Textbook of Endocrinology

Fifth Edition

Edited by

ROBERT H. WILLIAMS, M.D.

With Contributions by Thirty-eight Authorities

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DEDICATED

TO

Contributors of the past, who as investigators, educators, and authors have evolved the knowledge summarized in this book,

AND TO

Contributors of the future, who extensively dedicate their activities toward providing universally better health and more happiness, sharing their knowledge readily and collaborating freely in attaining these goals.

PREFACE TO THE FIFTH EDITION

Vast amounts of information are accumulating rapidly concerning metabolic processes involved in the formation, maturation, and function of body tissues and in the pathogenesis of many diseases, including atherosclerosis, heart disease, hypertension, cancer, mental disorders, and genetic abnormalities, among others. Indeed, every illness is associated with metabolic changes. Furthermore, in all body cells hormones influence the metabolism of nucleotides, proteins, lipids, carbohydrates, vitamins, water, and electrolytes. Therefore, knowledge of endocrinology and metabolism is important in every branch of medicine.

The contributors to this book have previously demonstrated excellence as investigators, teachers, and authors. Most of them are engaged in both basic and clinical investigations and teaching. They are adept in the practical application of basic knowledge to clinical problems and use this approach in discussing pathogenesis, diagnosis, and therapy. They have been encouraged to indicate where controversy exists, but to submit tentative conclusions based on available data.

Great efforts were made to restrict the length of each chapter; several chapters are about the same length as in the fourth edition or shorter. A small amount of repetition in different chapters has been permitted and encouraged for emphasis, and because many hormone activities are interrelated.

The authors were asked to use many figures, tables, and prominent headings to aid in clarification and rapid reference. Special attention was devoted to diagnostic tests and treatment, and emphasis given to measures that are most helpful.

The authors were urged to make their references selective and, especially, to include a number of recent reviews. They were told not to attempt to document each statement; sometimes one paragraph includes the results of many investigations.

This is predominantly a new book. Twenty-one of the 38 authors are new, and 12 chapters with new content have been added. In seven other chapters, there are one or more new authors. All of the chapters have been extensively rewritten.

The new chapters discuss (a) hormone actions on skin, on skeletal muscle, on blood elements, on allergic and immunologic reactions, and on cancer; (b) the pineal organ, gastrointestinal hormones, angiotensin-aldosterone system, and prostaglandins; and (c) the interrelationships of hormone secretion and action with cyclic nucleotide metabolism, protein metabolism, and aging.

Chapter 1 deals with major principles, especially with key regulatory and coordinating processes. It considers functions of the cell membrane and reciprocal communications and actions between it, the nucleus, and other intracellular organelles. This chapter also discusses the mechanisms for coordination of metabolic activities in large organisms. The endocrine system and the autonomic nervous system together form a single neuroendocrine unit, with the main endocrine and metabolic coordinative center in the hypothalamus. As discussed particularly in Chapter 12, specific areas in the hypothalamus are inhibited or stimulated by hormones or other constituents in plasma and by neurotransmitters. In turn, individual areas of the hypothalamus respond by releasing specific hormones that are transmitted either directly to the pituitary, or through the autonomic nervous system. The hypophysiotropic hormones consist of those that release ACTH, TSH, GH, FSH, LH, prolactin, and MSH and of those that inhibit the release of GH, prolactin, and MSH. Several chapters emphasize that the site and amount of action by a hormone depend upon its binding to its own specific receptor. From the hormone-receptor complex, messages are transmitted to other cell sites. As discussed particularly in Chapter 16, cyclic nucleotides act as intracellular messengers.

Chapter 25 emphasizes the extensive role of genetics in growth, maturation, aging, and other events, and Chapter 8 details genetic abnormalities in sex differentiation and development.

The special roles of vasopressin, aldosterone, glucosteroids, and angiotensin in water and electrolyte metabolism and in the maintenance of plasma volume and blood pressure are discussed in Chapters 3, 5, 19, and 20.

Hormonal interrelationships between the gastrointestinal tract, pancreas, and liver are presented in Chapters 9, 10, and 14. The roles of gastrin, secretin, pancreozymin, proinsulin, insulin, glucagon, enterogastrone, and serotonin are emphasized.

There are discussions of the latest developments regarding calcitonin, vitamin D metabolites, somatomedin (NSILA), chorionic somatomammotropin, catecholamines, prostaglandins, erythropoietin, thymic hormones, pherhormones, and hormones from ectopic sites.

Newer methods are mentioned for measuring many hormones: melatonin, hypothalamic hormones, vasopressin, oxytocin, anterior pituitary hormones, triiodothyronine, thyroxine, calcitonin, glucagon, glucagon-like hormone, gastrin, secretin, angiotensin, aldosterone, testosterone, estrone, estradiol, progesterone, placental hormones, proinsulin and its connecting peptide, prostaglandins, and erythropoietin. There are discussions of the diagnostic use of hypophysiotropic hormones, ^{131}I-cholesterol, and technetium. Several chapters contain tables listing the order of preference of tests for many clinical disorders.

There are descriptions of the therapeutic uses of calcitonin, mithramycin, o,p′-DDD, propranolol, clomiphene, streptozotocin, diazoxide, monocomponent insulin, clofibrate, cholestyramine, lithium, parachlorophenylalanine, methysergide, vitamin D derivatives, L-dopa, antifertility drugs, and other compounds.

The editor is grateful for the splendid cooperation and superb contributions of the authors, the great assistance given by Alison Ross and other manuscript editors, the excellent secretarial activities of Sharon Kemp, and the many contributions of the members of the W. B. Saunders Company.

ROBERT H. WILLIAMS, M.D.

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CHAPTER 1

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By Howard Rasmussen

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HORMONES AND CLINICAL MEDICINE

Claude Bernard was the first to appreciate that the composition of the fluids bathing the cells of multicellular organisms must be controlled. He proposed that the stability of this internal environment, which he termed the *milieu organique interieur,* gave the body a degree of functional freedom from the variability of the external one, the *milieu cosmique ambiant.* Since Bernard, it has become evident that such stability is attained by the coordinated activities of two major systems: the endocrine system and the autonomic nervous system.

At first glance, these two regulatory systems appear rather distinct. Information is carried by neural impulses in the autonomic system, and by the blood in the endocrine system. In general, autonomic responses are more localized and more rapid than hormonal ones. Closer scrutiny, however, reveals that this classification is indistinct. The nerve endings release chemical transmitters, acetylcholine and norepinephrine, which under some circumstances circulate in the plasma and can be considered endocrine gland products or hormones. There is a gradation from what might be termed a purely neural response through intermediate responses to a purely endocrine one.

The first response can be illustrated by the release of norepinephrine from sympathetic nerve endings in the smooth muscle of the wall of an arteriole; the second by the release of norepinephrine from the adrenal medulla; and the third by the release of parathyroid hormone from the parathyroid gland. Each response is elicited by an afferent stimulus which is neural in the first two instances and humoral in the third. The efferent response in the first is primarily neural, the norepinephrine acting primarily at the site of its release. In the second, the efferent response is initially neural (preganglionic fibers to adrenal medulla) but soon becomes endocrine because the norepinephrine is disseminated by the circulation and acts at widely different sites within the organism. The efferent response in the third is completely endocrine, the hormone being released directly under the influence of the chemical afferent stimulus.

The unique interrelationships between the two systems are even more apparent in the hypothalamus. This portion of the central nervous system is the highest integrative center of both the autonomic and endocrine systems, as well as the major site at which the activities of the two systems merge. In addition to its classic nervous functions, it is the site of synthesis of several polypeptide hormones. Hence in the largest sense the autonomic nervous system and the various endocrine glands represent a single neuroendocrine system that has evolved to integrate and coordinate the metabolic activities of the organism. Although this book deals primarily with the endocrine aspects of this larger system, references to the autonomic system are made, particularly to those aspects most clearly related to endocrine activity.

Before a discussion of the general aspects of endocrine organization is undertaken, another facet of the concept of the *milieu intérieur* remains to be considered.

As defined by Bernard, the *milieu intérieur* consists of the plasma and extracellular fluids bathing the cells of a multicellular organism. Yet, from all indications, life developed in a pre-Cambrian sea rich in magnesium and potassium, a milieu differing considerably from that of Bernard's *milieu intérieur* but strikingly similar in composition to the intracellular fluids of present-day animal forms. It is within this milieu that cellular metabolism operates. In reality the intracellular fluids of many simple organisms, such as yeast, as well as those of higher forms, are contained not in a single cellular compartment but in multiple membrane-bounded compartments, each with its own distinct composition. These intracellular fluid compartments are in fact the true chemical environment of life, the *milieu de la vie*.

Each cell of a multicellular organism has inherited a complex system of homeostatic controls with which to regulate and coordinate the activities of its several components. Much of modern biology is concerned with the elucidation and study of these cellular control systems. Considerable unity already has been discovered. For example, it is apparent that the mechanism for transporting glucose into a muscle cell is basically similar to that employed by a bacterial cell and that the intracellular hormone, cyclic AMP (3′,5′-AMP or C-AMP), was involved in regulating cell metabolism in lower forms long before it became an aspect of hormone action in the rat liver cell.

It is becoming increasingly clear that an understanding of these basic cellular control systems is necessary to define the basis of hormonal action and that the control of the composition of Bernard's *milieu intérieur* is achieved by adaptations to later needs of these ancient but highly sophisticated intracellular systems. In other words, extracellular homeostasis is but an evolutionary extension of intracellular homeostasis. Much of the present chapter is concerned with a discussion of these intracellular control systems and their relationship to hormones and to hormone action.

THE ENDOCRINE SYSTEM

Organization

Basic Concepts

In order to describe how endocrine systems are organized, it is necessary first to introduce certain concepts that have been borrowed from the field of systems analysis and servomechanisms. Basic to an understanding of these concepts are the definitions of systems and a consideration of whether these systems are open or closed. A system for the purpose of our discussion is an organized unit of activity from an enzyme or multienzyme complex to an entire organism or even a population of organisms. In viewing any one of these systems we can consider them in one of two fashions: either as open or as closed loop systems. The distinction between the two is simple yet consequentially profound. In an open loop system, a cause or input alters the effect or output, but the converse is not true. In a closed loop system, output influences the behavior of the system and its response to an input. In such systems it becomes meaningless to consider simple cause and effect. Not only are responses determined by the nature and strength of the stimuli, but the stimuli depend upon the responses according to the present organization and environment of the system in question.

The paradox of modern endocrinologic research has been that, at the physiologic level of analysis, it has been recognized and generally accepted that the endocrine system and its various subcomponents are organized in a hierarchy of closed loop systems. However, at the biochemical or cellular level of organization, nearly all considerations of the mode of action of hormones have been cast in the mold of open systems, cause and effect relationships in which the hormone acts upon the cell to cause a variety of effects but in which the cell does not in turn act upon the original stimulus.

This paradox has more than merely philosophic interest. The models of cellular organization that we build in innocence and enthusiasm today become the dogma of tomorrow and hence shape the intellect's quest for further understanding. It thus becomes imperative to state explicitly that the mammalian organism and its organized subcomponents, e.g., cells or metabolic pathways, all operate as closed loops. The entire system is a metabolic net. Homeostasis at the level of cell and organism depends fundamentally upon communication between the components. Stimulus (input) leads to response, but response (output), to be meaningful, must in turn influence the stimulus. Disease and dysfunction result when communication in either direction fails.

The most important general concept is that of *feedback control*, and particularly *negative feedback*. The simplest situation to consider is that of two variables, A and B. If $A = f(B)$ and $B = f(A)$, then a feedback relationship exists between the two (Fig. 1–1). If the concentration or effect of A is increased when B increases, then *positive feedback* exists, whereas if A decreases when B increases, *negative feedback* exists. These concepts are illustrated in Figure 1–1 by solid and broken arrows respectively.

The concept of feedback is derived from the operation of electrical networks. As it operates in biochemical or endocrine systems, however, it differs considerably in operational properties from electrical systems. Since much confusion exists on this point, and since many models of biochemical feedback have been constructed as analogues of electrical models, this difference is stressed below.

The most important feature of feedback in a physiologic or biochemical sense is that the *input* to the system is usually a concentration, and the