TURNER
BAGNARA

General Endocrinology

Sixth Edition

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Preface

During the five years since the fifth edition appeared, a wealth of new information about endocrinology has emerged. In this sixth edition we have attempted to distill from this body of new knowledge those elements that are essential to the student of modern endocrinology. Consistent with the aims of the first edition, which appeared in 1948, and in keeping with the goals of all the subsequent revisions, the current version is general in its coverage of the field. We have tried to emphasize basic principles and have illustrated them with examples taken both from clinical endocrinology and from the rapidly growing field of comparative endocrinology. Attention has been devoted to invertebrate endocrine systems, not only for their own sake, but because they demonstrate analogies important to the general endocrinologist. In covering comparative aspects our attention has not been focused solely on lower vertebrates; rather, information about mammals, including man, has been integrated into the discussion through the unifying theme of evolution.

Intensive research on the mechanisms of hormone action has provided many new data. Accordingly, we have given this area strong attention not only in those chapters dealing with specific hormones, but in Chapter 2, which deals with general aspects of the science of endocrinology. To enhance this discussion we have prepared a new illustration which describes a model that includes both hormone receptor mechanisms and sites of hormone action, either at the cell membrane or at the level of the nucleus. Appropriate attention has been given to the ultrastructure of endocrine glands, mechanisms of hormone secretion and transport, and hormone assay. New biochemical information about hormones has emerged and we have presented current chemical structures of pituitary hormones, releasing hormones, and gastrointestinal hormones. This new knowledge about chemical structures has provided a cogent vehicle for the discussion of hormone evolution. Important advances have led to the recognition of new hormones such as cholecalciferol. These and many other hormone-like substances are discussed in modern context.

All of the chapters have been brought up to date and some of the changes have been extensive. In previous editions information about neuroendocrine mechanisms has been scattered among several chapters. In this revision, Professor Turner has combined this material into a new Chapter 3, Neuroendocrinology. Consequently, the last chapter, Endocrine Mechanisms in the Invertebrates, has been completely reworked since it formerly contained much information about neurosecretion and neuroendocrine mechanisms. For similar reasons, the first two introductory chapters have been modified considerably. Chapter 16 has been greatly renovated, although it still retains its role of containing miscellaneous hormone groups. Much new information about gastrointestinal hormones is presented and the endocrine role of the pineal gland is discussed. It seems likely that in subsequent editions the material covered in this chapter will form the basis for new chapters.

Just as with previous editions, an extensive bibliography is found at the end of each of the chapters. We have not documented every fact; however, the citations have been carefully chosen to assist the interested students who may wish to explore specific areas in more detail.

We are grateful to many people who have contributed to this revision. Many colleagues have generously supplied figures, and these are acknowledged in the legends. Others have offered helpful suggestions. In particular, in this regard, we acknowledge the help of Professor Hideshi Kobayashi, Dr. Mac E. Hadley, and Mr. Steve Vigna. We are also grateful to the many users of this textbook who offered suggestions that were forwarded to us by the W. B. Saunders Company. It was in response to some of these that we decided to utilize many new drawings. These were skillfully prepared by Mr. Robert Hale of the University of Arizona. Important technical support in completing various parts of the revision was kindly supplied by my wife, Mary Louise, and by my student Sally Frost. Without their help this sixth edition would have been slow in coming.

JOSEPH T. BAGNARA

Greer, Arizona
July 4, 1976

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CHAPTER 1

Introduction

It is not likely that endocrinology could be defined in a manner entirely acceptable to all biologists since there are many points of view and many gaps in our information. There are some who regard it as the aspect of biology dealing broadly with the chemical integration of the individual. Others, following the classic definition of Bayliss and Starling, prefer to confine its scope to the ductless glands and the adjustments that their special products facilitate. It is probable that the first position is too flexible and the second too rigid. As the field is more critically explored and more becomes known about reactions at the cellular level, it is likely that certain unifying principles will emerge. Although broad definitions are desirable and essential, they must undergo change as new information is brought to light. Endocrinology stands to be enriched by the recognition of a wide spectrum of intermediate or transitional types of chemical integrations that do not fit current definitions.[52] As comparative studies are extended, many more deviations from the conventional functional patterns will undoubtedly be revealed and these must be given ample consideration.

The term *hormone* has probably been applied too loosely to a great variety of unrelated substances. Agents emanating from injured tissues have been called "wound hormones" and growth substances in plants "phytohormones"; agents released from nerve terminals have been classified as "neurohormones"; and even carbon dioxide has been referred to as a "hormone of respiration." Some have used the term "social hormone" to describe chemical agents that are released into the external environment and serve to influence the behavior of other individuals of the same species.[66] In termites, for example, the reproductive and soldier castes prevent other individuals from becoming members of their own castes by secreting materials that are ingested and act through the corpus allatum, an endocrine gland influencing differentiation.

Some of these agents, although they perform integrative functions, probably do not fall within the scope of endocrinology. However, it must be recognized that ductless glands are present in certain invertebrates and in all vertebrates. Moreover, one would be hard pressed to give a precise definition of an endocrine gland because all cells possess some secretory capacity and contribute to the internal environment of the organism.

As research broadens and deepens our knowledge of coordinatory systems, it becomes increasingly apparent that products of these systems participate in every bodily function, and even have profound influences upon the mental states and behavioral patterns of individuals. Studies on the invertebrates and lower vertebrates suggest that chemical integration by hormones and similar agents is an overall phenomenon prevailing throughout the animal kingdom, and that important actions may be exerted during developmental stages as well as in mature organisms. Further information is urgently needed on the evolutionary history of endocrine mechanisms. Comparative endocrinologists will probably discover more clues that will be of value in helping to interpret adjustments that must be operating at the human level. Information on regulatory mechanisms is accumulating rapidly and, as in all sciences, the established data must be reevaluated as current research yields new insights; this frequently necessitates modifications in interpretation and changes in terminology. It is imperative to remember that present theories are tentative.

Biologists are beginning to realize that the nervous and endocrine systems, both functioning to integrate the organism, are not so divergent and sharply delimited as was formerly supposed. A common physiologic attribute of these two systems is their ability to synthesize and release special chemical agents that are capable of spreading for varying distances. Nerve cells produce agents that act as chemical messengers either locally (*e.g.*, acetylcholine) or at a distance (*e.g.*, oxytocin). Many endocrine glands, through their hormones, affect the nervous sytem; on the other hand, endocrine organs are frequently stimulated or inhibited by products of the nervous system. Seldom does one encounter biologic phenomena that are controlled exclusively by either the nervous sytem or the endocrine system; most are under the overlapping authority of both systems. Furthermore, studies on neurosecretion leave no doubt that the nervous system has its own endocrine specializations for the release of hormones. The functional interlocking is so remarkable that nervous and endocrine elements are now regarded as constituting a *neuroendocrine system.*

Hormones act upon *target tissues* and *organs* by regulating the rates of specific biochemical reactions in the constituent cells. These biochemical adjustments are accomplished at the cellular level by virtue of their power to augment or restrain special enzyme systems. Hormones are released at the right time and in proper amounts in the normal organism, and maladjustments of severe consequence may be precipitated if the timing is wrong or if they are deficient or present in superabundance. Obviously, hormones are without effect unless the target cells and tissues are capable of responding to them. The competence of a particular hormone within the living body may be altered by a multitude of autopharmacologic substances that are always present with it in the body fluids.

The rapid coordinations of the body are controlled by the nervous system. Since hormones are generally conveyed by the circulation and must be transmitted through intercellular tissue fluids in order to reach their target organs, we find that they regulate processes such as growth, regeneration, reproduction, blood chemistry, molting, metabolic rate, pigmentation, etc. These are adjustments that require duration rather than speed.

TYPES OF CHEMICAL MESSENGERS

Admittedly, there are many transitional situations that do not fit into the framework of formal definitions, but some agreement on terminology is essential. The suggestion of Parkes and Bruce that the term *chemical messengers* be used broadly to include both internal secretions involved in integration of the individual and external secretions concerned with the integration of populations has some merit.[48] The categorization of such chemical messengers presents certain problems, largely because demarcations between groups are not always sharp; moreover, by their nature some categories can be readily defined while others are more vague. In any event, it must be remembered that the following categories of chemical messengers were established arbitrarily with the aim of providing the most convenient means for discussion and understanding. They are: (1) hormones, (2) neurohormones and neurohumors (neurotransmitters), (3) assorted chemical messengers, (4) phytohormones, and (5) pheromones.

Hormones

According to the original use of the word, hormones are chemical agents which are synthesized by circumscribed parts of the body—generally specialized ductless glands—and are carried by the circulating blood to another part of the body where they evoke systemic adjustments by acting on specific tissues and organs. In the course of time, there has been a tendency to restrict the term *hormone* to the regulatory products of endocrine glands, and to resist the trends to broaden its meaning to include such metabolites as carbon dioxide and the large category of substances (*e.g.,* embryonic evocators) that exert localized actions. In any case, hormones facilitate integrative adjustments within the individual and must be distinguished from a growing list of exocrine gland products (pheromones) that play important roles in integrating groups of individuals.

Though often it is difficult or impossible to separate the neural and hormonal components of regulatory processes, the complex of endocrine glands in the vertebrates is quite clear-cut. This system includes the pituitary, thyroids, parathyroids, adrenals, gonads, pancreatic islets, and the hormone-producing part of the gastrointestinal tract. In certain mammals, the placenta would have to be regarded as an endocrine gland since it is the source of various steroidal and protein hormones. During the course of vertebrate evolution, there has not been much change in the position of the endocrine structures within the body. Each of these endocrine organs will be considered according to structure, synthesis of hormones, regulation of function, action of hormones, and interrelationships with other components of the regulatory system. All these glands are comparatively small, are devoid of ducts, and have access to a rich vascular supply.

The most thoroughly studied endocrine glands are multicellular, but it is quite probable that unicellular types, sometimes capable of migrating through tissues, will be recognized. Instead of releasing their products upon a free surface, as exocrine glands do, these would discharge regulatory chemicals into the body fluids.

Regarding embryonic origin, the endocrine glands differentiate from all the germ layers. Those derived from mesoderm (adrenal cortex, gonads) produce steroidal hormones; those developing from ectoderm or endoderm secrete hormones that are either modified amino acids, peptides, or proteins.

Most internal regulating agents among the invertebrates are *neuroendocrine* in nature, but circumscribed ductless glands do exist. In the latter category may be mentioned the androgenic glands of crustaceans and insects,[17] the corpora allata and prothoracic (ecdysial) glands of insects, and the Y organs of crustaceans.

Neurohormones and Neurohumors

Within the nervous systems of all animals from coelenterates and flatworms to human beings, there are nerve cells that show cytologic indications of being capable of functioning as glands.[8, 41] These cells are neurosecretory in nature and release chemical messengers called *neurohormones.* Although the neurosecretory cells are capable of conducting impulses, their principal function is the synthesis and release of neurohormones. Actually, they combine the attributes of nerve cell and gland cell, since they receive information from neural centers via ordinary afferent neurons and respond through the release of chemical messengers. The neurohormones of the vertebrate neurohypophysis (oxytocin and vasopressin) are simple peptides, and their actions have been extensively studied. The various hypophysiotrophic factors of the vertebrate median eminence are thought to be neurohormonal peptides that are delivered via a portal blood flow to the adenohypophysis, where they regulate the output of hormones. Most of the neurohormones among invertebrates are also peptides and are involved in such processes as color change (crustaceans), molting and metamorphosis (insects), the initiation of regeneration (annelids), gametogenesis, and metabolism (certain annelids and arthropods).

The ingenious experiments of Loewi in 1921 helped explain why sympathetic and parasympathetic nerves usually have opposite effects upon the effector organs they supply. He used isolated frog hearts, with nerves intact, and arranged them so that Ringer's solution perfused through one heart could be introduced into another, completely separated heart. Stimulation of the vagus nerve (parasympathetic) to the first heart caused the contraction rates of both hearts to decrease; stimulation of the sympathetic nerves caused the rates of both hearts to increase. The two kinds of nerves apparently were releasing different agents into the perfusate as it irrigated the first heart. Further studies have shown that the parasympathetic terminals release acetylcholine, whereas most of the postganglionic terminals of the sympathetic nerves release norepinephrine with perhaps traces of related compounds. The adrenergic transmitter was formerly called "sympathin," but it is now known to be norepinephrine. Depending upon the kind of neurohumor released, it is customary to classify the fibers of the autonomic system as "cholinergic" or "adrenergic." Transmission in the central nervous system probably involves a whole family of chemical agents, including acetylcholine, norepinephrine, dopamine, and serotonin.

These agents released at axonal terminals are the products of conventional nerve cells and are called *neurohumors;* they have often been thought of as "local hormones" or "diffusion hormones." Although the capacity to produce neurohumors may be regarded as providing support for the concept that secretion is a fundamental property of all nerve cells, these ordinary neurons lack the glandlike specializations of the neurosecretory cells that are the source of neurohormones. The neurohumors function at nerve terminals in minute quantities, over very short periods of time. They may be promptly inactivated by means of enzymes or, particularly in the case of adrenergic terminals, the substance seems to be rendered ineffective by being returned quickly to the presynaptic neuron that produced it, where it is temporarily stored and discharged again as the need arises.[53] The neurohumors clearly are chemical messengers of great importance, but they differ from ordinary hormones in not being transported by the circulation. They differ from neurohormones with respect to their source, coming from conventional nerve cells in general instead of from neurosecretory cells. So many intergradations are encountered that it is impossible to distinguish clearly between neurohormones and neurohumors in all instances. It is instructive to recognize such intermediate situations for they serve to emphasize the great degree of flexibility and variation that exists among the mechanisms of neurochemical communication.[53]

Assorted Chemical Messengers

This is a convenient category in which to place the large variety of chemical messengers which fail in one or more ways to satisfy the requirements generally implied by the term "hormone." The cells of all organisms, whether unicellular or multicellular, produce and release substances of some kind which change the chemistry of internal and external environments. In this sense, no cell has completely lost its glandular properties even though it has differentiated highly in another direction. Many compounds, such as carbon dioxide and urea, have general origins within the body, in contrast to the more or less specific sources of endocrine gland secretions, and perform integrative roles of great importance.

Products of dead or injured tissues, such as histamine and leukocyte attractants, are known to participate in inflammatory processes. Erythropoietin is an integrative substance released by the kidneys and perhaps other organs in response to anoxia; its action is to promote proliferation of red blood cells by the bone marrow. *Thymosin,* a hormone-like factor from the thymus, is essential for the initiation of immune reactions in response to certain particulate antigens and to skin homografts. Extracts of a variety of tissues contain substances that inhibit cell division. These have been referred to as *chalones.*[17] *Nerve growth factor (NGF),* present in a variety of tissues, notably the submaxillary glands, stimulates profound growth and development of the nervous system, especially of sensory and sympathetic cells. A similar factor, *epidermal growth factor (EGF),* is often extracted with NGF; its principal effects are epidermal growth and keratinization.[21] *Secretagogues* are extrinsic factors present in food which, after absorption into the blood, act to stimulate the glands of the gastrointestinal tract. Inductive substances are of great importance during embryonic life; they are restricted in their origin and are not effective at great distances from their source. The *prostaglandins* were originally identified in human seminal fluid, but are now known to be present in most, if not all, mammalian tissues. They have a wide range of biologic actions, but are not hormones in the strict sense. It is important to recognize all of these deviant regulatory agents without subtracting from the classic connotations generally conveyed by the term *hormone.*

The extracellular synthesis of chemical messengers may occur within body fluids, when the necessary enzymes, substrates, and energy sources are available, and this may be more widespread than is currently appreciated.[7] A clear example is the synthesis of angiotensin II, an octapeptide having powerful vasopressor effects and, at least in certain species, the capacity of eliciting the secretion of aldosterone from the adrenal cortices. Renin is a proteolytic enzyme of the mammalian kidney, probably deriving from the juxtaglomerular apparatus; it is freed into the blood. It acts upon a blood protein (substrate) to produce angiotensin I, which is then enzymatically converted to the biologically effective angiotensin II.

It is known that whole human blood contains enzymes that are capable of bringing about a variety of transformations and interconversions of steroid hormones, and of particular significance is the conversion of the less to the more biologically active compounds.[10] One study showed that 60 per cent of the plasma testosterone (potent androgen) in the human female arose from the peripheral conversion of androstenedione (weak androgen).[34] The source of the plasma enzymes is unknown.

The concept of "cooperative steroidogenesis," whereby multiple organs participate in the step-by-step synthesis of steroidal hormones, deserves consideration, especially by comparative endocrinologists.[47] The endocrine status of the corpuscles of Stannius, derived from the kidney tubules or ducts in fishes, has been debated for years; it seems now that they can effect very limited steroid transformations. Their steroidogenic ability is very meager compared with such glands as the mammalian adrenal cortex, but they may have utility in the organism if they bring about only one key transformation. The steroidal hormones (ecdysones) of insects and crustaceans are commonly regarded as being synthesized by prothoracic glands and Y organs, respectively, but this can be questioned on the grounds that these structures lack the kind of ultrastructure characteristic of steroidogenic glands of vertebrates. There is no doubt that these organs condition the synthesis of hormonal steroids from cholesterol, but they may not possess the biochemical equipment required for all of the transformations. Although it has not been demonstrated, such organs could conceivably release essential enzymes or substrates, the actual synthesis of the finished hormone occurring in the body fluids.

Phytohormones

Since plants are devoid of nervous systems, it is clear that their biologic adjustments are accomplished largely through the synthesis and dispersal of chemical messengers.[58] Great advances have been made by plant physiologists and biochemists in elucidating such regulatory substances as auxins, gibberellins, the so-called "wound hormone" (traumatic acid), leaf-growth substances, root-growth regulators, kinins, and florigens. These plant agents are principally growth regulators, and many practical applications of economic importance have been found for them. The hormones of plants and animals are similar in many ways, but there are profound differences with respect to source and method of transmission.[42] The plant cells that synthesize and release phytohormones are not sufficiently differentiated to be considered circumscribed glands of internal secretion. Moreover, the plant hormones are moved mainly from cell to cell instead of being dependent upon vascular channels for transport to distant targets. It may be discovered, however, that certain animal hormones are disseminated to a greater extent by cell-to-cell transmission than is presently appreciated.

Raper showed that the development of sex organs in the fungus *Achlya* consists of a series of steps, each being governed by particular *ectohormones* (pheromones) released by other individuals and passed through the aqueous environment.[49]

Pheromones

While acoustical and visual modes of communication are the obvious primary mechanisms of transmitting information between individuals, the use of chemical signals is also very important. Chemical signals are of two classes; those that communicate between individuals of the same species (intraspecific) are called *pheromones,* while those operating between different species (interspecific) are termed *allomones* or *kairomones.* The former refers to chemicals which favor the producer of the substance, and the latter to those that favor the recipient.[40]

The term pheromone was originally applied to the sex attractants of insects but, with the accumulation of information, the term has been broadened to include various kinds of agents released into the environment and functioning in all major groups to integrate members of the population. The pheromones are not hormones since they are generally the products of exocrine glands; however, the capacity of the exocrine glands to produce pheromones is often dependent on hormonal stimulation.[5, 45, 50] In some species, specialized receptors have evolved. The chemical structures of an array of pheromones have been established, and while no broad generalizations are yet possible, it should be noted that most of these compounds are simple ones having low molecular weights. Many are derivatives of fatty acids or terpenes. These environmental agents may be ingested, absorbed through body surfaces, or perceived by olfaction. They evoke specific behavioral, developmental, or reproductive responses and these are of great significance from the standpoint of ecology and survival of the species. The pheromones differ from hormones in several respects: (1) they are transmitted via the external environment, (2) they are typically more species-specific than are hormones and (3) they elicit adjustments in the bodies of other individuals, whereas hormones typically confine their activities to the organism that produced them. The distinctions are not always clear-cut; there are instances in which the same endocrine gland product may be active within an individual (hormone) and between individuals of a colony (pheromone). Certain hormones from the corpora allata of termites probably function in this dual manner. There are instances of host hormones influencing reproductive processes in parasites inhabiting their tissues and organs. In such situations, one and the same substance serves as a hormone for the host and as a pheromone for the parasite. Pheromones perform important roles in many symbiotic and parasitic relationships involving animals of different species.[25] It seems appropriate for endocrinologists to consider pheromones for three reasons: (1) the exocrine glands that produce pheromones are often hormone-dependent, (2) hormone metabolites being eliminated from the system may function as pheromones in some species, and (3) the "primer" pheromones initiate prolonged physiologic adjustments involving the central nervous system and multiple endocrine glands, such as the pituitary and gonads. Their actions demonstrate graphically how environmental changes impinge upon the nervous and endocrine systems to evoke functional and behavioral changes.

Pheromones are grouped broadly into two categories: (1) signaling or releaser pheromones, which produce rapid and reversible responses through the central nervous system or along quick-acting neuroendocrine channels, and (2) primer pheromones, which activate a longer series of neuroendocrine events that develop slowly and require prolonged stimulation. Sex attractants and trail and alarm substances of insects are examples of pheromones having signaling effects. Among mammals, the aggressive behavior of unfamiliar male mice may be mentioned; this is related to a pheromone of urinary origin and to another arising from the foot pads. Removal of the olfactory bulbs or destruction of the nasal epithelium removes the aggressive behavior, but these procedures do not protect the animal from attacks by intact males. Secretions from the androgen-dependent chin gland of the Australian rabbit provide repelling or inhibiting signals for other males. Subordinate males have smaller chin glands than the dominant buck, and spend less time chinning objects within their territories, including does and young animals.[13]

Reproductive life of the honey-bee colony is regulated by a pheromone from the queen's mandibular glands, and this has been chemically identified as 9-ketodecanoic acid and synthesized. The secretion has a primer effect since it is ingested by the workers and acts to inhibit the development