphasized and tables of differential diagnosis are included which we hope will be convenient.

Virtually every statement and recommendation we have made is borne out by personal experience. We have also attempted to indicate our personal views on controversial matters, and to point out clearly deficiencies in present-day knowledge where they exist.

Our grateful thanks are due the many colleagues who have made this book possible, some by permitting use of illustrative material, and all by their intellectual contributions. We owe a debt of gratitude, also, to the many students whose ideas and enthusiasm have been a constant source of pleasure and inspiration.

Endocrinology could not have attained its present status without the extensive contributions of a number of pharmaceutical concerns. They have placed at the disposal of physiologists and clinicians large supplies of valuable and otherwise unavailable hormonal products and have subsidized research in both laboratory and clinic in a truly academic spirit. We acknowledge with gratitude the invaluable help, both in materials and in grants-in-aid, received for our own experimental and clinical work from these sources.

Our thanks, mingled with commiseration, are extended to the publishers; their patience and sympathetic understanding have been limitless.

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Introduction

ENDOCRINOLOGY IS DEFINED as the study of the glands of internal secretion, and clinical endocrinology as the study of diseases of these glands. Such a definition, although it appears to delineate the field adequately, is not entirely satisfactory. The "gland of internal secretion," and its secretion, the "hormone," defy precise definition. If we employ the term "gland" in its conventional morphologic sense, as an epithelial or endothelial structure, the posterior pituitary gland is removed from this category. If one seeks a functional definition, he will find Bayliss and Starling defining a hormone as "any substance normally produced in the cells of some part of the body and carried by the blood stream to distant parts, which it affects for the good of the organism as a whole." If this teleological phraseology seems out of place, one need but replace the words "for the good of the whole" by "homeostasis" in order to modernize this definition. However, it is so broad as to include almost all tissues of the body, thereby becoming useless. Thus, carbon dioxide has been referred to as a hormone of respiration quite legitimately on the basis of such a definition. Substances liberated or secreted by traumatized tissue have been referred to as "wound hormones." Acetylcholine could claim a place in the hormone galaxy. Where are the ever-increasing "gastrointestinal hormones" to be placed?

We have to resign ourselves to the position that membership in the "endocrine system" is accorded by convention and agreement, subject to change in general attitude. At the present time the following tissues are included: the anterior and posterior pituitary, thyroid, parathyroid, adrenal cortex and adrenal medulla, the pancreatic islets of Langerhans, the ovaries and testes, and the placenta. Internal secretory functions have occasionally been attributed to the thymus and spleen, but no conclusive evidence to this effect has been produced. The pineal body, once included in this category, has been removed from it, probably permanently; it is a vestigial structure, not a gland of internal secretion.

CLINICAL ENDOCRINOLOGY AND ENDOCRINE PHYSIOLOGY

Clinical endocrinologic observations date back to the beginnings of recorded history. Castration was performed, and the effects of castration were described in the earliest of records, and the similarity of eunuchs and congenital hypogonads was recognized (Matt. 19:32). The first deliberate experimental approach in this field was probably the work of Berthold, who castrated cocks and implanted testes into the capons. It has often been suggested that clinical endocrinology was launched by the famous report by the aging Brown-Sequard of the beneficial effects of testicular extracts that he injected into himself. This was certainly followed by a period of wild empiricism in "organotherapy," with little or no factual basis.

Certainly, the beginnings of endocrinology were clinical, and the foundations of our knowledge of endocrine physiology were laid by clinicians. Long before the discovery of the pituitary growth hormone, the important influence of the pituitary on growth was emphasized by the work of Pierre Marie and Benda on acromegaly and its relation to eosinophilic adenoma of the anterior pituitary. The contribution of clinical pathology to our knowledge of parathyroid physiology makes fascinating reading in Albright's historical essay.*

After the masters of clinicopathologic observation and interpretation came a host of minor deities. Observation was often less astute and, let it be said, less conscientious. Too frequently, a fanciful building was erected on too weak a factual foundation and unwarranted therapeutic conclusions were drawn. Whether such physicians acted in good faith or bad, the attitude of more critical minds toward this situation is best expressed by the term "endocriminology," reputedly coined by Harvey Cushing.

No attempt shall be made here to review the history of experimental physiology of the endocrine glands. Suffice it to state that physiology has repaid with compound interest the debt it owed the clinical pioneers. Modern clinical endocrinology is applied endocrine physiology.

METHODS OF STUDY

Hormones influence growth and development, nervous and metabolic processes. Under "normal" conditions, as long as these processes are integrated, in homeostasis, the contributions of individual hormones to this balanced state are indiscernible. Disease may upset the balance, or disturb the homeostatic state and, in certain instances, an analysis of observations may give some indication of the physiologic action of certain hormones. Definitive information has come from experimentation.

Experimentally, the endocrine balance may be altered deliberately by removal or destruction of a gland. Deficiencies thus produced are corrected by administering the missing hormones. This was originally accomplished by injecting suspensions of the gland, later by glandular extracts. When fractionated extracts, and later chemically pure hormonal substances, were used for replacement therapy, it was found that certain glands elaborate more than one hormone. The endocrine balance can also be upset by administering

* Superior numbers refer to bibliographic items, to be found at the end of each section.

excessive amounts of individual hormones. Much has been learned by this method of investigation.

It has come to be recognized that observations must be interpreted very critically. For example, in certain species (rat) injection of pituitary extracts is followed by an increase in size and insulin content of the islets of Langerhans. This was at first interpreted by some as indicating the presence of a pancreotropic (insulinotropic) hormone of the anterior pituitary. It is now generally accepted that such anterior pituitary extracts cause changes in the peripheral tissues (liver, muscles, blood) which in turn constitute a physiologic stimulus to the islets (p. 39).

Contributions by organic chemists, especially the isolation of chemically pure compounds from glands and of some of their metabolites from body fluids, leading ultimately to the identification and synthesis of hormones, have contributed enormously to the rapid progress in this field.

In Vitro Studies

In investigations designed to pinpoint hormone actions more precisely, increasing use is made of in vitro studies. These include studies on perfused isolated organs, on tissue slices, tissue homogenates, isolated cell fractions (mitochondria, microsomes), and cell-free organ extracts. For example, it has long been known that insulin lowers the level of circulating glucose. A great amount of further information has been obtained by incubating muscle slices (or rat diaphragm) with glucose and insulin, showing the increased glucose uptake by muscle tissue under the influence of insulin. In this instance an effect of the hormone added to the incubation medium can be demonstrated. In other instances adding the hormone to the system in vitro is totally ineffective, but effects on tissues or systems as enumerated above can be demonstrated if the hormone is administered to the living animal, and the effect on tissues or cell constituents is studied subsequently in vitro. An example of this type of investigation is that of thyroxine; adding thyroxine to the incubation medium neither raises the oxygen consumption nor does it exert any other effect. But increase of oxidation as well as other effects can be readily demonstrated at the tissue and at the enzyme level, if tissues from thyroxine treated animals are used.

It is not always easy to extrapolate from effects observed in vitro to what is happening in the intact organism. It must be remembered that in vitro experiments are of necessity carried out under highly artificial conditions. For example, neither in a recirculating perfusion experiment nor in an incubation vessel are metabolites removed, as they usually are by the circulating blood in the intact animal. This may create totally artificial equilibria between substrate and the metabolites originating from the actions of the hormone upon the substrate. There are evidently other factors too numerous to recount here, which contribute to the artificial nature of the in vitro experiment. In many instances there is strong evidence that the effects indicated in an in vitro experiment actually occur in vivo; the case of insulin action on muscle, quoted above, is an example. In other instances, the potentialities revealed by the in vitro experiment are not, or are only to a minor extent, realized in vivo. For example, it is known that following intravenous injection of estrogenic hormones they are rapidly cleared from the blood, and neither urinary excretion nor tissue analysis can, in balance, account for the loss. It was then found that upon incubation of an estrogenic hormone with liver tissue in vitro, the estrogen is rapidly metabolized (destroyed, inactivated). Yet in vivo this inactivation or destruction of the estrogen by liver plays but a minor role in short term, "acute" experiments; the rapid, immediate "disappearance" of the hormone is due preponderantly to biliary excretion.

It is therefore well to remember that an in vitro experiment will show what a tissue is capable of doing, or how a tissue is capable of reacting, but does not necessarily indicate that such is happening in vivo.

MODE OF ACTION OF HORMONES

It is often stated that hormones influence the activity or extent of certain processes in the body, but do not appear to initiate such processes. Hormones have therefore been likened to catalysts. The example of the thyroid hormone is often cited in this connection. The amount of this hormone in the circulation determines the level of oxidations, but the latter are merely lowered and not abolished by complete absence of thyroid hormone. In many instances the quantitative changes effected by a hormone cover so wide a range, raising the level of activity of a process from almost zero to ++++, that what actually is a quantitative change appears to be qualitative at first sight. This is well illustrated by the changes in function and enzymatic activity of the uterine and vaginal mucosa induced by estrogens and progesterone.

There is still considerable doubt as to the actual mechanism of hormone action on target organs. We do not know whether all hormones enter the cells or rather exert an effect by acting on the cell surface. It has been amply shown that hormones specifically influence the action of certain enzyme systems; numerous examples will be found throughout this book. Many of the known physiologic effects of hormones are evidently mediated by such effects on enzyme activities. However, this does not tell us how this effect on enzyme activity is brought about and the question as to the mode of action of a hormone is as yet unanswered. For a stimulating critical analysis of the problems of the mode of action of hormones, see O. Hechter.[2]

HORMONE AND TARGET ORGAN

The action of a hormone is gauged by the morphologic and/or functional response of a target organ. For example, estrogenic hormone increases the size (weight) of the uterus, which is one of the target organs of estrogenic hormones. The processes involved are complex. The increase in size and weight may be due to water retention (which involves changes in the electrolyte content of the tissue) or to tissue growth. Actually, both phenomena are involved.

The magnitude of response of a target organ is usually proportional to the amount of hormone administered, a greater amount eliciting a proportionally greater response. Frequently the dose-response relationship is linear, if the logarithm of the dose is plotted against the response. This quantitative relationship of course holds true only over a limited dosage range; further increase causes flattening out or plateauing of the curve. If increasing amounts of an estrogenic hormone are administered, the uterine weight will at first increase in proportion to the amount administered. However, a uterine weight will be reached which cannot be increased by increasing the dose. In most instances, the maximum effect obtainable is dependent on inherent qualities of the target organ. In certain instances there is reason to believe that either the quantity of specific enzymes or of substrates in the tissue are limiting factors.

The response of the target organ is dependent not only on hormonal, but also on nervous stimuli. Moreover, nutritional factors play an important role, influencing either the responsiveness of the target organ or the secretion of the hormone. A number of factors may thus contribute to what appears clinically as a hormonal deficiency. Inadequate secretion of a hormone may be caused by primary disease of the endocrine gland itself. On the other hand, the gland may be intact and intrinsically capable of normal function but may be nonfunctioning because of nutritional deficiencies. For example, hypopituitarism may be due to pituitary tumors in some cases and to severe undernutrition in others. Nutritional deficiencies may prevent adequate response of the target organ; for example, in certain species the uterus fails to respond normally to estrogenic stimulation in the absence of folic acid. Thyroid hormone production is stimulated by thyrotropic hormone, but if no elemental iodine is available within the thyroid cell, normal or even excessive amounts of thyrotropic hormone cannot induce the target response.

There is as yet little precise information regarding the influence of nervous factors upon target organ responsiveness. It appears probable that certain hormonal effects might be affected by the vasomotor status of the target organ. For example, psychogenic amenorrhea is particularly resistant to estrogenic therapy. It would appear that nervous influences in such cases decrease the responsiveness of the uterine and vaginal mucosa to the hormonal stimulus; whether or not this effect is mediated by vasomotor nerves is not known.

Certain types of target irresponsiveness have aroused considerable interest, because the clinical picture of a well-defined hormonal deficiency may be mimicked. Tetany due to "pseudohypoparathyroidism" is characterized by hypocalcemia and all signs and symptoms of true hypoparathyroid tetany. However, the parathyroids are morphologically intact and appear to secrete normally, but the target mechanisms are defective. In "nephrogenic diabetes insipidus" there is no deficiency of secretion of antidiuretic hormone, but a defect of the kidney tubule that renders it irresponsive to antidiuretic hormone. Similar target organ irresponsiveness to male sex hormone has been observed by us.

THE ROLE OF THE NERVOUS SYSTEM

Reference has been made above to the role of the nervous system in determining or influencing hormonal effects. However, we must conceive of the role of the nervous system in hormone production and release in a much broader sense. Firstly, certain hormones are actually elaborated in and secreted by nerve cells; epinephrine and norepinephrine are not only manufactured and secreted by the adrenal medulla (itself a differentiated and specialized part of the nervous system) but by ganglion cells, and probably by brain cells as well. Oxytocin and vasopressin are elaborated in certain hypothalamic nuclei. Whether other neurosecretions such as acetylcholine or serotonin are to be considered as neurally secreted hormones is a matter of definition. Secondly, neurosecretory products not conventionally referred to as

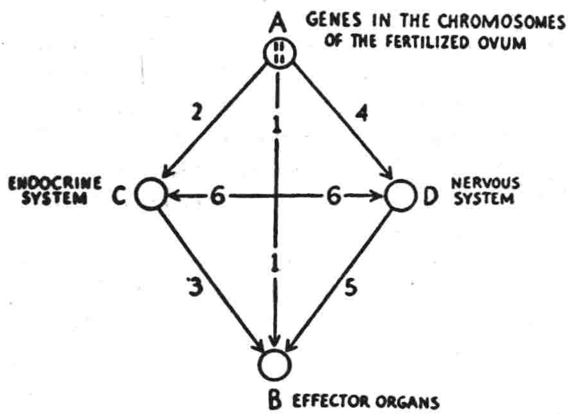

FIG. 1. Interrelations of endocrine system, nervous system, target organs, and genetic factors. (From J. Bauer, *Constitution and Disease,* 2nd ed., New York, Grune and Stratton, 1945.)

hormones but as "neurohumors" are elaborated in certain hypothalamic nuclei; they appear to pass along nerve fibers and to be transferred to the blood of the portal system of the pituitary stalk; thus they reach the parenchyma of the anterior pituitary and stimulate secretion of anterior pituitary hormones. In view of the fact that the hypothalamic nuclei are in nervous connection with higher brain centers, the latter can influence the liberation of those neurohumors and thus indirectly that of pituitary tropic hormones, and ultimately the secretion of gonads, thyroid, and adrenal cortex.

HEREDITY

Genetic factors may determine the level of function of endocrine glands or of target response, or may influence the nervous component. These relations are indicated in Fig. 1. Longitudinal growth may be considered as an