METABOLIC AND ENDOCRINE PHYSIOLOGY

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FIFTH EDITION

METABOLIC AND ENDOCRINE PHYSIOLOGY

An Introductory Text

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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 material 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. Barrnett, 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, M.D.

Preface to the Fifth Edition

When, 26 years ago, one of us (J. T.) participated in a conversation with Julius Comroe, Robert Pitts, Alan Burton, Horace Davenport, and Year Book's Fred Rogers to plan a series of monographs in physiology, he could not have predicted that anyone would be interested in publishing a *fifth* edition of *Metabolic and Endocrine Physiology*. Of our original fellow authors in the enterprise, only Horace Davenport, our great and good friend since 1940, survives. On this occasion, we remember the others not sadly but with pleasure: Comroe, a genuinely witty and wise scholar, investigator, teacher, and administrator; Burton, who was gently funny and extraordinarily literate and articulate in the Old World tradition; and Pitts, decidedly not a comic genius like the others, but a scientist-poet who found his inspiration up and down the renal tubule. To all of them we say, hail and farewell.

The authors of this edition, recently retired from teaching and research, have been privileged to watch the astonishing evolution of modern endocrinology for an aggregate total of 98 people years. When we began our respective graduate school training (J. T. in 1934 and H. M. T. in 1938), endocrinology had only recently achieved a degree of respectability, having been identified previously in the public consciousness primarily with giants, dwarfs, and bearded ladies in circuses. Insulin had only been discovered in 1921, the giants of steroid biochemistry were the avant-garde, and two decades had to pass before anyone knew the structure of a peptide hormone or of DNA. With the massive infusions of money into biomedical research in the 50s and 60s, growth of knowledge in endocrinology, as in all other fields, has been exponential. We and our colleagues have functioned as self-appointed Greek choruses, commenting on the action as we tried to follow new developments. In 39 years of teaching, we have been responsible for introducing over 4,000 medical students, and more than a few Ph.D. candidates, to the study of endocrinology.

Someone once said that all Michelangelo had to do was to find a large piece of marble and chip away everthing that was not David or Moses. Michelangelo had the great advantage of knowing precisely how he wanted David and Moses to look. In our case, the block of marble was vast, but we were never sure that we or anyone could chisel from it an introduction that would be both appropriate for students and acceptable to their teachers. Knowing how many demands were placed on our students by other teachers, we wanted to avoid overload; but at the same time, we know modern students too well to presume to condescend to them. We have settled, as in the past, for a narrative style, and we have tried, wherever it was possible, to demonstrate how contemporary ideas have their roots in older ones.

Our procedure was to read current material related to each chapter, to reread what we had written before, and either to preserve or rewrite segments in the fourth edition according to our assessment of need. In every case, we rewrote much that was retained and added a considerable number of new mini-essays. Most of the cyclic AMP chapter was rewritten to emphasize the concept of multiple second messengers, including calcium-calmodulin, and polyphosphatidyl inositol turnover. The prostaglandin chapter was expanded to include more on the leukotrienes. All aspects of neuroendocrinology were reevaluated, and accounts of new hypothalamic hormones, CRF, GHRH and PIF, have been included. There is new information on the mechanism of action of hormones in virtually all chapters. When it was announced that Brown and Goldstein were awarded the 1985 Nobel Prize in medicine, we repaired a longstanding deficiency by writing an entirely new chapter (Chapter 15) on lipoproteins and lipid transport.

We have directed this book to a population of students who have had courses in gross anatomy, histology (including ultrastructure) and biochemistry, but not pathology, immunology, or clinical medicine. While the prerequisite courses are certainly desirable, one of us (J. T.) has used previous editions of this book in one-on-one tutorials with Ph.D. candidates. He has been impressed by how much a conscientious student without prior training in anatomy or histology can extract from the book with the help of a good dictionary.

This is *not* intended to be a textbook of clinical endocrinology. The brief references to endocrine diseases and other clinical matters are included to illustrate the point that in this field, as in so many other areas of modern medicine, application of basic biochemical and physiological information is swift and pervasive.

Many old illustrations have been revised to reflect new knowledge, and we have drawn a large number of new ones. For these, we are grateful for the help of Ellie Carbone. We are also grateful to Chester Carlson, who invented xerography, and to every one (unknown to us) who made it possible for us to have a word processor in our home. Without them, this revision would have been quite impossible.

We look back with pleasure over a quarter century's association with Year Book Medical Publishers. We thank our Chicago friends for their careful and concerned editing and production.

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Contents

PART I

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 two observers' 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. 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 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 lot 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.

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*. Substances that act on cells that secrete them are called *autocrine*.

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

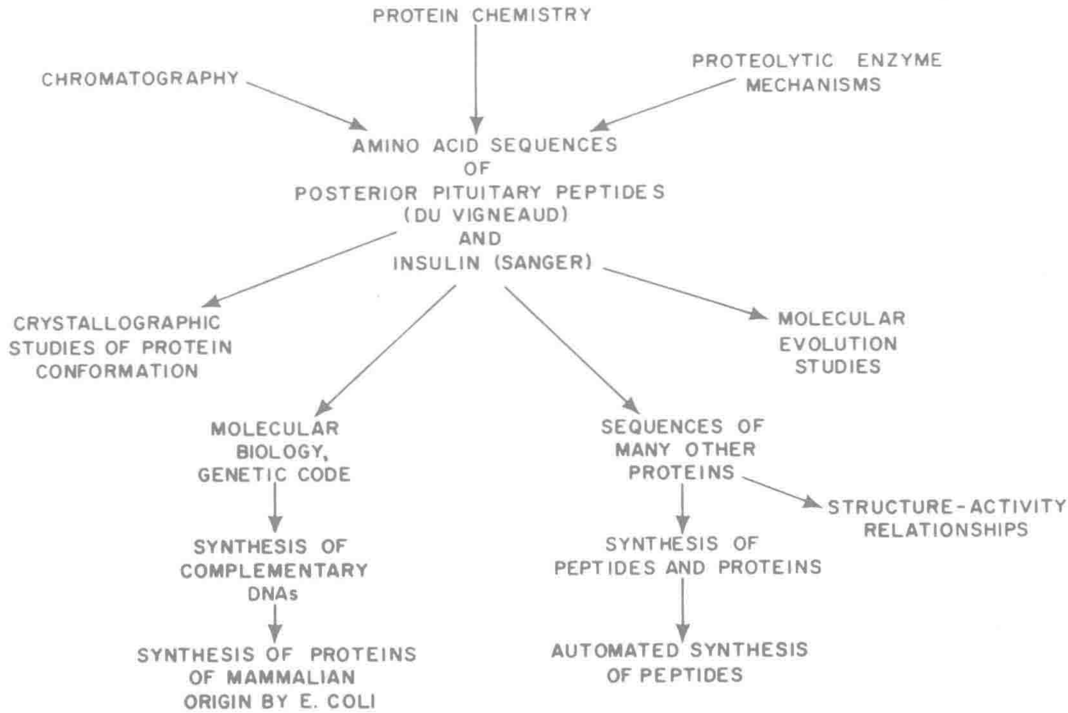

FIG 1–1.
Relationship of studies on hormones to history of biology.

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 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.

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 certain hydrolytic products of the phospholipid, phosphorylated phosphatidyl inositol. 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. Similarly, the responses of mast cells to a variety of stimuli and of lymphocytes to mitogens are strikingly like those of some hormone-sensitive cells to their respective hormones.

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 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.

Evolution of Endocrine Systems

Hormones, hormone precursors, and many of the agents that mediate or modulate hormone action (receptors, second messengers, prostaglandins, and other related substances) have been found in bacteria, worms, insects, and plants. It is somewhat startling to learn that protozoa, fungi, and *E. coli* contain a molecule that cross-reacts with anti-insulin antibody and stimulates glucose oxidation in isolated fat cells. Its function in *E. coli* is unknown. What sea coral does with its prostaglandins is equally mysterious.

Some of the functions of the hormone second messenger, cyclic AMP, in primitive forms have been studied intensively. In the slime mold, which is an aggregation of cells that were once dispersed as individual amoebae, cAMP is the primary aggregating stimulus and is secreted into the medium when nutrients are in short supply. Similarly, in glucose-deprived *E. coli,* the same substance causes the derepression of the lac operon which enables the organism to metabolize galactose.

Some hormones acquired different functions as organisms became more complex. Prolactin, for example, is an important osmoregulating hormone in amphibia, but its most prominent function in mammals is in the physiology of lactation. Other hormones may have different functions in different tissues of the same organism, i.e., angiotensin stimulates the production of aldosterone by the adrenal and also plays an important role in the central nervous system as a regulator of thirst. The behavioral effects of antidiuretic hormone and ACTH, in addition to their effects in the kidney and adrenals, respectively, illustrate the same point.

In general, regulatory molecules evolved long before the metabolic processes they were destined to regulate. In Francois Jacob's appealing metaphor, Nature appears to behave like a provident tinker or handyman who hoards molecular tools that acquire new regulatory functions as new and more complex metabolic needs evolve.

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).

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. The same hormones act in the male and the female to influence complementary functions, i.e., the differentiation and development of the spermatozoon and the ovum.

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, thought this is more obvious in the former than in the latter.

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

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
	CRF	Hypothal., CNS
	Somatocrinin (GRH, GRF)	Islet tumor, hypothal., CNS
	Angiotensins (A_2, A_3)	Blood (from precursor), CNS
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
	Beta lipotropin and enkephalin	Pituitary, CNS
	Calcitonin	C cells, thyroid
	Adrenocorticotrophic h. (ACTH)	Ant. pituitary
	Secretin	Gastrointestinal tract, CNS
	Cholecystokinin (CCK)	Gastrointestinal tract, CNS
	Gastrin	Gastrointestinal tract, CNS
	Gastric-inhibitory peptide (GIP)	Gastrointestinal tract
Glycoproteins	Follicle-stimulating h. (FSH)	Ant. pituitary
	Luteinizing hormone (LH)	Ant. pituitary
	Chorionic gonadotropin (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