WILLIAMS

Textbook of ENDOCRINOLOGY

SEVENTH EDITION

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DANIEL W. FOSTER, M.D.

IGAKU-SHOIN/SAUNDERS INTERNATIONAL EDITION

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PREFACE

Williams' *Textbook of Endocrinology* has played a major role in the evolution of modern endocrinology. Its aims were clearly stated in the preface to the first edition:

"The rapidity and extent of advances in endocrinology have made it increasingly difficult for the student and physician to take full advantage of information available for the understanding, diagnosis and treatment of clinical disorders. It is the realization of these difficulties that prompted the writing of this book. The main objective is to provide a condensed and authoritative discussion of the management of clinical endocrinopathies, based upon the application of fundamental information obtained from chemical and physiologic investigations."

The product was a book that over the years served as an effective bridge between clinical medicine and the science of endocrinology. On the one hand the clinical discipline profits immensely from scientific advances, and on the other hand clinical observations often raise important questions for investigation and on occasion provide answers that impact on the basic science. By accurately recording advances in both areas, the *Textbook of Endocrinology* has always conveyed the excitement of a rapidly changing discipline and simultaneously promoted the unity of a broad field that encompasses a spectrum from molecular biology to patient care. The influence of earlier editions was heightened because they were stamped by the personality of the editor, clearly reflecting his breadth of vision and remarkable capacity to teach and communicate. Perhaps Dr. Williams' most significant contribution was his capacity to select contributors who were at the forefront of their disciplines, thereby ensuring the freshness of each edition.

Because of its high standards, the editing of the book after the death of Robert H. Williams constituted a formidable challenge. Inevitably, the new editors have changed the focus somewhat. This is in part the consequence of recent advances in the field and in part a reflection of value judgments on the importance of current research. To convey the essence of a rapidly growing field in a single volume, it is necessary to be selective in both the extent and depth of coverage. This is especially true for a book designed for both the student and the practitioner of medicine, but the inevitable consequence is that some topics are less completely covered than others. We have aimed, however, at as broad a review as possible, and particular attention has been given to assembling up-to-date bibliographies that allow ready access to the literature for those requiring more detail. We trust that the final product is in keeping with the tradition and high standards of earlier editions.

We are particularly indebted to the contributors. Those who wrote in previous versions have devoted an immense effort in updating, and the new authors have expended an equal or greater effort in formulating their chapters *de novo*. Neither task is easy, and to our authors we say thank you. We also wish to express our appreciation to several associates and colleagues who, as experts in their fields, helped us with constructive and valuable criticisms: David W. Bilheimer, Neil A. Breslau, Michael S. Brown, Joseph L. Goldstein, Fred J. Hendler, Juha P. Kokko, William J. Kovacs, Kenneth Luskey, Michael R. McClung, Victor Schuster, Evan R. Simpson, and Peter J. Snyder. Finally, the book could not have been edited without the dedicated help of the co-workers in our offices—Brenda H. Hennis, Rita A. Koger, Darlene R. Reynolds, A. Joyce Rojas, Patricia C. Walker, and Dirk Wilson.

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DANIEL W. FOSTER

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SECTION 1
HORMONES AND HORMONE ACTION

1 Introduction

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The capacity of specialized tissues to function in integrated fashion as components of intact organisms is made possible in large part by two control mechanisms: (1) the nervous system, which transmits electrochemical signals as two-way traffic between brain and peripheral tissues or between tissues in reflex circuits; and (2) the endocrine system, which releases chemical mediators termed hormones into the circulation for action away from their sites of origin. The distinction between these two systems was clearly delineated by Starling in the Croonian Lectures for 1905 in which separate endocrine and neurogenic control mechanisms were described for the regulation of gastric function.[1] Endocrinology has traditionally been defined as that branch of biological science that concerns itself with the actions of hormones and the organs in which the hormones are formed. Its boundaries include the study of the anatomy and physiological function of the major endocrine organs, the secretory products of these organs, the mechanisms of hormone action, and the clinical manifestations of hormone dysfunction. In fact, there is no sharp distinction between the endocrine and nervous systems (Fig. 1–1). Thus, the nervous system liberates chemical agents that can act as local mediators or true circulating hormones, and hormones of several types also act as neurogenic mediators within the central nervous system. Furthermore, there is an intimate link between the nervous and endocrine systems at the level of the hypothalamus and the pituitary that serves to integrate the two systems into one functional control unit (see Chapter 17). The traditional concept of endocrinology has become even more blurred by the recognition that circulating hormones can also have local effects in the cells in which they are synthesized (e.g., locally formed estrogen in the central nervous system) or by diffusion into adjacent cells (e.g., the role of testosterone in regulating spermatogenesis, the effects of cortisol on the adrenal medulla, and the regulation of glucagon secretion by insulin). Consequently, there is a certain artificiality in attempting to define a specific arena of knowledge as endocrinology on either biological or clinical grounds.

Despite these theoretical problems, certain factors serve to unify the discipline. First, regardless of their site of action, the central focus is on hormones. Second, the synthesis of these hormones is controlled in general by the same type of regulatory mechanism, namely, feedback control in which the concentration of the hormone signals the need for more or less production. Third, there is a tight coupling between basic and clinical endocrinology. Clinical phenomena are frequently of fundamental import to basic science, and virtually all advances in the basic science of endocrinology have clinical ramifications. The

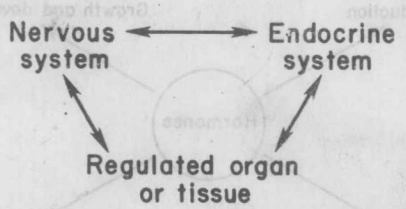

Figure 1–1. Integrated control systems in body. Degree of control by nervous and endocrine systems varies. For example, the thyroid gland is under almost exclusive endocrine control by thyroid-stimulating hormone, whereas the adrenal medulla is essentially regulated exclusively by the nervous system. However, both glands are equally part of endocrinology because they produce hormones.

subjects covered in this book seem appropriate for this concept of endocrinology, although they vary from those central to the discipline to those at the periphery.

THE FUNCTION OF HORMONES

Hormonal function involves four broad domains—reproduction; growth and development; maintenance of the internal environment; and production, utilization, and storage of energy (Fig. 1–2).

REPRODUCTION. Hormones not only regulate gametogenesis but also control the dimorphic anatomical, functional, and behavioral development of males and females that is essential for sexual reproduction. It is of particular interest in this regard that no exclusive male or female hormones have been identified. All hormones characterized to date are present in both sexes, and both sexes have receptor mechanisms that allow response to all hormones. Sexual dimorphism is the result of differences in the amounts of individual hormones and differences in their patterns of secretion, rather than of their presence or absence. It follows that sexual reproduction requires a precise genetic programming that allows for the synthesis of an appropriate enzyme complement in the ovary or testis, which in turn catalyzes the formation of the appropriate amounts of hormones at the critical stages of life. The endocrinological control of reproduction encompasses every phase of the process, including many behavioral aspects.

GROWTH AND DEVELOPMENT. Endocrine control is fundamental for growth and development and involves the interaction of hormones of all classes including peptide, steroid, and thyroid hormones. It is of equal importance that hormones are involved in the limitation of growth. For example, if closure of the epiphysis did not occur, skeletal growth would presumably continue for an indefinite period. Hormonal interactions involved in the regulation and control of growth are multiple. It is probable that many hormones influence growth by regulating its final common mediator, the somatomedins.

MAINTENANCE OF INTERNAL ENVIRONMENT. Hormones are critical to maintenance of the internal environment necessary to sustain structure and function. Thus, they are involved in regulating and stabilizing body fluids and their electrolyte content; blood pressure and heart rate; acid-base balance; body temperature; and mass of bone, muscle, and fat. Of the major homeostatic systems, only respiration does not have a significant element of endocrine control.

ENERGY PRODUCTION, UTILIZATION, AND STORAGE. Hormones are the preeminent mediators of substrate flux and the conversion of calories into energy production or storage. In the anabolic state following a meal, excess calories are stored as glycogen and fat under the influence of insulin. In the catabolic state that occurs postprandially or after more prolonged fasting, glucagon and other counterregulatory hormones induce glycogen breakdown, gluconeogenesis, and mobilization of amino acids and fatty acids to preserve the plasma glucose in a safe range for function of the central nervous system while providing additional substrate for other tissues.

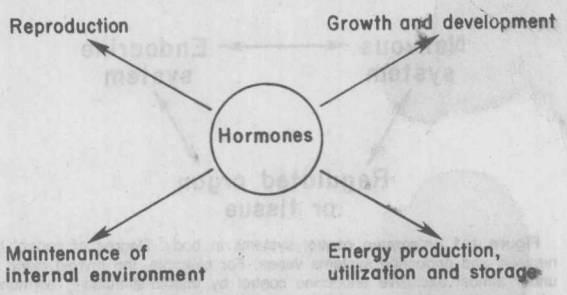

Figure 1–2. The four primary arenas of hormone action.

INTERACTION OF HORMONES

The effects of hormones are complex (see Chapters 3 and 4). A single hormone can have different effects in various tissues and in the same tissue at different times of life. Similarly, some biological processes are under the control of single hormones, whereas others require complex interactions between several hormones (Fig. 1–3).

ONE HORMONE: MULTIPLE ACTIONS. An example of a hormone with multiple effects is testosterone. Some of its diverse actions include: fusion of the labioscrotal fold in the male embryo during embryogenesis, induction of male differentiation of the wolffian ducts, regression of the embryonic breast (in some species), growth of the male urogenital tract, induction of spermatogenesis, growth of beard and body hair, promotion of muscle growth, retention of nitrogen, increased synthesis of erythropoietin, temporal regression of scalp hair, hyperplasia of the sebaceous glands with increased sebum production, development of prostatic hyperplasia in aging males of several species, secretion of the ejaculate, and virilization of the hypothalamus. It was originally believed that androgen exerted these diverse effects by distinct mechanisms. However, one of the most important findings from genetic studies and from modern molecular biology is that diverse effects can be modulated by a single mechanism. In the case of testosterone, these various actions can be explained by binding of the hormone (or its active androgen metabolite dihydrotestosterone) to a high-affinity cytoplasmic receptor protein followed by transport of the hormone-receptor complex to the cell nucleus of target tissues where

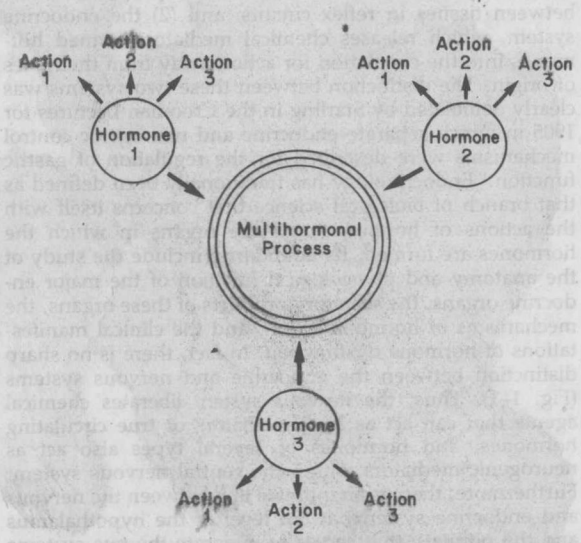

Figure 1–3. Actions of hormones. A single hormone may act independently or in concert with other hormones. For example, in this scheme the multihormone process might be maintenance of the plasma glucose, hormone 1 being insulin, hormone 2 glucagon, and hormone 3 epinephrine. Each hormone may also act to control or influence more than one process.

binding to DNA promotes the synthesis of messenger RNAs. The diverse actions of the hormone are due not to different mechanisms of action but rather to the fact that different cells at different stages of development are programmed to respond to the hormone-receptor complex in different ways. Alternatively, the action of a hormone may be enhanced or inhibited by the presence of other hormonal or nonhormonal regulators. Although it is theoretically possible that some action of testosterone might be mediated by another mechanism, modern studies strongly suggest that the simplified conceptual framework just described is correct. The mechanism of action of a hormone may be uniform, but not all its effects are direct. Testosterone, for example, enhances erythropoietin formation, and it is the latter that stimulates erythropoiesis and causes the differences in hemoglobin that exist between men and women. The same pattern of multiple effects from a single mode of action is seen with most hormones, including peptides that act at the cell surface.

ONE FUNCTION: MULTIPLE HORMONES. It is commonplace to think of hormones and their actions in isolation, but virtually all complex processes under endocrine regulation are influenced by more than one hormone. A classic example is maintenance of the plasma glucose within a narrow range: high enough to prevent dysfunction of the central nervous system on the one hand, and low enough to prevent the detrimental effects of hyperglycemia on the other. Such regulation could not be accomplished smoothly by a single hormone no matter how powerful. Primary control at the upper boundary of normality is exerted by insulin, which modulates hepatic glucose production and enhances glucose transport into cells for both utilization and storage, thereby protecting against hyperglycemia. The preeminent glucose-elevating hormone is glucagon, which stimulates glucose production in the liver via glycogen breakdown and gluconeogenesis whenever plasma glucose approaches hypoglycemic levels, thus protecting the central nervous system against dysfunction due to substrate/energy depletion. Because hypoglycemia is a greater risk to life than hyperglycemia, a back-up set of glucose-raising hormones is released as the plasma glucose concentration falls to dangerous levels: epinephrine, norepinephrine, cortisol, and growth hormone. Thus, at least six hormones play important roles in maintaining the plasma glucose directly. This list is not exhaustive since other hormones influence the process indirectly: e.g., thyroxine, which may influence appetite; somatostatin, which may block insulin or glucagon release and slow nutrient absorption from the gut; and gastric inhibitory polypeptide, which may enhance insulin release in response to glucose absorption (see Chapter 25). Another example of multiple hormonal control is lactation, which involves (at a minimum) prolactin, placental lactogen, glucocorticoids, thyroxine, estrogen, progesterone, and oxytocin.

The presence of such complex control mechanisms has two major implications. First, it allows for a remarkable degree of fine tuning; thus, blood glucose can be maintained within normal limits under nutritional conditions that vary in the extreme. Second, complex control mechanisms for vital functions may provide safety insofar as alternative mechanisms can take over when one hormone in the series is deficient (a fail-safe function). Even in systems that are under predominant control by one hormonal system, other hormones commonly play permissive roles. For example, the differentiation of the male external genitalia is mediated by dihydrotestosterone, but growth hormone and thyroxine are essential for normal growth and development of the genitalia during postnatal life.

CHEMICAL NATURE OF HORMONES

Hormones fall into two broad categories. The majority are peptides or amino acid derivatives, a category that includes complex polypeptides such as luteinizing hormone and chorionic gonadotropin, intermediate-sized peptides (insulin and glucagon), small peptides (thyrotropin-releasing hormone), dipeptides (thyroxine and triiodothyronine), and derivatives of single amino acids (catecholamines, serotonin, and histamine). The remainder are steroids, derivatives of cholesterol that are of two types: those with an intact steroid nucleus (adrenal steroids and gonadal steroids), and those in which the B ring of the steroid has been broken (vitamin D and its various metabolites).

The existence of diverse structures for chemical mediation implies that the evolution of the mechanisms for chemical control must have taken place over a long time. However, there is no fixed relationship between hormones in primitive and in more advanced species. In some cases, such as estrogen, essentially the same molecule has wide distribution in the animal kingdom. Conversely, some hormones, such as the steroid hormone ecdysone of insects, has no known counterpart in humans. Occasionally, homologies between structures of different hormones (e.g., that between prolactin, placental lactogen, and growth hormone) allow deductions to be drawn regarding patterns of evolution.

Regardless of their chemical structures or how they evolved, all hormones share several characteristics. First, they are present in the circulation in low concentration. The plasma concentration of steroid and thyroid hormones ranges between pM and μM, while that for peptide hormones is generally between 1 and 100 fM. Second, because they are present in such small amounts, they must be directed to sites of action by specific mechanisms. This commonly is accomplished by specific receptors in target tissues that recognize and bind the hormone with high affinity. There is considerable variability in the degree of restriction of the receptors; some, such as the insulin receptor, are present in virtually all tissues, whereas others, such as the aldosterone receptor, appear to have a more limited distribution. Although receptors are essential for hormone response, they may not in themselves be sufficient. Thus, some tissues possess receptors but lack some other molecule(s) necessary for the usual hormone response. For example, insulin receptors are present on erythrocytes but the red cell does not exhibit typical insulin responses. It is generally true, nevertheless, that the principal target organs for a given hormone contain the largest complement of receptor molecules and that as a consequence the concentration of that hormone in the target tissue is higher than in the circulation.

Another mechanism by which hormones can be directed to specific target tissues is by direct delivery within a restricted circulation; the liver is a major target tissue for insulin not because of unique receptor content, but because the amounts delivered to hepatic tissue through the portal circulation is higher than those that reach peripheral tissues through the systemic circulation. The same is true for the delivery of the various releasing factors from the hypothalamus to the pituitary through the hypophyseal portal system, and for the delivery of hormones from the adrenal

cortex to the adrenal medulla. Because of dilution and the rapid clearance of these hormones from the systemic circulation, their concentrations in the circulation-restricted sites are much higher than those achieved systemically.

A third means of targeting is by direct diffusion to adjacent sites; testosterone synthesized in the Leydig cells of the testes diffuses into the adjacent spermatogenic tubule to achieve the high level of the hormone necessary to promote spermatogenesis as well as being released into plasma. A fourth mechanism is local formation of hormone within a tissue from circulating precursors. One example is the formation of dihydrotestosterone from testosterone within androgen target tissues such as prostate. Similarly, estradiol can be formed from circulating androgenic precursors in target tissues such as the brain. Thus, there are a variety of means by which the action of hormones can be focused or magnified in specific tissues.

The concept of a target tissue, important as it is, should not be exaggerated. Consider, for example, the action of insulin. By most criteria the major sites of action are liver, muscle, and adipose tissue. However, insulin has distinct or permissive effects in almost every tissue of the body including pancreas, kidney, brain, lung, immune system, platelets, nervous system, and bone. The same type of gradation is true for the action of many, probably most, hormones. Thus, "targeting" of hormone action may actually influence the magnitude or amplitude of hormonal response rather than determine whether a response will occur. In rigorous terms, the all-or-none concept of a target tissue should be replaced by quantitative assessments: i.e., whether a tissue is a major or a minor site of hormone action.

HORMONE SYNTHESIS, STORAGE, AND RELEASE

The synthetic mechanisms that result in hormone formation are not unique. Thus, peptide hormones are synthesized by the same biochemical pathways as other proteins and are subsequently processed by cleavage and/or chemical modification to form the active molecules. Often the initial product is a large molecule that is progressively shortened in distinct steps: e.g., preproparathyroid hormone → proparathyroid hormone → parathyroid hormone. Steroid hormones and catecholamines are synthesized from small-molecular-weight precursors. In the case of steroid hormones the parent molecule, cholesterol, is modified by sequential cleavage of carbon-carbon bonds and hydroxylations to form the varied products. For many years it was assumed that endocrine organs possessed unique enzymatic capacities that allowed these reactions to take place. It is now established that the site of hormone synthesis need not be exclusive and can occur in diverse tissues. Glucagon is formed in the wall of the gastrointestinal tract as well as in the pancreas, and many peptide hormones are formed in the central nervous system, the pituitary, and the gastrointestinal tract. Human chorionic gonadotropin appears to be synthesized in almost every tissue of the body. Even when hormones cannot be synthesized *de novo* in a tissue, they may be derived by transformation reactions. Estrogen, for example, can be formed from testosterone and androstenedione in ovary, brain, adipocytes, and hair follicles. The synthesis of the active forms of vitamin D is even more complicated. The prohormone, 17-dehydrocholesterol, or provitamin D_3, is synthesized in the skin and converted there to vitamin D_3, which enters the circulation and is then sequentially hydroxylated in the liver (25-hydroxyvitamin D_3) and the kidney (1α,25-dihydroxyvitamin D_3).

Although the concept that an endocrine organ is the sole site of hormone formation is inaccurate, the major endocrine organs synthesize and regulate these hormones more efficiently than tissues not formally considered endocrine glands. Three fundamental characteristics distinguish them from nonendocrine tissues that happen to make hormones. First, rates of synthesis are generally greater in the major endocrine organs. Thus, placenta produces far greater amounts of chorionic gonadotropin per unit weight than does liver or testis. Second, appropriate processing machinery is available to complete conversion of prohormones to hormones. Pro-opiomelanocortin, for example, is efficiently converted to corticotropin (ACTH) in the pituitary but not in the brain. Third, endocrine glands contain mechanisms for release of the hormone into the circulation, often, but not always, by a regulated process.

The rate of release of hormone is determined ultimately by the rate of its synthesis. This is a consequence of two factors. First, most mechanisms characterized for the control of hormone levels act by controlling the rate of synthesis. There are exceptions (e.g., TSH enhances thyroxine release before enhancing thyroxine synthesis), but the vast majority of tropic hormones and control factors act to regulate rates of hormone synthesis. Second, in most instances only limited quantities of hormones are stored within the body. For example, the testicular testosterone content is invariably small so that the total amount must turn over several times each day to explain the daily production rate in normal men. Variable amounts of peptide hormones are stored in the pancreas and pituitary; these serve a critical function in emergencies and periods of stress but are generally depleted within hours to days. The general rule is for continual synthesis and turnover of hormones. Two major exceptions to the generalization of limited storage are thyroxine and 1α,25-dihydroxyvitamin D_3. In both instances, precursor forms of the actual hormone—thyroglobulin and either 7-dehydrocholesterol or vitamin D_3—are stored to serve as a reservoir for potential hormone formation. The consequence is to provide a safeguard against long periods of iodine deficiency or absence of sunlight, respectively. In the case of most hormones, however, no such safeguards exist.

TRANSPORT

Water-soluble hormones are transported in plasma in solution and require no specific transport mechanism. The more insoluble hormones require carrier mechanisms, namely, transport proteins. Since in most instances only the free or unbound hormone enters cells, the transport proteins act as reservoirs with the bound hormone in dynamic equilibrium with a small amount of free hormone in the plasma. As unbound hormone enters cells, it is replaced by hormone newly released from the carrier protein. This ensures that all cells have access to even the most insoluble of the hormones.[2] Transport proteins are of two types. Albumin and prealbumin bind many small ligands and can be considered general transport molecules. The specific transport proteins—thyroxine-binding globulin (TBG), testosterone-binding globulin (TeBG), cortisol-binding globulin (CBG)—have restricted binding sites of high affinity. They resemble intracellular receptor proteins in their specificities and binding characteristics.

It is important to note that these specific transport systems are nonexclusive since alternative systems can

function in their absence. Thus, in hereditary deficiency of TBG, thyroid hormones are transported adequately by albumin and prealbumin. Likewise, in analbuminemia, hormones can be carried by other proteins. No situation is known in which transport of hormones ceases or causes disease in and of itself.

Several general features of transport proteins have been identified. First, they have a profound effect on clearance rates for hormones. In general, the greater the capacity for high-affinity binding of a hormone, the slower is its clearance rate.[3] This follows from the fact that the rate of metabolic clearance (usually by liver and/or kidney) is determined by the level of free (or readily available) hormone. Women, for example, have higher levels of TeBG and clear those hormones that are tightly bound to TeBG (testosterone and dihydrotestosterone) about half as rapidly as men.[3] Second, the transport proteins usually have binding capacities much higher than the physiological concentration of most hormones. This means that when hormones are overproduced or given in pharmacological amounts for therapy, enormous quantities of even the most insoluble hormones can be delivered to tissues. Third, since the rate of hormone production is ultimately determined by the level of free hormone, synthesis can be adjusted appropriately to compensate for changes in the concentration of the transport proteins. As a consequence, increases or decreases in the amounts of specific transport protein have little effect on endocrine control mechanisms in the steady state although they may cause diagnostic confusion by altering total concentrations of hormone in plasma. To illustrate, an increase in CBG is followed by a transient decrease in the level of free cortisol, which in turn is followed by an increase in cortisol production until CBG is saturated sufficiently for the free hormone level to approximate normal. It follows that changes in transport proteins cause endocrine pathology only if the regulatory feedback systems are impaired, which basically means that the endocrine gland is abnormal. The most common clinical problem involving transport proteins has to do with the increases in TBG that accompany estrogen therapy or pregnancy where measurement of total thyroxine may suggest hyperthyroidism in a euthyroid subject.

How hormones are transported across cell membranes has not been resolved completely. In the case of peptide hormones that bind to cell-surface receptors, the hormone-receptor complexes can be internalized by endocytosis.[4] This mechanism is active in the sense that energy is required, but since it has not been demonstrated to occur against a concentration gradient it is not considered active transport in the classic sense. The internalization process may serve primarily to deliver the hormones to intracellular sites of degradation and hence function as a termination signal to limit hormone action. In the case of hormones with cytosolic receptors, it has been suggested that hormone bound to transport proteins might be selectively transported across the membranes of some cells, but the bulk of evidence suggests that free hormone diffuses passively across cell membranes down activity gradients.[3] The presence of intracellular proteins that bind the hormones may tend to keep the intracellular concentration of the free hormone low and thus favor the diffusion process.

FEEDBACK RELATIONSHIPS

The distinguishing characteristic of endocrine systems is the feedback control of hormone production. The paradigm for feedback control is the interaction of the pituitary gland with the thyroid, adrenal gland, and gonads in which hormones produced in peripheral endocrine organs feedback on the hypothalamic-pituitary system, regulating the production of the trophic hormones that control the peripheral endocrine glands (Fig. 1–4). Virtually all hormones are under some type of feedback control, some by cations (calcium on parathyroid hormone), some by metabolites (glucose on insulin and glucagon), some by other hormones (somatostatin on insulin and glucagon), and some by osmolality or extracellular fluid volume (vasopressin, renin, aldosterone).

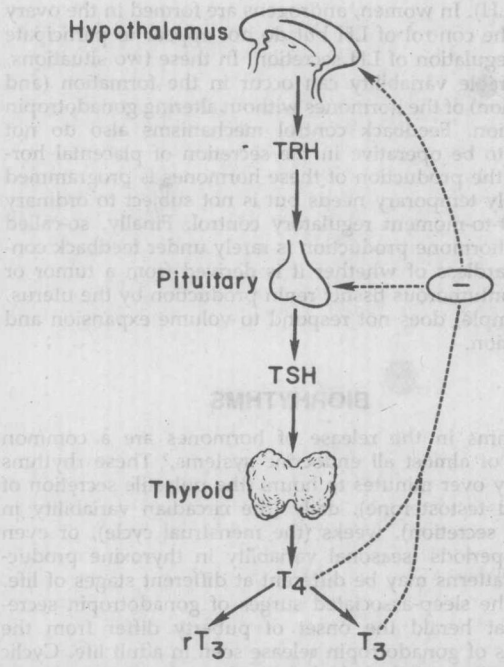

Figure 1–4. A classic feedback system: control of thyroid hormone release. When thyroid hormone levels are inadequate the repressive effect of T_3/T_4 on the hypothalamus and pituitary is removed. TRH release stimulates TSH, which in turn activates thyroxine synthesis in the thyroid gland. When T_3/T_4 levels are adequate, inhibition of TRH/TSH release occurs. Conversion of T_4, a prohormone, to T_3 is probably also regulated.

The feedback relationship is the reason why simultaneous assessment of hormone/effector pairs is frequently useful in the assessment of pathological states. Plasma insulin must be interpreted in terms of the simultaneously drawn plasma glucose. TSH levels may be interpretable only in terms of the serum thyroxine level. Furthermore, the feedback relation is the basis for most dynamic tests of endocrine function, and disturbances in these relationships are almost invariably involved in pathological states that perturb endocrine function. This concept is so pervasive in endocrinology that it could be argued that feedback control, rather than the hormones themselves, is the distinguishing feature of the endocrine system. Feedback control is not invariable, however. Thus, estrogen production in men and testosterone production in women are not regulated in this manner. In both situations, gonadotropin production is controlled by the predominant steroids (testosterone in men and estradiol and progesterone in women). Estrogens in men are synthesized predominantly in extraglandular tissue from circulating androgens, and under physiological conditions the amounts of estrogen formed do not influence the secretion of luteinizing hor-

mone (LH). In women, androgens are formed in the ovary under the control of LH but do not appear to participate in the regulation of LH secretion. In these two situations, considerable variability can occur in the formation (and expression) of the hormones without altering gonadotropin production. Feedback control mechanisms also do not appear to be operative in the secretion of placental hormones; the production of these hormones is programmed to supply temporary needs but is not subject to ordinary moment-to-moment regulatory control. Finally, so-called ectopic hormone production is rarely under feedback control regardless of whether it is derived from a tumor or from nontumorous tissue; renin production by the uterus, for example, does not respond to volume expansion and contraction.

BIORHYTHMS

Rhythms in the release of hormones are a common feature of almost all endocrine systems.[5] These rhythms can vary over minutes to hours (the pulsatile secretion of LH and testosterone), daily (the circadian variability in cortisol secretion), weeks (the menstrual cycle), or even longer periods (seasonal variablity in thyroxine production). Patterns may be different at different stages of life. Thus, the sleep-associated surges of gonadotropin secretion that herald the onset of puberty differ from the rhythms of gonadotropin release seen in adult life. Cyclic or pulsatile variations in hormone concentrations due to alterations in release are more apparent when the half-life of the hormone is short. For example, insulin, with a half-life of five to six minutes, shows extreme variations in concentration, whereas insulin-like growth factors (somatomedins) have a slow turnover and consequently have almost constant values in plasma throughout the day.

Hormonal rhythmicity is caused by a variety of factors. Some, such as sleep-associated alterations and stimulation of prolactin secretion by the suckling reflex, are due to neurogenic factors. Others, such as the circadian variability in glucocorticoid production, are controlled by environmental factors acting through uncertain mechanisms. The menstrual cycle is the result of a complex interplay between positive and negative feedback systems.

Perhaps the most puzzling of the endocrine rhythms is that involved in the pulsatile secretion of hormones from the pituitary and the ensuing pulsatile release of hormones from the endocrine glands. In simplistic terms, such oscillations can be envisioned as resulting from inertia or time delay in the negative feedback system that controls its operation.[6] In this sense, inertia is the time required for a signal to pass along the whole of the feedback loop. For example, if the synthesis of testosterone requires x seconds, an increase in LH levels cannot be followed by an increase in testosterone production for x seconds. This type of oscillation becomes magnified by the time required for plasma testosterone to influence LH production. At a minimum, then, the magnitude of the oscillations is a function both of the half-life of the effectors in plasma and of the inertia built into the system. It is of considerable interest, furthermore, that such oscillations may be fundamental to the operation of feedback systems; indeed, the administration of luteinizing hormone–releasing hormone (LHRH) by a constant infusion rather than in a pulsatile fashion results in inhibition rather than enhancement of LH secretion under some conditions.[7,8] Furthermore, the frequency of pulsatile stimulation may alter the ratios of the gonadotropins released from the pituitary.[9] The mechanisms by which these rhythms operate, the reasons why attenuation does not occur in the steady state, and the physiological ramifications of the rhythms in endocrinology are still poorly understood.

ENDOCRINE PATHOLOGY

Endocrine disorders can be divided into six broad categories—subnormal hormone production, hormone overproduction, the secretion of abnormal hormone, resistance to hormone action, abnormalities of hormone transport or metabolism, and multiple hormonal abnormalities. There is considerable overlap among these groups. For example, impaired hormone production because of enzyme deficiency can lead to increased synthesis of another hormone, as in the overproduction of adrenal androgen in patients with cortisol deficiency due to a defect in steroid 21-hydroxylase. Hormone overproduction can accompany clinical evidence of deficient hormone action in the hormone-resistance states. Finally, hormone overproduction, underproduction, and resistance to hormone action may occur at different times in the course of a disease in a single individual, as is frequently seen with insulin in patients with non–insulin-dependent diabetes and obesity. Nevertheless, a categorization based on the fundamental defect provides a useful means of analyzing endocrine pathology.

SUBNORMAL HORMONE PRODUCTION. Diminished or absent hormone secretion can have several causes. Absence or malformation of endocrine organs can be due to embryonic factors, as in the sublingual thyroid and in gonadal dysgenesis. Alternatively, the endocrine organ may develop but lack some enzyme essential for hormone synthesis, as seen in some forms of congenital goiter and in the various types of congenital adrenal hyperplasia. More commonly, a normal endocrine gland is destroyed by some secondary process. Such processes can include granulomatous or infectious agents as in tuberculosis of the adrenals; infarction as in the postpartum necrosis of the pituitary that leads to Sheehan's syndrome; autoimmune disorders as in Hashimoto's thyroiditis; chemical exposure as in testicular damage due to cancer chemotherapy; or a variety of forms of physical damage including radiation, surgical extirpation, and thermal injuries. Despite the multiple etiologies now recognized for hormone underproduction, the cause in many instances remains unknown. A common example is primary hypothyroidism without goiter, in which no evidence may exist for an autoimmune mechanism. In general, the results of hormone deficiency are well understood because the manifestation can be reproduced by removal or ablation of the appropriate endocrine organ in experimental animals.

HORMONE EXCESS. Hormone overproduction is less well understood than is hormone deficiency because fewer animal models exist for such disorders. Causes are diverse. Tumors, either benign or malignant, can affect an endocrine gland, as in Cushing's syndrome arising from a carcinoma or an adenoma of the adrenal cortex. Tumors of nonendocrine tissues can secrete hormones such as ACTH or human chorionic gonadotropin (hCG) that drive target glands to hypersecrete and cause disease. The mechanism that controls normal hormone secretion can be set at an abnormal level, as in Cushing's disease with bilateral adrenal hyperplasia due to ACTH-secreting pituitary microadenoma. Hyperplasia and autonomous tumor formation in some instances form a continuum; for example, prolonged hyperplasia of the parathyroid glands in renal

insufficiency can lead eventually to true autonomous hyperparathyroidism. Stimulatory substances can be produced as part of an autoimmune reaction; for example, the production of thyroid-stimulating immunoglobulins in Graves' disease. Overproduction can be permanent as in most of the above illustrations, or transient as may occur in viral thyroiditis. It is of particular interest that hyperfunction does not occur for all endocrine organs; no clear-cut syndrome of testosterone excess in males has ever been characterized.

PRODUCTION OF ABNORMAL HORMONES. Most pathological states involve the production of too much or too little of hormones normally produced by endocrine glands, but in some circumstances abnormal hormones can be produced. A single gene mutation may alter both structure and function. Thus, a mild form of diabetes mellitus may be produced by an abnormal insulin molecule formed as the result of a single gene mutation; the abnormal insulin does not bind well to the insulin receptor and thus is ineffective.[10] Occasionally immunoglobulins function as hormones, as in the thyroid-stimulating immunoglobulins that occur in hyperthyroidism (see Chapter 21) and the antibodies to the insulin receptor that can sometimes mimic the action of insulin (see Chapter 3). In other cases, hormone precursors or incompletely processed peptide hormones may be released into the circulation; this is common in the case of the so-called ectopic hormone production by many carcinomas (see Chapter 36). Finally, multiple genes specify the structures for some hormones, some of which are not expressed normally but might be expressed in pathological states (see Chapter 2).

RESISTANCE TO HORMONE ACTION. Hormone resistance, which is defined as a defect in the capacity of normal target tissues to respond to a hormone, was first recognized by Albright and colleagues in their characterization of pseudohypoparathyroidism in 1942.[11] That disorder is now known to result from several hereditary defects, the most common of which resides in the guanosine triphosphate–binding protein in cell membranes that activates the catalytic subunit of adenylate cyclase after binding parathyroid hormone (see Chapter 29). Syndromes of hormone resistance have been described for many hormones and involve abnormalities in cell-surface and intracellular receptors, defects in hormone metabolism within cells, and abnormalities in other steps involved in normal hormone action.[12] Resistance can be hereditary (as is true for the androgen resistance in the testicular feminization syndrome) or acquired (the insulin resistance of obesity). Studies of hormone resistance states have been of particular importance in establishing the role of hormone receptors both in normal hormone action and in the pathogenesis of disease. A common feature of hormone resistance is the presence of a normal or elevated level of the hormone in the circulation. This is the inevitable consequence of the fact that most hormone production is under some type of regulatory feedback control so that failure of hormone action leads to increased hormone production. Since partial defects can be compensated by an increased hormone concentration and have little clinical consequence, hormone resistance may go unrecognized. It should be suspected whenever hormone levels are inappropriately high in the face of either clinical normality or symptoms and signs of hormone deficiency.

Hereditary resistance to those hormones that are essential for life (e.g., cortisol, ACTH) is inevitably partial since severe or complete defects in the action of these hormones are incompatible with life. Fetuses with such complete defects are probably eliminated as stillbirths or abortions. When severe defects exist (absence of any functional androgen receptor in complete testicular feminization), it can be assumed that the hormone is not essential for the life of the individual. It is interesting that neither resistance to estrogen action nor a hereditary defect in estrogen synthesis has been described. This implies that estrogen action in implantation of the blastocyst[13] may be essential for life, so that affected individuals do not survive for expression of the defect.

ABNORMALITIES OF HORMONE TRANSPORT AND METABOLISM. Under ordinary circumstances, abnormalities of hormone transport or metabolism do not result in endocrine pathology. For example, in two extreme situations—hereditary absence of thyroid-binding globulin or cirrhosis of the liver with a markedly diminished rate of cortisol catabolism—no endocrine pathology results because feedback control mechanisms compensate for the defects. Hormone production is controlled by the level of free hormone and consequently can be adjusted up or down as required. Consequently, abnormalities of this type most commonly cause deviation of laboratory parameters from normal but do not cause either hyper- or hypofunction. The important point is to recognize that unusual hormonal values do not necessarily imply functional pathology. Under artificial circumstances, however, such abnormalities may in fact cause pathology. For example, administration of physiological replacement doses of glucocorticoid to an individual with cirrhosis of the liver may cause florid Cushing's syndrome, since free hormone levels will be high in the face of diminished plasma binding and uncontrolled entry of hormones into the circulation. Defects of hormone metabolism are more likely to cause endocrine pathology than are defects in transport because alternative mechanisms of transport exist for virtually all hormones.

MULTIPLE HORMONE ABNORMALITIES. The original paradigm for disorders involving multiple hormones is hypopituitarism, which may involve widespread hormonal deficits. More important, familial disorders are now characterized that involve hyperfunction (the multiple endocrine neoplasia [MEN] syndromes, Chapter 32) or mixed patterns of hyperfunction and hypofunction of various endocrine glands (the polyglandular endocrinopathy syndromes, Chapter 33). These syndromes are of importance out of all proportion to their frequency for at least two reasons. First, it is mandatory once the diagnosis is made to evaluate patients for involvement of additional endocrine glands and to evaluate relatives at risk before the development of serious manifestations of the disorders. Second, analysis of the mechanisms by which these relatively rare single gene defects predispose individuals to the development of these disorders may allow understanding of the pathogenesis of more common endocrine diseases.

SUMMARY

In this brief introduction we have attempted to outline some of the principles of endocrinology that will be covered much more extensively in the remainder of the book. Our purpose has been to show that endocrinology is in many ways an orderly clinical discipline, by which we mean that the general principles are usually informative whether applied to normal physiology or to endocrine disease.

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2

Genetic Control of Hormone Formation

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INTRODUCTION

In the recent past a large increment has been added to existing knowledge of the working of the cell, largely owing to advances in the fields of molecular and cellular biology. Recombinant-DNA technology makes it possible to analyze the precise structure and functions of the fundamental genetic substance of life itself. The uncovering of the unique properties of DNA has provided the conceptual framework with which to begin a systematic investigation of the origin, development, and organization of life.[1]

The polypeptide hormones constitute an important and diverse set of regulatory molecules whose function is to convey specific information among cells and organs. This type of communication arose early in the development of life and evolved into a complex system for the control of growth, development, and reproduction and for the maintenance of metabolic homeostasis. These hormones consist of approximately 100 small proteins ranging from as few as three amino acids (thyrotropin-releasing hormone) to 192 amino acids (growth hormone). In a broader sense they function both as hormones in which their actions are mediated on distant organs by way of their transport through the bloodstream, and as local cell-to-cell communicators (Fig. 2–1). This latter function of the polypeptides is exemplified by their elaboration and secretion within neurons of the central, autonomic, and peripheral nervous systems, where they probably act as neurotransmitters. These multiple modes of expression of the peptide-hormone genes have aroused great interest in the specific functions of these peptides and the mechanisms of their synthesis and release.

The purpose of this chapter is to review the structure and expression of genes encoding peptide hormones. The synthesis of nonpeptide hormones such as catecholamines, thyroid hormones, and steroid hormones involves the action of multiple enzymes and hence the expression of multiple genes, and is discussed in the individual chapters devoted to such hormones.

DEVELOPMENT OF MOLECULAR ENDOCRINOLOGY AS A DISCIPLINE

The era of molecular endocrinology was inaugurated in the early 1950s with the determination by Popenoe and du Vigneaud[2] (and their co-workers) of the amino acid sequences of vasopressin and oxytocin. In ensuing years, the amino acid sequences of approximately 40 different polypeptide hormones and regulatory peptides were estab-

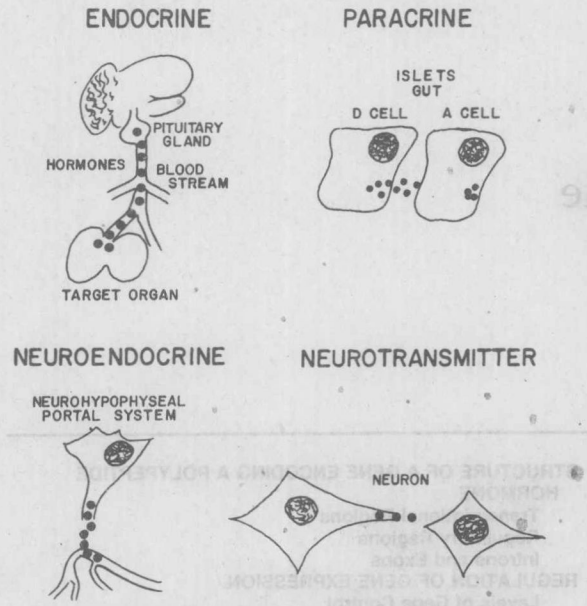

Figure 2–1. Different modes of utilization of polypeptide hormones in expression of their biological actions. Many of the peptide hormones are expressed in at least four ways in fulfilling their functions as cellular messenger molecules: (1) *endocrine* mode, for purposes of communication among organs; (2) *paracrine* mode, for communication among adjacent cells, often located within endocrine organs; (3) *neuroendocrine* mode, for synthesis and release of peptides from specialized peptidergic neurons for action on distant organs via the bloodstream—e.g., neuroendocrine peptides of hypothalamus; and (4) *neurotransmitter* mode, for action of peptides in concert with classic amino acid-derived aminergic transmitters in neuronal communication network. Identical polypeptides are often utilized in nervous system both as neuroendocrine hormones and as neurotransmitters. In many instances, identical gene product is utilized in all four modes of expression.

lished. Much of the success of structural analyses of the polypeptide hormones was made possible by advances in methods for the isolation of proteins and the development of automated techniques for their sequencing. A major breakthrough for studies of physiological and cellular endocrine regulation came with the application of the principle of the radioimmunoassay.[3] Exploitation of this technique provided insight into the workings of endocrine control mechanisms under physiological and pathological circumstances. The availability of both natural and synthetic peptides in homogeneous form allowed the production of specific antisera for use in radioimmunoassay and immunocytochemical studies. The purified peptides were also used to study receptors of hormones and for the construction of specific receptor assays. These studies led to the synthesis of numerous analogues that have proved useful as potent agonists and antagonists.

Development of the powerful techniques for producing recombinant DNA resulted in an acceleration of studies of cellular control mechanisms. The successful cloning of the structural genes for insulin[4] and growth hormone[5] established that the genetic engineering of recombinant-DNA molecules can be utilized to determine the structures of proteins by way of decoding the nuleotide sequences. One remarkable aspect of this technique is that it allows a segment of genetic material to be removed from its normal context and replicated in microorganisms in high yields; this segment can then be reintroduced into a variety of cells where it can be studied and manipulated under controlled circumstances.

To a large extent, this technique of gene cloning has altered the approaches used to garner new information on the structure and function of polypeptide hormones. Instead of isolating minuscule amounts of peptide from large amounts of tissue and analyzing amino acid sequences, it is now possible to obtain DNA templates from the messenger RNAs (mRNAs) encoding the polypeptides. Recombinant-DNA molecules prepared from these RNA templates can be cloned and amplified, thereby producing large amounts of DNA for nucleotide sequencing and deduction of the amino acid sequences. Genes have now been cloned for approximately 50 different hormonal regulatory peptides, many of which are present only in trace amounts in the tissues from which they originate.

The expansion of technology for DNA sequencing raises the prospect that the primary structure of the entire mammalian genome may be known by the year 2000.[6,7] At present, approximately 10^7 of the 10^9 base pairs of the mammalian genome have been determined. Continued efforts in the field of DNA sequencing and the likely development of even more rapid and efficient methods make it reasonable to expect that the rate of acquisition of sequence information will accelerate.

Determination of the structures of genes, however, provides only the foundation of information about how the expression of genes is controlled. As a consequence, scientists are just now gaining insight into the cellular mechanisms involved in regulation of gene expression. Recombinant-DNA molecules provide powerful probes with which to analyze the effects of regulatory molecules on gene transcription in intact animals and in cultured cells. Of even greater potential importance is the ability to introduce specific DNA sequences that encode polypeptides into foreign cells and into the germ lines of laboratory animals. In addition, selective alteration of the sequences of genes by site-directed mutagenesis permits a molecular dissection of the structural aspects of the gene required for accurate control. Once the mechanisms of gene control are understood, it should then be possible to correct genetic defects in humans by specific engineering of DNA. Such gene-transfer experiments have already been performed in laboratory animals. Introduction of foreign genes into the germ line of mice by microinjection of DNA into fertilized ooytes gives rise to expression of these foreign genes in the offspring. Current methods, however, do not allow for introduction of these genes into specific loci that are under physiological control.

EVOLUTION OF PEPTIDE HORMONES AND THEIR FUNCTIONS

Peptide hormones arose early in the evolution of life. Indeed, polypeptides that are structurally similar to mammalian peptides are present in lower vertebrates, insects, yeasts, and bacteria.[8] An example of the early evolution of regulatory peptides is the alpha-factor (mating pheromone) of yeast, which is structurally similar to mammalian gonadotropin-releasing hormone.[9] Other such examples are glucagon-like immunoreactivity in the corpus cardiacum of the tobacco hornworm; pancreatic polypeptide and vasoactive intestinal peptide-like substances in the earthworm; and cholecystokinin, neurotensin, and substance P in coelenterates (hydra and sea anemone). Insulin, corticotropin, and somatostatin are reported to exist in ciliated protozoa (Tetrahymena) as well as in various strains of *Escherichia coli*. Thus, genes encoding polypeptide hormones, and particularly regulatory peptides, evolved early in the de-

velopment of life and initially fulfilled only the function of cell-to-cell communication to cope with problems concerning nourishment, growth, development, and reproduction. As specialized organs connected by a circulatory system developed during evolution, similar, if not identical, gene products became hormones for purposes of organ-to-organ communication. Perhaps as a consequence of the development of the blood-brain barrier, the local cell-to-cell regulatory functions of the polypeptides in the brain may have been maintained apart from the endocrine functions of peptides in the rest of the body, thus explaining the presence of many of the peptide hormones in specific neuronal populations within the central nervous system. The peptidergic neurons that populate the hypothalamus may represent a transition between the cell-to-cell communication and organ-to-organ regulatory functions of the peptides.

The known regulatory peptides number in the hundreds, and additional peptide hormones will be found in the isolation of substances responsible for specific biological activities or by the decoding of gene sequences. The potential number of unique amino acid sequences that are possible is immense. For example, if all possible combinations of the 20 amino acids were utilized, 2×10^{11} different peptides, each of 10 amino acids, could exist. A typical mammalian cell expresses genes encoding between 5000 and 10,000 different proteins, and among differentiated cells the total repertoire is probably somewhere around 50,000 proteins. By searching for similarities among the approximately 2000 different protein sequences that are known, Doolittle[10] estimated that, when it is possible to identify subtle similarities among different proteins indicative of their common origin from an ancestral protein, there may be as few as 1000 fundamental proteins, each probably distinct with regard to its functional properties. For example, one may envision distinct amino acid sequences that are specific for binding sites of cellular receptors, chelation of heavy-metal ions, expression of proteolytic activity, structural components of membranes, and hydrolysis of ATP. The finding that the coding sequences of genes are separated into blocks (exons) by intervening DNA sequences (introns), and that the exons appear to constitute distinct functional domains, lends credence to the hypothesis that specific protein-encoding gene segments have maintained that function essentially unchanged throughout evolution, presumably because of the special selective advantages of the function to the organisms.

STEPS IN EXPRESSION OF A PROTEIN-ENCODING GENE

The steps involved in transfer of information encoded in the polynucleotide language of DNA to the polyaminoacid language of biologially active protein involves transcription, posttranscriptional processing, translation, and post-translational processing. The expression of genes and protein synthesis can be considered in terms of several major processes, any one or more of which may serve as specific control points in the regulation of gene expression (Fig. 2–2):

1. *Rearrangements and transpositions of DNA segments.* A process that occurs in evolution, with the exception of the immunoglobulin genes.
2. *Transcription.* Synthesis of RNA, a process that results in the formation of complementary RNA copies of the two gene alleles and is catalyzed by RNA polymerase II.
3. *Post-transcriptional processing.* Specific modifications of the RNA, including the steps in formation of mRNA from the precursor RNA by way of excision and rejoining of RNA segments (introns and exons), as well as modifications of the 3′-end of the RNA by polyadenylation and of the 5′-end by addition of 7-methylguanine "caps."
4. *Translation.* Sequential assembly of amino acids by way of base pairing of the nucleotide triplets (anticodons), of the specific "carrier" aminoacylated transfer RNAs to the corresponding codons of the mRNA bound to polyribosomes and, finally, polymerization of the amino acids into the polypeptide chains.
5. *Post-translational processing and modification.* Final steps in protein synthesis consisting of one or more processes of cleavages of peptide bonds, resulting in the conversion of biosynthetic precursors, or prohormones, to intermediate or final forms of the protein, derivatization of amino acids (glycosylation, phosphorylation, acetylation), and the folding of the processed polypeptide chain into its native conformation.

Each of the specific steps of gene expression requires the integration of a large number of precise enzymatic and other biochemical reactions. It is likely that these processes have developed in a way to provide high fidelity in the reproduction of the encoded information, as well as to provide control points for the expression of the specific phenotype of cells.

The post-translational processing of protein supplies a means of creating diversity in gene expression through the modifications of the protein. Although all the functional information contained in the protein is ultimately encoded in the primary amino acid sequence, the specific biological activities of proteins are usually a consequence of the higher-ordered secondary, tertiary, and quaternary structures of the polypeptide. Given the wide range of specific modifications of the amino acids that are possible, such as glycosylation, phosphorylation, acetylation, and sulfation,[11] any one of which may affect the specific conformational properties of the protein, a single gene may ultimately encode a wide variety of specific proteins as a result of post-translational processes.

Polypeptide hormones are synthesized in the form of larger precursors that appear to fulfill several functions in biologial systems (Fig. 2–3), including (1) intracellular signaling, by which the cell distinguishes among specific classes of proteins and directs them to their sites of action; and (2) the generation of multiple biological activities from a common gene product by regulated or cell-specific variations in the post-translational modifications (Fig. 2–4).[12]

All the peptide hormones and regulatory peptides studied thus far contain signal or leader sequences at their amino termini; these sequences are hydrophobic and recognize specific sites on the membranes of the rough endoplasmic reticulum, resulting in the transport of nascent polypeptides into the secretory pathway of the cell (Figs. 2–2 and 2–3).[12] The consequence of the specialized signal sequences of the precursor proteins is that proteins destined for secretion are selected from a great many other cellular proteins for sequestration and subsequent packaging into secretory granules and export from the cell.

In addition, most, if not all, of the smaller hormones and regulatory peptides are produced as a consequence of post-translational cleavages of the precursors within the Golgi complex of secretory cells.