textbook of ENDOCRINE PHYSIOLOGY

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To H.R.N.

PREFACE

This book was initially designed to meet the needs of students enrolled in undergraduate and graduate endocrinology courses at the City University of New York and those preparing for comprehensive examinations in the biological sciences. Suggestions from colleagues and students at other institutions for increasing the versatility of the text have been incorporated.

The courses at the City University emphasize applications of molecular biology to the understanding of whole animal physiology, and are concerned predominantly with the roles of hormones in the regulation of metabolic processes. Most of the discussion relates to mammals, but examples are freely drawn from studies of other vertebrates.

Since the lectures are attended by students majoring in psychology, anthropology, and other disciplines, most of the material has been written for comprehension by those having no preliminary preparation beyond elementary animal physiology and basic biochemistry. Passages concerned with controversial issues, topics of limited interest, and those requiring advanced knowledge of biochemistry have been placed in small type. Beginning students can omit the small-type sections without loss of text continuity. Since the topics are clearly demarcated, the instructor of an elementary course can easily delete portions which do not serve his particular needs; for example, sections on the biosynthesis or metabolism of hormones can be omitted without detracting from the understanding of the functions or mechanisms of action of hormones. The index provides ready access to specific information.

A functional approach has been adopted. Each of the hormones is presented in conjunction with the discussion of a specific physiological process. Thus, the endocrine pancreas is introduced in the section on regulation of plasma glucose concentrations, and thyroid gland physiology appears in the part concerned with regulation of metabolic rate and body composition. However, a separate section has been devoted to the pituitary gland and hypothalamus because only certain aspects of the discussion of those structures can be conveniently incorporated into such topics as growth and reproduction. The decision to present an entire section on the pineal and thymus glands reflects special interests of the author and the belief that some aspects of this fascinating area have been too long neglected.

A text suitable for student use must be limited in size; this precludes encyclopedic treatment. No attempt has been made to present a comprehensive survey of the literature. The references at the ends of the chapters contain mostly review articles. It is assumed that students will freely utilize the reviews, the papers cited therein, and additional library resources as they prepare term papers and oral reports. They will thereby become familiar with the work of individual investigators whose names do not appear in the bibliography, but without whom the science of endocrinology could not exist.

The presentation has been varied to provide some insight into the kinds of information obtainable elsewhere. The morphology of the pituitary gland is described in detail because of numerous functional implications; but the morphology of most other endocrine structures has been either omitted or presented in abbreviated form. Parathyroid hormone physiology has been singled out for historical review. And comparative aspects receive special treatment in the section on water and electrolyte metabolism. It is certain that any endocrinologist undertaking the task of writing a text with limited scope will make some other selection.

It is, of course, presumptuous for any individual to pretend to be an expert on all aspects of endocrinology. The volume of current literature in each of the areas is overwhelming. It is therefore fortunate, indeed, that numerous publications written by specialists in individual fields are available. However, students have a real need for a unified text written by a single author; that is why this book was written. Constructive criticism from those more knowledgeable in specific areas is welcomed.

My husband, Henning Norbom's patience, understanding, sense of humor, and steadfast refusal to entertain complaints of fatigue or frustration, contributed substantially to completion of the project. I am also deeply grateful to Carol C. Halpern for providing both inspiration and help with the literature survey. Many colleagues and students have given encouragement and constructive suggestions, and I especially wish to thank B.R., L.K.M., U.J.B., E.J.D., S.D.J., and M.C.G. It has been a special pleasure working with Trudy Nicholson, who made the original drawings, and with the production staff at the Williams & Wilkins Co.

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I

WHAT ARE HORMONES? WHAT DO THEY DO?

1. General Nature of Vertebrate Hormones

ATTEMPTS TO DEFINE A HORMONE

Until quite recently it was possible to present a simple, straightforward, and totally acceptable definition of the term "hormone." The nine components of the definition are examined in this chapter. The first two still apply to the spectrum of agents with which the vertebrate endocrinologist is concerned; problems which have arisen in conjunction with the seven others reflect changing concepts that have grown out of newer research.

According to the definition, hormones are (1) *physiological regulators* (2) *effective in minute quantities* (3) *synthesized by living cells* (4) *in glands* which (5) *secrete directly into the bloodstream*; the secretions are (6) *transported by the circulating blood* to (7) *specific target organs* located (8) at a *site distant from the site of synthesis* where they (9) *exert specific actions*.

Hormones Are Physiological Regulators

They speed up or slow down biological functions which proceed at a different rate in their absence. (The term "chalone" has been used to designate hormones with inhibitory actions, but it has recently taken on more specialized meaning.)

Heart muscle contracts when no hormones are present, but it contracts with greater force when exposed to adrenalin. Fat is broken down in adipose tissue, but the degradation rate is slowed by insulin.

Some processes appear to be totally dependent upon hormones; for example, mammalian egg cells do not ripen in their follicles, and accessory reproductive structures remain immature when appropriate hormones are missing. But hormones can only "awaken" existing potential. No quantity or combination of hormones can induce ovulation in gastric mucosa cells or milk synthesis in heart muscle.

While hormones *are* physiological regulators, many regulators are not hormones. Inorganic ions are ruled out by component 3 of the above definition. Glucose is ruled out by component 2 since large quantities are needed.

But, what about carbon dioxide? Minute quantities produced by living cells travel in the bloodstream to regulate "target organs" such as the respiratory center of the medulla oblongata. Carbon dioxide meets all criteria for a hormone except component 4; it is produced by all kinds of cells. The term "parahormone" is useful for designation of such regulators; a list of parahormones might include histamine, the kinins, and possibly also the prostaglandins (but not glucose).

Distinctions between *vitamins* and hormones are not always obvious. Members of the "B complex" clearly do not qualify as hormones because they are needed in the diet and are distributed to all kinds of cells. But vitamin D can be totally synthesized within specific sites in the body (Chapter 15), minute quantities of its metabolites travel with the blood to "target organs," and the actions exerted are similar to those of "typical" hormones.

Hormones Are Effective in Minute Quantities

Just what is meant by "minute" deserves comment. Daily dietary requirements for the human adult include *40–100 g* of protein, *1–2* $\times$ *10^{-3} g* of thiamine and perhaps *1* $\times$ *10^{-6} g* of vitamin B_{12}. While milligram quantities of certain hormones may be injected (especially when degradation is rapid or when it is necessary to maintain high plasma concentrations), *microgram (10^{-6} g)* quantities of others are quite effective. Pituitary gland thyrotrophs respond vigorously to the presence of a few *picograms (10^{-12} g)* of hypothalamic hormones in the surrounding medium, while *femtograms (10^{-15} g)* of angiotensin II can effectively stimulate the hypothalamic neurons that affect drinking behavior.

Hormones Are Synthesized by Living Cells

This is often true. However, some glands release prohormones which require extracellular metabolic conversion. The kidney secretes renin, a *proteolytic enzyme* which acts on a plasma protein to promote formation of an active hormone.

Hormones Are Secreted by Glands

The term "ductless" is usually inserted to distinguish between *endocrine* glands emptying their products into the bloodstream and *exocrine* glands such as those secreting sweat and saliva. But just what is a gland? Little is accomplished by defining a gland as a structure specialized for secretion.

A search for *morphological* characteristics common to endocrine glands is not rewarding. The thyroid gland has *follicles*; the parathyroid, *cords* of cells; the endocrine pancreas, *clumps* of cells (islets). Three different cell arrangements are characteristically found within the mammalian adrenal cortex, while calcitonin is secreted by cells scattered throughout the thyroid gland.

The problem is further complicated by posing the question, "If a structure is clearly identifiable with other organ systems, can it still be classified as an endocrine gland?" The hypothalamus, in common with other parts of the brain, contains neurons which synapse with other neurons and transmit impulses. Some of these cells synthesize, store, and secrete substances which qualify as hormones.

The kidney synthesizes and secretes erythropoietin, 1,25-dihydroxycholecalciferol, and prostaglandins, among other humoral regulators. The liver produces its own specialized secretions; it also plays a key role in metabolism of hormones and converts steroid hormones of one type to others having different biological activity. The lungs, heart, salivary glands, stomach, uterus, and intestine have been included in the ever growing list of structures implicated in hormone secretion. Recent research on prostaglandins raises the possibility that all kinds of cells produce hormones. Certainly the evidence grows daily that all cells secrete something.

Hormones Are Secreted into the Bloodstream

This part of the definition rules out *intracellular regulators*, *neurotransmitters*, and *pheromones(ectohormones)* which act on other organisms; but it also raises problems. If cells produce a prostaglandin which acts locally but which also enters the circulation to act elsewhere, is the prostaglandin a hormone in the latter instance but not in the former?

Acetylcholine is clearly a neurotransmitter; it is produced by neurons and it does not pass through the circulation to reach synapses, ganglia, or parasympathetically innervated muscles and glands. But norepinephrine, which is produced by neurons and sent directly to sympathetically innervated muscles and glands, is also secreted into the bloodstream by the adrenal medulla. The heart, gut, blood vessels, and salivary glands give identical responses to norepinephrine from both sources; are they responding to a hormone in one case but not in the other?

Hypothalamic neurons secrete hormones, some of which are directly sent into a restricted part of the circulatory system. The terms "neurohormone" and "neurosecretion" have been used to distinguish such regulators from hormones secreted by "typical" endocrine glands. Recent research findings have blunted the distinction.

Embryonic inductors are usually excluded from the list of hormones, because most act directly on neighboring cells and may complete their function before development of the circulatory system. However, some (*e.g.*, medullarin) do enter the circulation.

Pheromones are described in endocrinology texts because their production is usually hormonally controlled, and because their actions are commonly exerted on the endocrine systems of affected individuals.[1, 4, 7] (The term "primer pheromone" describes such agents, whereas *behavioral or release pheromones* affect neuronal pathways.)

Pheromones were first studied in insects. In addition to practical applications, the knowledge gained has theoretical implications for vertebrate physiology.

Sex attractants released by females of unwanted insect species have been used to gather large numbers of males which can then be sterilized and released to mate with normal females. This permits eradication of a single species without environmental pollution. Vertebrate females are known to release pheromone "trails" which attract males.

Worker bees ingest an ovary-inhibiting pheromone released by the queen. Something released into the urine by female mice inhibits reproductive cycles of other females within the same cage. Similarities between such phenomena and the use of ovarian hormones produced by female vertebrates as oral contraceptives have been noted.[1] Ectohormones have been implicated in reduction of fertility of rodents subjected to crowding (although other mechanisms including alterations of adrenocortical function have been proposed). One may speculate on the possibility that pheromones play a role in recent acceptance of voluntary fertility control among humans concerned with population density, without denying the importance of other factors.

Grouped females of several species (including rats) develop synchronized estrous cycles; could pheromones account for the reported synchrony of menstrual cycles observed in young women residing in the same college dormitory or summer camp cottage? Urine from foreign mice and voles induces abortion in females of the same species inseminated by other males.[58] Can such information be used to develop a human pheromone preparation for voluntary control of human fertility?

Olfactory cues not consciously recognized may affect human behavior. The complexity of neuronal pathways leading from "olfactory" components of the human brain supports the concept. *Copulin* has been identified in genital regions and urine of rodents in estrus and monkeys in the follicular phase of the menstrual cycle, and it is known to play a role in attraction of the male[66]. While we like to believe that human sexual behavior is controlled by conscious processes, a pheromone has been identified in vaginal washings of human females during the period immediately preceding ovulation.[44] Some unexplained attractions between individuals and the pleasures of kissing (or nose rubbing) may well have an olfactory component. Infant pheromones stimulate maternal behavior and lactation in rodents; perhaps this will lead to development of a human pheromone preparation which can be taken by women who would like to nurse their infants but are unable to produce sufficient milk.

Pheromones are difficult to study.[44, 45, 66] Structures implicated in their production include ovaries, uterus, oviducts, testes, pre-putial glands, sebaceous and sweat glands, kidneys, gastrointestinal tract, and lungs. They are produced in minute quantities as components of highly complex mixtures, and available methods for assay are cumbersome, time-consuming, and subjective. Many seem to be released in "inactive forms" (*e.g.*, as conjugates) and require hydrolysis by bacterial enzymes outside the body.

Mammals are known to exhibit changes in sensitivity (*e.g.*, according to the stage of the menstrual cycle) and to respond to both concentration and chemical nature of the pheromone. Stimuli presented with the pheromones also affect responses; *e.g.*, a single agent may arouse one response when present along with barking and another with growling. Even location may be important; "territorial" pheromones released by larger animals high off the ground can be more effective than those released lower by smaller members of the group.

Hormones Are Transported by the Circulatory System

This follows logically from component 5 of the definition. But is it important? Hypothalamic hormones may travel only millimeter distances through a highly restricted portion of the circulatory system, and target sites affected may be no larger than neuromuscular junctions of the toe receiving acetylcholine produced meters away. Functions of "brain hormones" released into the cerebrospinal fluid may not be qualitatively different from those of hormones entering the blood circulation.[65]

Hormone Act on Specific Target Organs

This component of the definition may one day be discarded completely. Thyroid-stimulating hormone has been cited as an example of a specific regulator, since it stimulates epithelial cells of the thyroid gland follicles (with no known influences on neighboring interfollicular cells) and seems to be devoid of action on most other endocrine glands. But it also affects certain hormone-secreting hypothalamic neurons, and large doses promote lipolysis in adipose tissue. Thyrotrophin release factor was once thought to "specifically" promote secretion of thyroid-stimulating hormone, but it also affects prolactin release.

Insulin regulates metabolic processes in liver, heart, skeletal muscle, mammary gland, and probably also neurons affecting glucose metabolism. Its effects on plasma concentrations of glucose, fatty acids, and small ions and its influence on appetite extend to every cell type. Physiological concentrations of testosterone affect testes, prostate glands, seminal vesicles, larynx, skeletal muscle, skin, bone (and bone marrow), liver, kidneys, thymus gland, pituitary gland, and brain; and it would be difficult indeed to find cells escaping the influence of thyroxine. Each day brings new information on the presence of prolactin receptors in tissues not previously regarded as target organs. Moreover, each of the hormones indirectly affects other cells through influences on secretion or metabolism of other hormones.

The Action of Hormones Is Exerted at a Site Distant from the Site of Synthesis

As noted above, distances traveled by some hormones are exceedingly short; except for the possibilities of restricting the quantities of hormone required and the range of action when hormones go directly to their effector sites, little functional significance can be associated with the distance traveled.

Hormones Exert Specific Actions

Acceptance or rejection of this part of the definition depends upon the point of view. On the positive side, it can be said that thyroid-stimulating hormone exerts obvious influences on the thyroid gland which cannot be mimicked by other known hormones, and that stimulation of protein synthesis by insulin is different from stimulation by growth hormone.[16] However, there has been a growing tendency to seek out common denominators for mechanisms of action of *groups* of hormones. It will be noted in Chapter 3 that large numbers of peptide hormones enhance the formation of cyclic 3′,5′-adenosine monophosphate (cAMP) in responsive cells, and that cAMP functions as a "second messenger." Many of the actions of the hormones can be induced by agents (hormonal or not) which stimulate formation of, or act like cAMP.

The "second messenger hypothesis" suggests that specificity of hormone action resides in the presence within the target cell membrane of a *unique hormone receptor*. Thus, thyroid cells respond to thyroid-stimulating hormone because they have receptors for the latter, but they lack receptors for glucocorticoids, follicle-stimulating hormone, and so forth. *Responses* to hormones depend upon unique features of cell metabolism. Thus, *any* agent which stimulates production of cAMP in the thyroid gland can promote synthesis of thyroid hormones, while any agent stimulating production of cAMP in certain cells of the adrenal cortex can promote synthesis of adrenocortical steroids. Each cell type "does its own thing" when appropriately stimulated

THE CHEMICAL NATURE OF HORMONES

Hormones Synthesized from Amino Acids

Most (but certainly not all) hormones are synthesized from amino acid precursors. The very small molecules (modified amino acids and some low molecular weight peptides) are chemically identical in all vertebrates, although functions subserved may be quite different. Melatonin which affects movement of pigment granules in the skin of cold-blooded vertebrates is the same as melatonin which affects reproductive functions of hamsters.

As peptide molecules increase in size and complexity, species differences emerge; but hormones from one group may be