Metabolic and Endocrine Physiology

An Introductory Text

FOURTH EDITION

JAY TEPPERMAN, M.D.

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Preface to the First Edition

THE TIME has long since gone when anyone could presume to say to the beginning student: "Here are the facts of physiology which you must learn in order to prepare yourself to be a physician." Every attempt to describe the state of development of a field of physiology at present must involve arbitrary selection of material, emphasis colored by the personal experience and limitations of the author, and the occupational risk of offending the sensibilities of one's colleagues and fellow authors. This is not to be regarded as a plea for sympathy, since my choice to write a review of endocrine physiology was a free one, but the reader should reflect, for a moment, about the problems involved in constructing such a review.

In the first place, the preparation or (in the educationist's patois) the "readiness" of our first-year medical students in this area is quite variable. I have seen students who have been exposed to excellent undergraduate courses in endocrinology on the one hand and some who were quite virginally innocent of any knowledge about the glands of internal secretion on the other. The future application of this information by individual students may be equally variable; some of our students have elected to become specialists in this field and have devoted their lives to study, teaching and research in it, while others have chosen to work in some branch of medicine which they manage to visualize as nonmetabolic (although it is difficult to understand how they contrive to do this). In the intermediate zone there is a whole spectrum of professional activities, which range from internal medicine and gynecology through general practice to psychiatry, in which the facts and concepts of endocrinology and metabolism are not merely pertinent but crucial in the diagnosis of disease and the management of sick people.

These variations in educational origin and professional destination of our students are confusing enough, but when one adds to this the nature of the material to be presented, the confusion is compounded. The rate at which new knowledge is accumulating in the field of endocrinology cannot be appreciated by anyone who has not been obligated to try to keep up with some of it. These essays are beads drawn on rapidly moving targets.

This, then, is one author's account of the current state of knowledge of endocrinology as he understands it, and it is directed to an imaginary undifferentiated, totipotential first- or second-year medical student (I would not be desolate, however, if a colleague or fellow-teacher were to experience an occasional "shock of recognition" in these pages). Some students, like the little girl who wrote the review of a book on penguins, may find more here than they care to know. Others may find much less, and for them I have included key references (mainly to monographs, symposia and recent review articles) which were selected to guide the reader back to original sources. I intend to indicate, wherever possible, how the physiological idea is applied in the clinic, for I do not subscribe to the view that a physiological insight that has practical application is necessarily less interesting or beautiful than one for which there is as yet none. This is not to be construed as a promise to omit mention of concepts which may not yet have been applied to the practice of medicine or public health, or to refrain from discussing certain theories and speculations. It seems to me that the fantasies and daydreams of physiology are an important part of the art, and that they do no harm if they are clearly identified. The good ones will one day be validated by experiment and the bad ones will be punctured and discarded in due time.

It is assumed that by the time the student attempts to read this account he will have acquired some information about the gross and microscopic anatomy and embryology of the endocrine glands, and that he is familiar with the broad outlines of carbohydrate, fat and protein metabolism. No attempt will be made here to recapitulate in detail material which is readily available in any standard textbook of histology or biochemistry.

The selection of illustrative experiments from our own experience is not intended to convey the impression that the data cited have any special significance or originality. It often indicates merely that the ma-

terial was more readily available to me than other similar data would have been. It is obviously impossible to give more than a very small sample of the kinds of data on which statements made in the text are based. In fact, it would be unfair to both the reader and the data to attempt too broad a reporting of more or less original information. Therefore, in the few examples I have used, I have tried consciously to include samples taken from every wavelength of the biological research spectrum from the molecular to the epidemiological.

There are two widely used methods of drawing diagrams of the endocrine system: in one, the endocrine organs, kidneys, gastrointestinal tract, etc., are represented by more or less faithful cartoons of their gross anatomical structure (the "Giblet School"); in the other, the related structures are rendered simply as engineers' "black boxes" (the "Mondrianesque School"). Many of the diagrams to be presented herein are in the latter category, and they are intended both as guides to and summaries of the discussion. The encircled numbers represent subsections of the text which are identified by the corresponding numbers in the text. These diagrams have been designed to show the structures and hormones to be discussed and some of their interrelationships.

No one can really understand any subject unless he has some knowledge of the historical development of the modern idea. When I have attempted historical accounts of some of the subjects to be covered in this section in lectures, I have noticed a certain restiveness on the part of students who appeared to be impatient to reach topics that seemed more likely than Minkowski's dogs to be included in an examination. While I have been unable to permit myself the luxury of extended historical treatment of the subject, I could not bring myself to present this inventory without giving some indication that the intellectual edifice of physiology was built over many years by patient and devoted individuals to whom we and those who follow us owe a great debt. Therefore, I have included abbreviated chronologies of some subjects at the beginnings of most chapters. In addition to serving as a small tribute to our professional ancestors, these chronologies illustrate beautifully the interchange of information between clinic and experimental laboratory that has occurred mainly in the past century, and promises to be even more fruitful in the future.

Acknowledgments

There is no doubt that this enterprise could not have been completed without the help of my wife, Dr. Helen Tepperman. In addition to teaching me most of the material in Chapters 5 and 11 and helping in the collection and evaluation of much source information for all other chapters, she read every word of this account in three successive drafts, criticized gently but firmly, and made many valuable suggestions for improving the final product.

I am grateful, too to Dr. Alfred Farah, Chairman of the department in which I work, for his encouragement and help in many ways. I have requested and received welcome help from each of the following: D. Tapley, R. Barnett, G. Sayers, M. Karnofsky, J. L. Kostyo, H. Rasmussen, R. C. Haynes, Jr., D. Sabbatini, D. H. P. Streeten, M. Voorhess, L. Gardner, A. Moses and L. Raisz.

I owe a special debt to Nicolas Apgar and Julia Hammack for the great care and skill with which they prepared the illustrations, and to Shirley Martin for expert secretarial help. I am grateful, too, to the publishers for their understanding cooperation.

JAY TEPPERMAN

Preface to the Fourth Edition

ALMOST ALL of this book has been rewritten and reillustrated with many new teaching diagrams. It is directed primarily to beginning medical students, but other populations of students may find it useful. As in previous editions, I have assumed that the reader has some knowledge of histology (including ultrastructure) and biochemistry.

The student who experiences the dysphoria induced by overloading brain circuitry with information can be assured that his teachers have a similar problem. This book is the result of my examination of countless kilograms of source material. It is humiliating to reflect that my sources represent only a small fraction of the available information about endocrinology. The following chapters, which consist mainly of collages of mini- (in some cases, micro-) essays, are distillates of what I hope will be judged a representative aliquot.

I have been a more or less conscientious endocrinology watcher since 1934, when my histology professor, Philip E. Smith, described the effects of hypophysectomy in a class lecture. Ever since, I have followed the remarkable investigative achievements of my contemporaries with mounting admiration and, in many cases, with awe. This small book is my tribute to their imagination, enthusiasm and industry. My pleasure in their accomplishments is enhanced by the realization that much of what they have done rests firmly on the foundations established by the Philip Smiths of the world, who, in turn, stood (like Newton) on the shoulders of their professional ancestors.

This edition differs from the preceding three in one important respect. Modern students are often stimulated to pursue an idea to its sources, and I have therefore included many more references than I did previously. Most of these are quite recent, but they contain many citations of earlier literature. This policy has made it possible for me to guide the student to authorities for individual statements.

Many people helped me with this revision, sometimes when they were unaware of their help. My colleagues of the Gordon Research Conference on Hormone Action have done a lot for my continuing education. My colleagues of the Endocrine Faculty Group, especially David Streeten, Arnold Moses, Myron Miller, Jorge Torretti and Ross Jacobs, have taught me much. Donal Walsh, John Fain, Mike Czech, Howard Morgan, Fred Goldberg, Guy Williams-Ashman, Phil Felig, Denis McGarry and others have helped with preprints and in other ways.

My department chairman, Irwin Weiner, made it possible for me to complete this job under a six-month term of self-imposed house arrest by relieving me of teaching and administrative duties for that time.

As always, Helen Tepperman made it possible for me to accomplish this revision. She took over my teaching responsibilities in addition to her own, directed our research laboratory and assessed my writing for accuracy and lucidity as it accumulated. My gratitude is boundless.

I am grateful also to Al Ayres and Patty Cave for the new illustrations and to Elaine Holohan for secretarial help.

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PART 1 Introduction

1

Overview of Hormonal Mechanisms

NO MULTICELLULAR ORGANISM can long survive without some sort of internal communications system that can transmit messages from one part to another. In animals there are two major communications systems: (1) *The nervous system,* with all of its projections and arborizations, which is analogous to an elaborate system of telegraphy in which there is a "wire" connection from the source of initiation of the message to the place where reception of the message has its effect; and (2) *the endocrine system* (really a loosely affiliated group of subsystems), which uses the circulatory system to carry messages in the form of highly specialized chemical substances called hormones—a "wireless" system. Hormones are recognized by target cells, which have been preprogrammed by the process of differentiation to respond to their presence by acting in predictable and stereotypical ways. In collaboration the nervous system and the endocrine system maintain the "constancy of the internal milieu," as Claude Bernard described it with remarkable prescience about a century ago. The features of the internal milieu, whose constancy is vigilantly monitored by the "wired" and "wireless" communications systems of the body, are the concentrations of solutes in the blood, as well as blood pressure and blood flow. Whether we describe regulation of serum glucose concentration, serum free fatty acid, calcium or blood pressure, the equilibrium state is one in which the forces that tend to elevate the variable under study and those that tend to depress it are in perfect balance so that a steady state exists. A perturbation that displaces the variable (X) upward galvanizes appropriate neural or endocrine cells into action to restore equilibrium. A depression of X may recruit other sentinel cells to defend against downward displacement of X. The history of physiology from Bernard through W. B. Cannon to the present day, when physiologic regulations are often described in terms of computer programs, has been largely a progressively more complex description of this principle. Prominent among the sentinel cells that help to maintain the constancy of the internal milieu are those that synthesize and secrete hormones—cells of the endocrine glands.

At one time neurobiology and endocrinology were explored by investigators who saw little connection between the two fields. One of the most striking features of the recent history of both enterprises has been the realization that they are in fact closely related to one another and are functionally interdependent. As we shall see, it is possible for a reflex arc to consist of a neural afferent component and an endocrine efferent component (see Chapter 5). In fact, since the recent discovery of morphine-like peptides in the pituitary and in the central nervous system, it is even possible to suggest a Bernardian theory of pain, which may be conceived of as an equilibrium state maintained by pain signals opposed by anti-pain signals—a balance that can be tipped in either direction, with consequent recruitment of the opposing force. Certainly the discovery of a large number of peptides in the central nervous system, some of them long identified as "gastrointestinal" hormones, has provided the neurobiologist and the endocrinologist with parallel problems and shared interests.

Endocrinology then, like neurobiology, is concerned with communication: with messages-as-molecules, which are recognized by discriminators on or in sensitive cells and, by elaborate molecular means, transduced into a response. The response, most of the time, is physiologically advantageous to the whole organism. When a hormone is inappropriately overproduced, as in hyperthyroidism, or by a neoplasm, the response may be maladaptive—in fact, destructive. The remainder of this book contains an account of one observer's understanding of the chemical signals, the cells that produce them and the cells that respond to them.

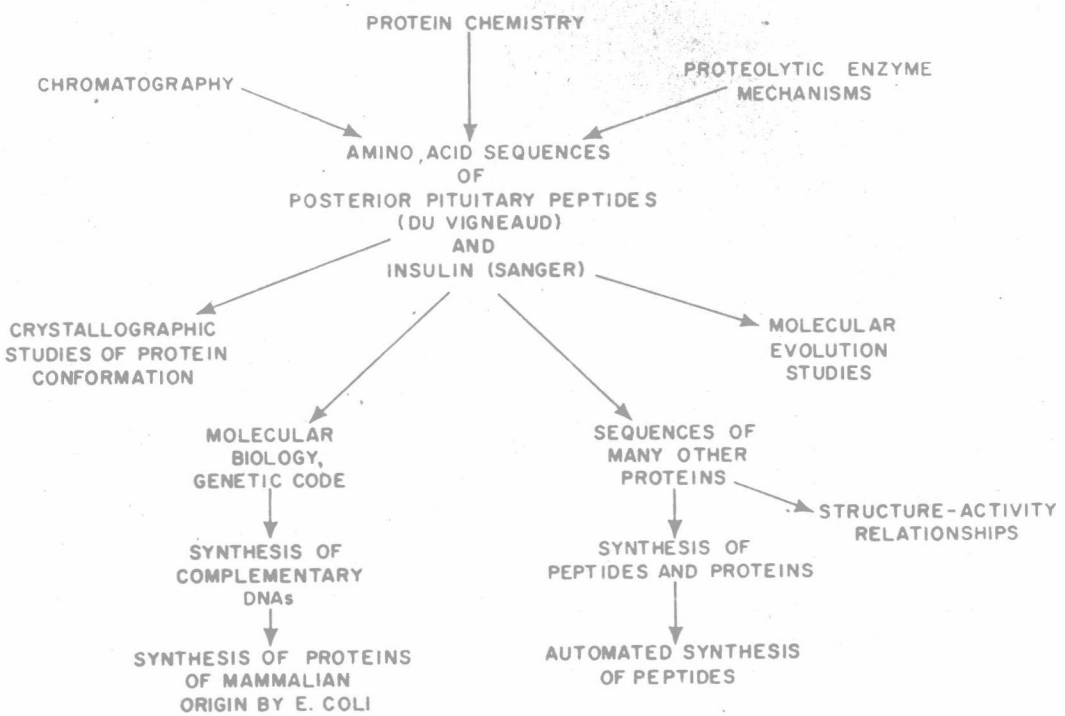
History of Endocrinology

Endocrinology has its roots in the observations and descriptions of physicians and philosophers in ancient times. References to a disease that must have been diabetes mellitus can be found in Egyptian papyri of 1500 B.C. Allusions to goiter and to the effects of castration in man and animals were among the first clinical descriptions of disorders that later proved to be endocrine in nature. It should be noted that old clinical descriptions of endocrine diseases were provided not only by western observers but also by ancient Chinese and Indian clinicians.

If one plots the major discoveries in many areas of endocrinology on a time scale, the resulting display represents a mini-course in the history of biology and medicine. After scattered clinical descriptions in ancient times and through the middle ages, progress was very slow indeed. During the last half of the 19th century a quantum leap forward occurred in many fields, both in the quality and detail of clinical description and in the beginning of our understanding of mechanism. The historical reasons for this acceleration of the pace of discovery are no doubt complex, but we can discern some interesting correlations with the development. In the first place, the industrial revolution resulted in the generation of capital that could be applied to research in many fields, but most impressively in chemistry. The brilliant flowering of organic chemistry in Germany was stimulated by the needs of textile manufacturers who required dyes for their products. Similarly, some of Pasteur's most famous work was done in his capacity as consultant to the wine industry of France. Since endocrinology deals with the interactions of specific chemical substances, the developing sciences of chemistry and physics made possible the description of endocrine mechanisms in molecular terms.

Another revolution occurred in the latter half of the 19th century—one that was basic to the growth of endocrinology as well as to that of all biology and medicine, i.e., the study of experimental animal models. Pioneers such as Claude Bernard and Oscar Minkowski demonstrated that it was possible to make controlled and reproducible observations in the laboratory: in other words, to cross-examine nature. If this activity had been prohibited or proscribed, most of what we now know about endocrinology would have been impossible to learn. All of the substances that we now call hormones began as "substance X" or "factor ?"—as a result of experiments on whole animals, frequently suggested by prior observations

Fig 1–1.—Relationship of studies on hormones to history of biology.



in sick people. "Koch's postulates" of endocrinology evolved into the following sequence:

1. Extirpation of putative gland.
2. Description of biologic effects of operation.
3. Injection of extract of gland.
4. Demonstration that injection of extract corrected deficits described in 2.
5. Isolation, purification and identification of active substance.

By World War II a large amount of information had accumulated in the field of endocrinology, much of it fundamental to later developments. But the availability of a battery of new techniques after that war produced an unprecedented quickening of the tempo of discovery. Concurrently there was an enormous expansion of the research force and research laboratory plant, with the result that the literature of endocrinology, like that of all other aspects of biomedical knowledge, is now growing at an exponential rate. This means that new discoveries are being made constantly, and that old ideas must be reexamined periodically in the light of new facts. This is being done by authors of review articles and in the proceedings of an ever-increasing number of symposia.

The flow of information and understanding from the physical sciences and from basic biologic insights into hormone research has not been undirectional. In surprisingly many cases, investigators working on endocrine problems have made fundamental contributions to all of biology. An example of this is shown in Figure 1–1.

Some Problems in Definition

Hormones are usually defined as chemical messengers that are secreted directly into the bloodstream by specialized cells capable of synthesizing and releasing them in response to specific signals. A few or many target cells are equipped to detect the hormone and to show a typical response to it. The physiologic concentration range for most hormones is 10^{-7} to 10^{-12}, i.e., they are effective at very low concentrations. Often, hormones are described as exerting their effects over long distances via the bloodstream *(telecrine)*. Substances that are secreted by one cell and exert their biologic effects by local diffusion are called *paracrine*.

These are difficult distinctions to make, since some authentic hormones, especially those of the hypothalamus, travel a very short distance before encountering their target cells. Others, like testosterone and estrogens, have both telecrine and paracrine actions, since they are known to act locally near their cells of origin as well as at a distance after having traveled through the bloodstream. To make definitions even more confusing, at least one hormone, testosterone, is present in high concentration in the seminiferous tubules and in their efferent duct system and is presumed to affect ductular structures, which are responsible for the transport and maturation of newly formed spermatozoa.

In addition to hormones, there are many other chemical substances that have a regulatory or modulatory role in the control of biologic processes. The *neurotransmitters*, mainly acetylcholine and the catecholamines, are synthesized in nerve cells and released from nerve endings. Other probable (or possible?) neurotransmitters have been described, among them serotonin, gamma aminobutyric acid (GABA) and histamine. These characteristically exert their effects over very short distances and, typically, for much shorter periods of time than are required for the action of peptide, protein, steroid and thyroid hormones. At one time, neurotransmitters were not considered to be in the domain of the endocrinologist, but recent interesting developments in neuroendocrinology (to be reviewed) have changed that.

Prominent in the category of chemical compounds that exert their effects near their cells of origin are those called *"autacoids."* These include histamine, slow-reacting substance (SRS·A), bradykinin and many compounds generated during inflammatory responses. Later we will examine some of the relationships of hormones with these materials.

Other categories of information-carrying chemical substances function as agents or deputies or *"second messengers"* for hormones at the intracellular level. Among these are the cyclic nucleotides, cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP), calcium and perhaps other ions as well. It is an arresting thought that examination of the mechanism of action of a hormone in a hormone-sensitive cell and that of a neurotransmitter in a stimulated neuron reveals common thematic patterns and similar biochemical machinery.

Another set of compounds cannot easily be classified; perhaps *modulators* of hormone and neurotransmitter action would be most appropriate to describe the effects of a series of substances called *prostaglandins*. These ubiquitous materials will be described in Chapter 4. Their most distinctive feature is that they are often synthesized in response to hormonal and neurotransmitter stimulation, and in some instances they tend to enhance the hormone effect, whereas in others they appear to blunt the effect.

All of these regulatory substances are extremely

potent agents that are effective at low concentrations, but it should be recalled that they are not the only sources of information on which cells act or fail to act. *Circulating substrates* (e.g., glucose, free fatty acids and lipid in other forms) and amino acids constitute an important set of instructions to individual cells and groups of cells. Similarly the circulating levels of calcium, phosphorus, sodium, potassium, iodine and other ions serve important regulatory functions. Hormones do not circulate as solutions of pure amines, proteins, peptides and steroids. Hormone-responsive cells live in a complex and continually changing environment of fuels and ions, and the regulations that occur in them are the results of the effects of both the hormonal and nonhormonal information in which they are bathed.

Integrative Functions of Hormones

The endocrine glands are involved in all of the important life transactions of the organism.

Differentiation

In the developing embryo, hormones play a crucial organizing role, most notably in differentiation of the generative tract (testosterone) and in differentiation of the CNS (thyroxine). Hormones are also essential for differentiation of the developing spermatozoon.

Reproduction

Reproductive functions generally require hormones for their successful accomplishment. Fertilization, implantation, pregnancy and lactation all involve the actions of many hormones in both male and female.

Growth and Development

Hormones are required for growth and development of the maturing individual. Growth hormone, thyroid hormones and insulin are all required for optimal growth, and the inappropriate presence of insulin antagonists or sex steroids can inhibit growth.

Adaptation

Hormones are necessary for adaptation to the quantity and quality of food ingested, both acutely and over a longer time scale. Similarly, hormones are necessary for successful adaptations to changes in fluid and electrolyte availability in the environment.

Aging and Senescence

The inexorable process of aging is associated with diminished secretion of gonadal hormones in both the female and male, though this is more obvious in the former than in the latter.

Thus the influence of hormones can be observed at all of Shakespeare's seven ages of man. They are crucially involved in both the survival of the individual and the perpetuation of the species.

Classification of Hormones

The earliest chemical characterizations of hormones occurred in the early 20th century with the elucidation of the structures of the catecholamines. The golden age of steroid biochemistry, when the structures of the gonadal steroids were proved, took place in the 1930s. Within little more than a decade, the structures of estrogen, progesterone, testosterone, cortisol and adrenal androgen were solved.

Although much basic information about peptide chemistry existed before 1953, the modern era of amino acid sequencing of peptides and proteins began at about that time with reports on the structures of posterior pituitary peptides by du Vigneaud and his school. The first larger peptide for which an amino acid sequence was established was insulin. Sanger's pioneer work on insulin was a landmark not only in endocrinology but in all other subdivisions of biology. As the technology of peptide chemistry became more widely known, the structures of all of the peptides and proteins listed in Table 1–1 were described, and many of these substances have been synthesized.

In Table 1–1 the major sources of the hormones listed also are given. However, recent studies on the cellular localization of many hormones have revealed that such peptides as thyrotrophin-releasing hormone (TRH), somatostatin (SRIF), adrenocorticotrophic hormone (ACTH), and gonadotrophin-releasing hormone (GnRH) are found not only in the hypothalamus or pituitary but also in other discrete locations in the CNS. These discoveries were made possible by the development of the powerful method of immunofluorescence, by which intracellular hormones can be highly selectively labeled and displayed by covalently binding a fluorescent probe to a specific antibody. Perhaps even more surprising is that certain peptides previously associated with secretory cells of the gastrointestinal tract (e.g., gastrin, substance P and cholecystokinin [CKK]) also occur in extrahypothalamic parts of the brain. When these discoveries are examined in the light of developing knowledge

about the localization of endogenous morphine-like peptides in the CNS, it is clear that we are on the threshold of a new era in neurobiology. Although little is now known about the precise function of CNS peptidergic neurons, there is a strong possibility that they may be important modulators of the functions of CNS neurons. Classification of a substance as a "hormone" is no guarantee that it will not turn up in some other capacity in the future.

The special class of glycoprotein hormones enumerated in Table 1–1 is worth noting. These substances are dimeric proteins, and at least three of them (luteinizing [LH], chorionic gonadotrophin [GG], and thyroid-stimulating hormone [TSH]) share an identical subunit. The elucidation of the structures of these glycoproteins has proved to be especially important in the development of radioimmunoassay methods for their detection (see below).

Sometimes chemical classification is less useful than another type of classification, e.g., according to *gland of origin*. There are at least six hormones produced by cells of the anterior pituitary gland: prolactin (PRL), LH, follicle-stimulating hormone (FSH), adrenocorticotrophin (ACTH), thyrotrophin (TSH) and growth hormone (GH, or STH). In addition to these, β lipotrophin, a precursor of endogenously produced peptides with morphine-like properties, has assumed a prominent place among pituitary hormones.

Specific subgroups that are structurally related are often discussed together, e.g., the catecholamines: dopamine, norepinephrine and epinephrine, or the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3).

Some hormones play regulatory roles in certain aspects of physiology and therefore are conveniently grouped *according to function*. Examples of these are vasopressin (ADH), aldosterone and angiotensin,

TABLE 1–1.—CHEMICAL CLASSIFICATION OF HORMONES

CHEMICAL CLASS	HORMONE (ABBREV.)	MAJOR SOURCE
Amines	Dopamine	CNS
	Norepinephrine	CNS, adrenal medulla
	Epinephrine	Adrenal medulla
	Melatonin	Pineal
Iodothyronines	Thyroxine (T_4)	Thyroid
	Triiodothyronine (T_3)	Peripheral tissues (thyroid)
Small peptides	Vasopressin (antidiuretic h.; ADH)	Post. pituitary
	Oxytocin	Post. pituitary
	Melanocyte-stimulating h. (MSH)	Pars intermedia
	Thyrotrophin-releasing h. (TRH)	Hypothal., CNS
	Gonadotrophin-releasing h. (GnRH, LHRH)	Hypothal., CNS
	Somatostatin (SRIF)	Hypothal., CNS, pancreatic islets
	Angiotensins (A_2, A_3)	Blood (from precursor)
Proteins	Insulin	β cells, pancreatic islets
	Glucagon	α cells, pancreatic islets
	Growth h. or somatotrophin (GH, STH)	Ant. pituitary
	Placental lactogen (PL)	Placenta
	Prolactin (PRL)	Ant. pituitary
	Parathyroid h. (PTH)	Parathyroid
	Calcitonin	C cells, thyroid
	Adrenocorticotrophic h. (ACTH)	Ant. pituitary
	Secretin	Gastrointestinal tract
	Cholecystokinin (CCK)	Gastrointestinal tract
	Gastrin	Gastrointestinal tract
	Gastric-inhibitory peptide (GIP)	Gastrointestinal tract
Glycoproteins	Follicle-stimulating h. (FSH)	Ant. pituitary
	Luteinizing hormone (LH)	Ant. pituitary
	Chorionic gonadotrophin (CG)	Placenta
	Thyroid-stimulating h. (TSH)	Ant. pituitary
Steroids	Estrogens (E_2, E_3)	Ovary, placenta
	Progesterone (P)	Corpus luteum, placenta
	Testosterone (T)	Testis
	Dihydrotestosterone (DHT)	T-sensitive tissues
	Glucocorticoids	Adrenal cortex
	Aldosterone	Adrenal cortex
	Cholecalciferol (vit. D) metabolites	Liver, kidneys

which collaborate in maintenance of fluid and electrolyte homeostasis. Similarly, hormones secreted by cells of the islets of Langerhans are not chemically related but are closely related functionally: insulin, glucagon and somatostatin. Parathyroid hormone, calcitonin and the cholecalciferols (vitamin D derivatives) are all important in homeostatic regulation of body calcium.

Hormone systems may involve diverse hormones of different chemical types. For example, the gonadotrophic system in the female includes the following:

1. One or more CNS neurotransmitters.
2. Peptidergic neurons that secrete gonadotrophin-releasing and -inhibiting factors.
3. Three different types of anterior pituitary cells: one that secretes LH, one that produces FSH and one that is the source of PRL.
4. Steroid hormones produced in specific ovarian cells and in the corpus luteum (estrogen and progesterone).
5. Target tissues in the generative organs, the breast and the brain.
6. An FSH inhibitor produced in the ovary.

Note that this system uses chemical messengers, which are monoamines, small peptides, glycoproteins and steroids. Similar systems are constructed around the testis, the adrenal cortex and the thyroid.

Shared Characteristics of Hormones

Certain generalizations may be made about all hormones, whatever their chemical class. Among these are the following:

Reactions in Sensitive Cells

Hormones do not initiate reactions in sensitive cells. This is a restatement of the principle that the capacity of the responsive cell to be stimulated or inhibited by a hormone was built into the cell when it differentiated. The hormone, by interacting with its receptor, initiates a sequence of events, which collectively constitute the response. Often the response is a coordinated one that involves acceleration of some biochemical processes and concurrent inhibition of others. A closer examination of the cellular mechanism of action of hormones will be given in the next section.

Secretion Rates

Hormones are not secreted at uniform rates. Some, like pituitary growth hormone and ACTH, show diurnal fluctuations that are linked to sleep-awakening cycles. Others (e.g., the gonadotrophins) are secreted in complicated cycles that participate in ovulation, menstruation, pregnancy and lactation. Some pituitary hormones are secreted in pulsatile fashion, with a regular periodicity measured in minutes. Others, like insulin, glucagon, growth hormone and glucocorticoids, are secreted at rates that are determined by the levels of circulating substrates, catecholamines and other hormones.

Metabolic Inactivation/Excretion

Hormones are continually lost from the body by processes of metabolic inactivation and/or excretion. Thus a constant, basal hormone production must be maintained to compensate for loss. It follows that the production rate must be increased to compensate for temporary increases in hormone requirement. Thus the processes of hormone *secretion* and hormone *synthesis*, although they can be dissociated from one another in some experimental circumstances, are closely linked phenomena.

Information Transfer Systems

Hormones function in closed-loop systems of information transfer. Operationally this means that when a hormone begins to act on a sensitive cell or system of cells, a "turn-off" signal of greater or lesser strength is also initiated. Feedback inhibition of a stimulated gland may occur as the result of an *increased concentration of another hormone* (e.g., when thyroxine, elicited by an increase in pituitary TSH secretion, feeds back on the pituitary thyrotrophe to prevent its stimulation by TRH from the hypothalamus). Another general mechanism by which an activated gland can be back-inhibited is by *correction of the physiologic disequilibrium that originally activated the gland*. We will examine a number of examples of this paradigm in later sections, which deal with fuel homeostasis, calcium regulation and electrolyte balance.

Time Scales

Hormones act on different time scales. If one arranges chemical messengers according to the time scales over which they work, from seconds to days, the following rank order is apparent:

Neurotransmitters (milliseconds)
Peptides (minutes)
Proteins and glycoproteins (minutes-hours)

Steroids (hours)
Iodothyronines (days)

This description should be qualified by the observation that a peptide or protein hormone whose effect may be readily detectable in a few minutes may exert its action over a period of hours or days if it is continuously present.

Conceptual Framework for Study of Hormones

In our study of each hormone we would like to have certain information.

Precise Chemical Structure and Properties of Hormones

In many cases a knowledge of the chemistry of a hormone involves not only the naturally occurring substance but also synthetic variants produced by the organic chemist: synthetic analogues often have desirable properties that are absent from the natural hormone. They can be more or less potent than the original hormone or they can display selective effects of the original while eliminating undesirable effects. Sometimes analogues are found to exhibit antihormone actions that are useful both in research and in the clinic. The use of a series of analogues may help to elucidate structure-biologic activity relationships.

Biosynthesis of Hormones

Peptide hormones are synthesized on ribosomes affiliated with the endoplasmic reticulum and packaged into secretory vesicles in the Golgi apparatus. It is now apparent that, in such cases as insulin, glucagon, ACTH and parathyroid hormone, the final, secreted hormone is a cleavage product of a larger molecule, which has been designated a *pro*hormone. In fact, in the case of insulin, the prohormone itself is derived from an even larger molecule, *pre*-proinsulin. Although there is still no universally accepted explanation for the existence of pre- and prohormones, they may play a role in secretion of hormones into the lumen of the ER and (particularly in the case of insulin) in positioning the constituent amino acids in the molecule so that disulfide bonds can be formed conveniently.

The special case of synthesis of thyroid hormones will be considered later. However, these hormones are derived from hydrolysis of a high molecular weight glycoprotein, thyroglobulin. This prohormone differs from most in being stored, not in secretory granules within the cells that synthesize it, but as large colloid droplets shared by many epithelial cells that constitute a follicle. Thyroglobulin, as well as the glycoprotein hormones, illustrates the point that posttranslational modification of a newly synthesized protein may be an important feature of hormone synthesis. This process, which involves the addition of oligosaccharides to the protein, is presumed to occur in the lumen of the endoplasmic reticulum and in the Golgi apparatus.

In all cases, protein and peptide hormones are stored in secretory vesicles or as hormone precursor (thyroglobulin). The steroid hormone-producing cells in the ovary, corpus luteum, testicular Leydig cell and adrenal cortical cell do not characteristically store large amounts of prepackaged hormone. Instead they store hormone precursor, cholesterol ester, in the form of lipid droplets. In the case of these hormone-producing cells, the signal for hormone release is very tightly coupled to that for acceleration of hormone synthesis. As the hormone newly synthesized from stored cholesterol is formed, it is promptly detectable in venous blood draining the organ.

Hormone Secretion

Identifiable signals elicit the release of the hormone under study. These may be few and highly selective, as in the case of parathyroid hormone, or many and intricately interrelated, as in the case of insulin, or aldosterone release. As we consider each hormone, we will attempt to assess the relative importance of release signals, since the endocrine gland's response to signals often helps to define the role of its hormonal product in the vital economy of the intact individual.

Inhibition of Hormone Secretion

There are at least two categories of hormone release inhibitors: (1) those that may function physiologically in regulation of hormone release and (2) pharmacologic agents that may be helpful in elucidating the nature of the hormone release mechanism. An example of the first type of inhibitor is the feedback inhibition of ACTH release by cortisol or the inhibition of insulin release by sympathetic nerve stimulation. An example of the second is as follows: if the microtubular system of a cell is believed to be involved in extrusion of hormone from storage vesicles, failure to secrete the hormone on signal by a colchicine-treated cell (colchicine is a microtubule toxin) is taken as circumstantial evidence that unimpaired microtubular function is required for the secretory process.