ENDOCRINE DISORDERS

A PATHOPHYSIOLOGIC APPROACH

WILL G. RYAN

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Endocrine Disorders: A Pathophysiologic Approach

by

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DEDICATED TO
"B," and all she means to me.
Ted, for keeping me intellectually well fed.
Agnes, who taught me to "agress."
Anne, Will Jr., and Billy, for being just a
little bit silly.

Foreword

DOCTOR FULLER ALBRIGHT, the late great clinical endocrinologist, concluded a presentation with a projected slide which stated, "I HAVE TOLD YOU MORE THAN I KNOW!" To tell more than one knows, for too many of us, is all too easy. In this volume, Dr. Will G. Ryan has succeeded in a far more rigorous task; he has told *less* than he knows. From the huge mass of endocrine pathophysiology and clinical endocrinology he has culled the core concepts and facts. He has presented them simply (not simplistically) and as accurately as a rapidly expanding body of knowledge will allow. The result is an admirable foundation upon which a sturdy structure may be built. It should serve well those students, young as well as superannuated, who are seeking a solid introduction to modern clinical endocrinology.

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Center

Preface

A ONE-MAN AUTHORSHIP of any text attempting to cover the disciplines of endocrinology and metabolism is a bodacious endeavor and I hope that I have accomplished this to an adequate degree without too many sins of omission or commission. The book is intended to be an introductory text for students, who likely have already had some exposure to the subject matter in physiology and other "basic" sciences, and a review for the internist or generalist, for whom I hope that the subject matter is sufficiently sophisticated, current and concise to be consulted when not having the time to tackle weightier tomes. The book is in no way intended to be competitive with multiauthored standard texts, but rather an "aperitif" to enhance the digestion of more detailed subject matter. A selected list of general references appears at the end of the last chapter.

The book is written from the viewpoint of one who has had about fifteen years of experience in both research and clinical practice of endocrinology and I have tried to emphasize the subject matter appropriately.

It seemed inappropriate to discuss pathophysiology without at least a brief review of physiology, and clinical application is extensively used.

A possible shortcoming in a book such as this is the small number of illustrations. Therefore, the beginning student may wish to have at hand the beautiful illustrations of F. Netter in *The Ciba Collection of Medical Illustrations.*

I hope that the average reader will learn as much from reading as I have learned from writing this treatise and I expect that because of this experience, subsequent editions will be better. Finally I would like to express appreciation to my colleagues, Doctors T. B. Schwartz, John T. Garland and Gretajo Northrop for their review of certain sections and helpful comments, and to Ms. Karen Lee Williams for her expert secretarial and other support.

WILL G. RYAN

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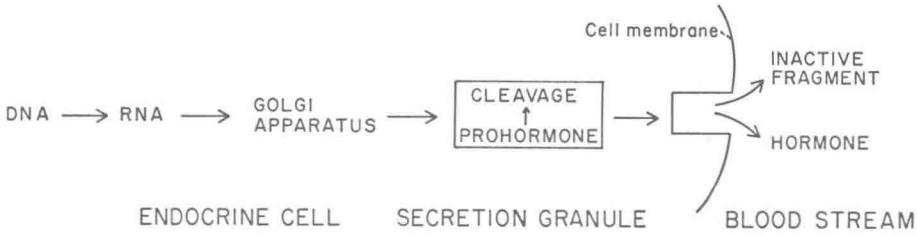
Introduction

ENDOCRINOLOGY, the study of the glands of internal secretion, is a rapidly developing field and therefore our concepts of what constitutes endocrinology are evolving or changing almost daily. The classic concept of endocrinology is the study of recognizable groups of cells shaped into an organ called a gland which secretes a substance called a hormone (from the Greek word *hormeos* meaning "I excite") which travels through the blood to various areas in the body to regulate the function of the cells there. This concept has become considerably more complex with new knowledge of how hormones are manufactured or how they perform their function. The classic glands around which the science of endocrinology is built are: the pituitary, located just beneath and attached to the brain; the thyroid, in the lower portion of the neck; the parathyroids, adjacent to the thyroid gland; the adrenals, situated above each kidney; the islets of Langerhans, situated within the substance of the pancreas; the ovaries in the pelvis; and the testes in the scrotal sac. The pineal gland, situated between the hemispheres of the brain, remained a mysterious organ for many years and it has only recently been discovered that it probably controls sexual function, at least in lower animals. It is of interest that the philosopher Descartes seemingly in desperation decided that the pineal gland was the seat of the soul. The thymus gland which lies in the upper anterior mediastinum has recently been found to secrete a hormonal substance which controls development of the lymphatic system. Its function too was clouded in mystery for many years and it was felt for some time that it caused the death of young infants through a state called "status thymolymphaticus," a term which has subsequently been abandoned.

Manufacture of Hormones by Endocrine Cells

Peptide hormones, like other proteins, are manufactured in the ribosomes under the control of messenger RNA and are packaged at or near the Golgi apparatus into secretion

Fig. 1-1.—Diagram of sequence of peptide hormone secretion from gland cell.



granules. Some hormones appear to be manufactured in a larger form called prohormones, the most notable and first recognized among which is proinsulin. Within the secretion granule these prohormones are degraded to the active hormone. The granule then migrates to the periphery where it apparently fuses with the cell membrane and then discharges its contents into the bloodstream (Fig. 1–1). The preceding is probably true of most peptide hormones. The secretion of steroid hormones is somewhat less clear, and they do not appear in secretion granules.

Mechanism of Action of Hormones

Present knowledge would appear to show two main types of action of hormones: that of the peptide hormones and that of the steroid hormones. The peptide hormones, which mostly circulate in the free state, fit into specific receptors on the cell wall (Fig. 1–2). They then in some way (through a transducer of some kind perhaps) activate cell membrane bound adenyl cyclase which catalyzes the conversion of ATP to cyclic AMP. Cyclic AMP then activates a protein kinase which in turn converts an inactive form of an enzyme (possibly through phosphorylation) to an active enzyme, which then carries out a primary function of the hormone. The classic or first described example of this is the conversion of inactive phosphorylase to active phosphorylase for the degradation of glycogen in the liver under the influence of glucagon or epinephrine. Subsequent secondary events occurring within the cell are less clear at the present time. Cyclic AMP is inactivated by the enzyme phosphodiesterase which may be inhibited by certain xanthines, thus prolonging its action. Peptide hormones appear to circulate freely within the plasma and attach directly to the cell wall.

The other main example of mechanism of hormone action is that of the steroids (which circulate attached to relatively specific proteins), in which the steroid is released from its carrier protein within the bloodstream, traverses the cell membrane where it is then attached to another steroid receptor protein, which then travels to the nucleus where it in some way causes gene activation or derepression, subsequently stimulating the production of messenger RNA and protein synthesis. The most extensive studies of this have been done in the chick oviduct in its response to estrogen. Thyroid hormone which also circulates attached to a carrier protein appears to act in a similar manner to the steroid hormones but its action at this time is less clear. To emphasize that this is not the complete picture of hormone action, it has been found that the transport of glucose and amino acids into the cell under the influence of insulin occurs promptly without an increase in cyclic AMP. Insulin also appears to *decrease* adenyl cyclase in adipose and other tissues. In regard to the steroids the action of hydrocortisone may be seen within minutes to increase the blood pressure possibly through a direct action on the vascular walls. Thus further investigation into other mechanisms of hormone action is indicated.

The pituitary secretes several hormones, four of which control the function of the thyroid, adrenals and gonads. Because of its multiplicity of functions it was known as the master gland. However, recent evidence has shown that it is largely under control of the hypothalamus and the hypothalamus is probably at least partially controlled by many of the other portions of the brain. Thus it can be seen that the nervous and humoral systems of the body are closely interrelated and provide to a large measure the control or integrative functions of the body. As mentioned previously, the classic concept of glands and hormones and their interrelationships has become somewhat less clear by the addition of new knowledge. For instance, in the kidney the juxtaglomerular apparatus cells under the influence of a decrease in blood pressure or body sodium (and other conditions to be discussed later) release an

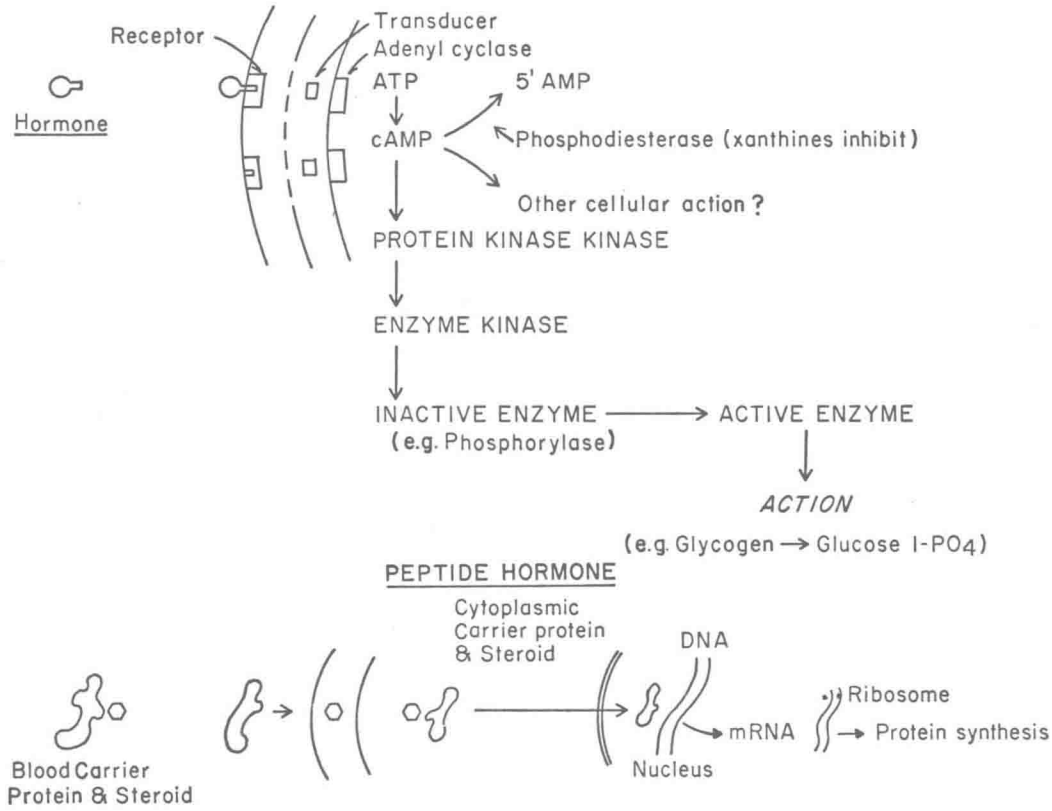


Fig. 1-2.—Proposed mechanisms of action of peptide and steroid hormones.

enzyme called renin which by acting on a peptide in the blood produces angiotensin I, which in turn is acted on by another converting enzyme to produce a powerful vasoconstrictive substance, angiotensin II. Angiotensin II in turn increases blood pressure by a direct effect on the smooth muscle of the blood vessels causing them to constrict, and also acts to stimulate the adrenals, which produce a salt retaining hormone (aldosterone), which in turn helps to maintain plasma volume. The kidney also produces another hormone called erythropoietin which stimulates the production of red blood cells and possibly other hormones as well..

In the gut are located cells which are not discrete glandular structures but nevertheless produce hormones which control the function of both the endocrine and exocrine pancreas, gallbladder and stomach. As another example of less precisely clear glandular function pituitary growth hormone does not act to produce growth itself but rather acts on the liver to produce a substance called somatomedin (of which there may be more than one type) which then in turn acts on cartilage, bone and other structures to produce growth. Lastly, a group of fatty acid substances called prostaglandins, so named because they were discovered in high concentrations in the prostate, are found in most cells throughout the body and have potent

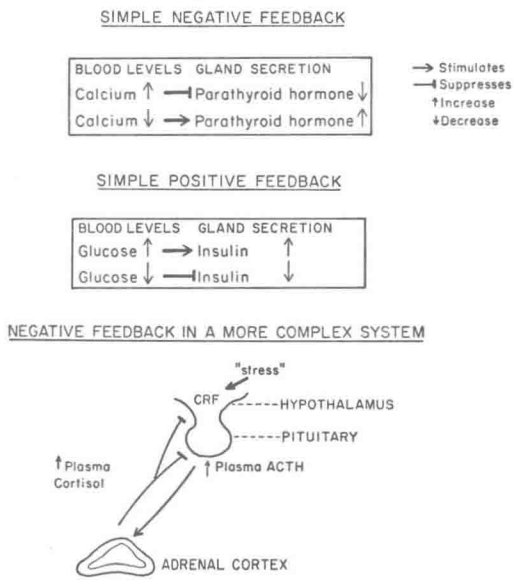
hormonal effects, possibly primarily acting locally to control blood flow to various organs. Thus, as with most subjects, investigations have shown the increasing complexity of the relationships in regulation of the various hormones.

Most hormones are necessary for life. Some such as growth hormone and thymosin appear to be necessary to only certain stages of development and others such as the gonadal hormones are necessary only for the reproduction of the species.

Control of Glandular Function

Most glandular function is regulated by what is known as feedback control. That is, when the hormone which the gland is producing is present in adequate or excessive amounts in the bloodstream, production of the hormone by the gland is decreased or shut off. A decrease of the circulating substance stimulates the production of the hormone. One most characteristic example of this is the relationship between parathyroid activity and serum calcium. As serum calcium increases parathyroid activity decreases, whereas if serum calcium decreases the parathyroid activity increases. This would be considered an example of *negative* feedback control. An example of *positive* feedback control would be the relationship between blood sugar and the beta cells of the islets of Langerhans which produce insulin. As blood sugar increases more insulin is produced, whereas if the blood sugar decreases below normal levels the release of insulin is stopped (Fig. 1–3). As is discussed later, these specific relationships are more complicated than this but for simplicity we will use these examples for the present. A more complex example of regulation of gland function is provided by the relationship between the pituitary and its target glands as also seen in Figure 1–3. It seems somewhat paradoxical in clinical terms that the more complex the regulation of the hormonal system, the easier it is to regulate or replace such hormones. Other types of feedback control are discussed under the chapters on specific glands.

Fig. 1-3.— Proposed mechanisms of "feedback" control of glandular function.



Measurement of Hormones

Hormones in body fluids are found in small concentrations varying from micrograms (10^{-6}) (one millionth gram) to as little as a few picograms (10^{-12}) (one trillionth gram) per milliliter. Thus, as a general rule the technics for their measurement must be very sensitive and precise. The three usual methods of measure are bioassays, chemical assays and displacement (radioimmuno- or competitive binding) assays. The displacement assays, utilizing highly radioactive compounds, are the most sensitive and precise methods for measuring most hormones found in blood and are the ones most frequently used today for both research and clinical procedures.

Bioassays are generally used for research purposes as they tend to be somewhat cumbersome and do not in general have a high degree of reproducibility. Their prime advantage over other methods of assay, however, is that they do measure an action of a hormone on the whole animal or tissue or

isolated cell and thus are useful in the study of specific properties of a hormone biologically and in the purification of a hormone whose structure is unknown or which has not been chemically synthesized. One example of the bioassay used in a whole animal (in vivo) is the mouse convulsion assay used for the measurement of insulin. The principle of the assay is to inject enough of the material with insulin activity to produce enough hypoglycemia in a mouse to make it have a convulsion. This assay is not very precise and is relatively insensitive. Because of the insensitivity of this assay attempts have been made to measure insulin in biologic fluids utilizing pieces of tissue such as a rat diaphragm or fat pad or isolated fat cells in vitro. The principle of such assays is to see how much glycogen deposition might be produced or how much glucose uptake or carbon dioxide production might be stimulated in these various tissues or cells. Although these assays are sensitive enough to measure insulin in amounts found in biologic fluids, they tend not to be very reproducible. Also biologic fluids exhibit considerable activity in these systems which apparently is not due to insulin itself. Many ingenious assays have been devised to measure various hormones and their effects but the only one in general clinical use today is the assay of urinary gonadotrophins in which extracts of urine of varying concentrations are injected into 21-day-old mice and the effects on uterine weights are determined, the results being reported in mouse units per 24 hours of urine. This assay is also somewhat imprecise and cumbersome and therefore is being replaced by radioimmunoassays to a considerable extent..

Chemical methods of assay are more useful clinically, particularly for hormones or their metabolites which are found in larger concentrations in either urine or serum. Prominent among these is the assay for protein-bound iodine which measures the iodine in the thyroxine molecule which normally is found in the blood in concentrations of approximately 4–8 μg per deciliter. Other chemical determinations of hormones prominent in clinical use are the measurements of the hydroxysteroids and ketosteroids in the urine, which are the metabolites, respectively, of cortisol produced by the adrenal, and androgens produced partially by the gonads. Average normal urinary excretion ranges of these are up to about 15 mg per 24 hours. Gas chromatography has also been useful in the measurement of the metabolites of androgens found in urine.

The third class of measurement of hormone, *the displacement assays,* exemplified by the radioimmunoassay, competitive protein binding assay and receptor assay, is the most commonly used and precise of the methods of assay of most hormones, particularly peptide hormones, in general use today both clinically and for research. Because of their importance and probable domination of the measurement of hormones for the next several years, the principles of these assays are discussed in some detail here. The pioneering work of Berson and Yalow in the late 1950's for the radioimmunoassay of insulin laid the foundation for the development of this type of assay which has been extensively developed and utilized during the past decade. The development of the radioimmunoassay involved the following: animals were injected with insulin to induce antibodies to insulin that would bind insulin rather specifically and at a very low concentration. A tracer insulin was then prepared by iodinating insulin with ^{131}I and subsequently ^{125}I (the half-life of ^{125}I is advantageous) to a very high specific activity. The antibody concentration was then adjusted so that it would bind approximately 70% of a very small amount of this labeled tracer hormone. On adding progressively larger amounts of unlabeled insulin it was found that the unlabeled insulin would displace greater amounts of the labeled insulin from the antibody. The radioactive insulin bound to antibody was then separated from the radioactive unbound insulin, originally by paper electrophoresis

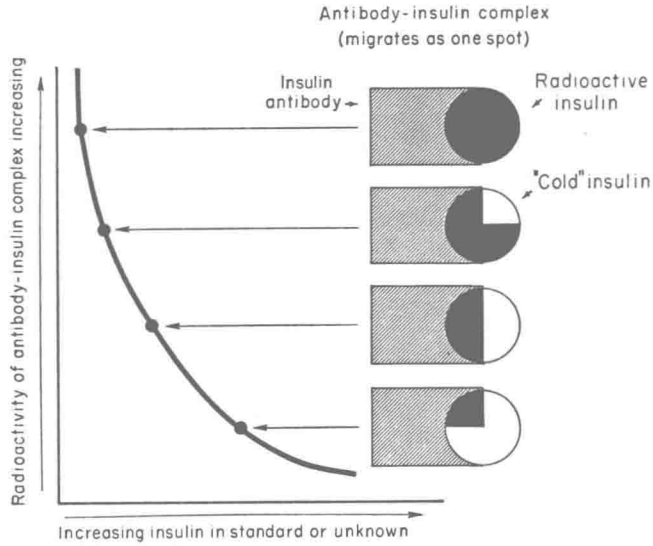


Fig. 1-4.—Schematic description of a typical Berson-Yalow radioimmunoassay (from Tepperman, J.: *Metabolic and Endocrine Physiology*, 3rd edition [Chicago: Year Book Medical Publishers, 1973].)

but subsequently by a number of other methods. A standard curve could then be prepared from the bound/free (B/F) ratios as shown in Figure 1–4, which provided a highly sensitive and precise measure of the concentration of insulin in the assay system. This assay technic subsequently was applied to growth hormone and thyroid-stimulating hormone as well as most other peptide hormones, and by a variety of methods was eventually applied to the measurement of steroid hormones and drugs such as digitalis. The principle was then utilized in measurement of thyroid hormone, using instead of an antibody the thyroid binding globulin found normally in plasma. Subsequently this competitive protein binding assay was applied also to the steroid hormones, particularly cortisol, testosterone and other androgens.

Pathology of the Endocrine Glands

The various pathologies associated with the endocrine glands may be looked upon primarily as processes inducing overproduction or underproduction of hormones. Glands may also produce tumors which may be either active in hormone production or inactive. Excessive production of hormones is usually associated with either hyperplasia of a gland, which may be due to excessive stimulation by known or unknown substances, or active tumors or carcinomas of the glands. Sometimes carcinomas of lung or other organs may produce hormones or other substances which may stimulate other glands if they are producing trophic hormones, or have direct effects on tissues which are similar to that of overactivity of a gland itself. This effect is usually referred to as ectopic hormone production.

Deficiency of hormone production may be due to a variety of reasons. Congenital hypoplasia of a gland may occur. Destruction of a gland may be due to inflammation, radiation, surgical loss, pressure of surrounding tumor tissue or unknown factors causing atrophy of the gland. Enzymes involved in the production of the hormone within the gland may be congenitally absent causing deficient production of the hormone, which usually leads to hyperplasia of the gland in an effort to compensate for this. Other pathologic syndromes associated with endocrine glands may be due to lack of response to hormones of the target tissues themselves. This latter effect may be possibly due in some instances to lack of a hormone receptor, lack of a receptor protein