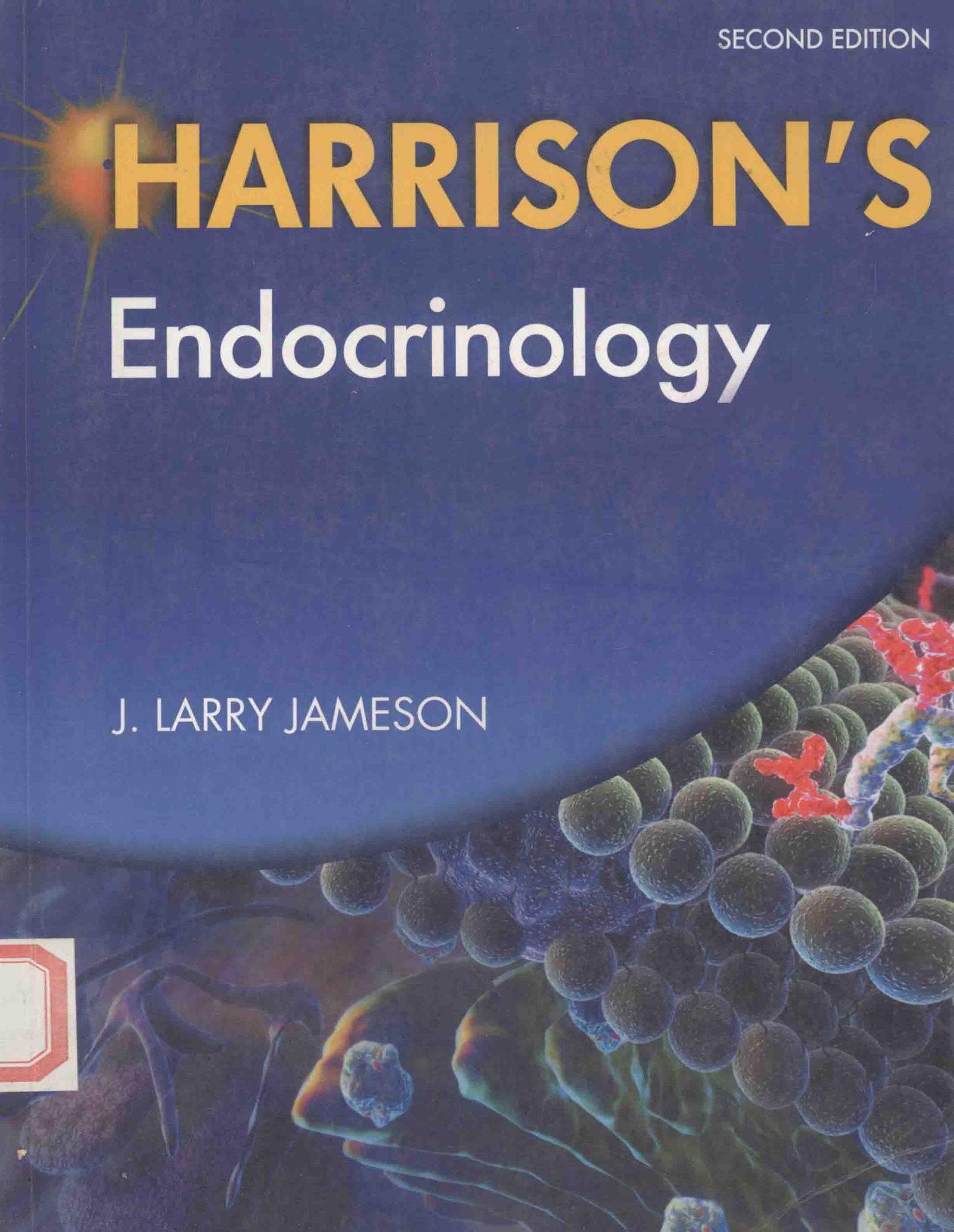
SECOND EDITION

HARRISON'S

Endocrinology

J. LARRY JAMESON



Second Edition

HARRISON'S Endocrinology

Editor

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PREFACE

The editors of *Harrison's Principles of Internal Medicine* refer to it as the "mother book," a description that confers respect but also acknowledges its size and its ancestral status among the growing list of Harrison's products, which now include *Harrison's Manual of Medicine*, *Harrison's Online*, and *Harrison's Practice,* an online highly structured reference for point-of-care use and continuing education. This book, *Harrison's Endocrinology,* second edition, is a compilation of chapters related to the specialty of endocrinology.

Our readers consistently note the sophistication of the material in the specialty sections of *Harrison's*. Our goal was to bring this information to readers in a more compact and usable form. Because the topic is more focused, it was possible to increase the presentation of the material by enlarging the text and the tables. We have also included a Review and Self-Assessment section that includes questions and answers to provoke reflection and to provide additional teaching points.

The clinical manifestations of endocrine disorders can usually be explained by considering the physiologic role of hormones, which are either deficient or excessive. Thus, a thorough understanding of hormone action and principles of hormone feedback arms the clinician with a logical diagnostic approach and a conceptual framework for treatment approaches. The first chapter of the book, Principles of Endocrinology, provides this type of "systems" overview. Using numerous examples of translational research, this introduction links genetics, cell biology, and physiology with pathophysiology and treatment. The integration of pathophysiology with clinical management is a hallmark of *Harrison's*, and can be found throughout each of the subsequent disease-oriented chapters. The book is divided into five main sections that reflect the physiologic roots of endocrinology: (I) Pituitary, Thyroid, and Adrenal Disorders; (II) Reproductive Endocrinology; (III) Diabetes Mellitus, Obesity, Lipoprotein Metabolism; (IV) Disorders Affecting Multiple Endocrine Systems; and (V) Disorders of Bone and Calcium Metabolism.

While *Harrison's Endocrinology* is classic in its organization, readers will sense the impact of the scientific renaissance as they explore the individual chapters in each section. In addition to the dramatic advances emanating from genetics and molecular biology, the introduction of an unprecedented number of new drugs, particularly for the management of diabetes and osteoporosis, is transforming the field of endocrinology. Numerous recent clinical studies involving common diseases like diabetes, obesity, hypothyroidism, osteoporosis, and polycystic ovarian syndrome provide powerful evidence for medical decision-making and treatment. These rapid changes in endocrinology are exciting for new students of medicine and underscore the need for practicing physicians to continuously update their knowledge base and clinical skills.

Our access to information through web-based journals and databases is remarkably efficient. While these sources of information are invaluable, the daunting body of data creates an even greater need for synthesis and for highlighting important facts. Thus, the preparation of these chapters is a special craft that requires the ability to distill core information from the ever-expanding knowledge base. The editors are therefore indebted to our authors, a group of internationally recognized authorities who are masters at providing a comprehensive overview while being able to distill a topic into a concise and interesting chapter. We are grateful to Emily Cowan for assisting with research and preparation of this book. Our colleagues at McGraw-Hill continue to innovate in health care publishing. This new product was championed by Jim Shanahan and impeccably produced by Kim Davis.

We hope you find this book useful in your effort to achieve continuous learning on behalf of your patients.

J. Larry Jameson, MD, PhD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener C, Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (editors) Bloomfield G, Brown CD, Schiffer J, Spivak A (contributing editors). *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 17th ed. New York, McGraw-Hill, 2008, ISBN 978-0-07-149619-3.

The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

CONTENTS

SECTION V

DISORDERS OF BONE AND CALCIUM METABOLISM

CHAPTER 1

PRINCIPLES OF ENDOCRINOLOGY

J. Larry Jameson

The management of endocrine disorders requires a broad understanding of intermediary metabolism, reproductive physiology, bone metabolism, and growth. Accordingly, the practice of endocrinology is intimately linked to a conceptual framework for understanding hormone secretion, hormone action, and principles of feedback control. The endocrine system is evaluated primarily by measuring hormone concentrations, thereby arming the clinician with valuable diagnostic information. Most disorders of the endocrine system are amenable to effective treatment, once the correct diagnosis is determined. Endocrine deficiency disorders are treated with physiologic hormone replacement; hormone excess conditions, usually due to benign glandular adenomas, are managed by removing tumors surgically or by reducing hormone levels medically.

SCOPE OF ENDOCRINOLOGY

The specialty of endocrinology encompasses the study of glands and the hormones they produce. The term *endocrine* was coined by Starling to contrast the actions of hormones secreted internally (endocrine) with those secreted externally (*exocrine*) or into a lumen, such as the gastrointestinal tract. The term *hormone*, derived from a Greek phrase meaning "to set in motion," aptly describes the dynamic actions of hormones as they elicit cellular responses and regulate physiologic processes through feedback mechanisms.

Unlike many other specialties in medicine, it is not possible to define endocrinology strictly along anatomic lines. The classic endocrine glands—pituitary, thyroid, parathyroid, pancreatic islets, adrenal, and gonads—communicate broadly with other organs through the nervous system, hormones, cytokines, and growth factors. In addition to its traditional synaptic functions, the brain produces a vast array of peptide hormones, spawning the discipline of neuroendocrinology. Through the production of hypothalamic releasing factors, the central nervous system (CNS) exerts a major regulatory influence over pituitary hormone secretion (Chap. 2). The peripheral nervous system stimulates the adrenal medulla. The immune and endocrine systems are also intimately intertwined. The adrenal glucocorticoid, cortisol, is a powerful immunosuppressant. Cytokines and interleukins (ILs) have profound effects on the functions of the pituitary, adrenal, thyroid, and gonads. Common endocrine diseases, such as autoimmune thyroid disease and type 1 diabetes mellitus, are caused by dysregulation of immune surveillance and tolerance. Less common diseases such as polyglandular failure, Addison's disease, and lymphocytic hypophysitis also have an immunologic basis.

The interdigitation of endocrinology with physiologic processes in other specialties sometimes blurs the

role of hormones. For example, hormones play an important role in maintenance of blood pressure, intravascular volume, and peripheral resistance in the cardiovascular system. Vasoactive substances such as catecholamines, angiotensin II, endothelin, and nitric oxide are involved in dynamic changes of vascular tone, in addition to their multiple roles in other tissues. The heart is the principal source of atrial natriuretic peptide, which acts in classic endocrine fashion to induce natriuresis at a distant target organ (the kidney). Erythropoietin, a traditional circulating hormone, is made in the kidney and stimulates erythropoiesis in the bone marrow. The kidney is also integrally involved in the renin-angiotensin axis (Chap. 5) and is a primary target of several hormones, including parathyroid hormone (PTH), mineralocorticoids, and vasopressin. The gastrointestinal tract produces a surprising number of peptide hormones such as cholecystokinin, ghrelin, gastrin, secretin, and vasoactive intestinal peptide, among many others. Carcinoid and islet tumors can secrete excessive amounts of these hormones, leading to specific clinical syndromes (Chap. 22). Many of these gastrointestinal hormones are also produced in the CNS, where their functions remain poorly understood. As new hormones such as inhibin, ghrelin, and leptin are discovered, they become integrated into the science and practice of medicine on the basis of their functional roles rather than their tissues of origin.

Characterization of hormone receptors frequently reveals unexpected relationships to factors in nonendocrine disciplines. The growth hormone (GH) and leptin receptors, for example, are members of the cytokine receptor family. The G protein–coupled receptors (GPCRs), which mediate the actions of many peptide hormones, are used in numerous physiologic processes, including vision, smell, and neurotransmission.

NATURE OF HORMONES

Hormones can be divided into five major classes: (1) *amino acid derivatives* such as dopamine, catecholamine, and thyroid hormone (TH); (2) *small neuropeptides* such as gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), somatostatin, and vasopressin; (3) *large proteins* such as insulin, luteinizing hormone (LH), and PTH produced by classic endocrine glands; (4) *steroid hormones* such as cortisol and estrogen that are synthesized from cholesterol-based precursors; and (5) *vitamin derivatives* such as retinoids (vitamin A) and vitamin D. A variety of *peptide growth factors*, most of which act locally, share actions with hormones. As a rule, amino acid derivatives and peptide hormones interact with cell-surface membrane receptors. Steroids, thyroid hormones, vitamin D, and retinoids are lipid-soluble and interact with intracellular nuclear receptors.

HORMONE AND RECEPTOR FAMILIES

Many hormones and receptors can be grouped into families, reflecting their structural similarities (**Table 1-1**). The evolution of these families generates diverse but highly selective pathways of hormone action. Recognizing these relationships allows extrapolation of information gleaned from one hormone or receptor to other family members.

The glycoprotein hormone family, consisting of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), LH, and human chorionic gonadotropin (hCG), illustrates many features of related hormones. The glycoprotein hormones are heterodimers that have the α subunit in common; the β subunits are distinct and confer specific biologic actions. The overall three-dimensional architecture of the β subunits is similar, reflecting the locations of conserved disulfide bonds that restrain protein conformation. The cloning of the β-subunit genes from multiple species suggests that this family arose from a common ancestral gene, probably by gene duplication and subsequent divergence to evolve new biologic functions.

As the hormone families enlarge and diverge, their receptors must co-evolve if new biologic functions are to be derived. Related GPCRs, for example, have evolved for each of the glycoprotein hormones. These receptors are structurally similar, and each is coupled to the $G_s\alpha$ signaling pathway. However, there is minimal overlap of hormone binding. For example, TSH binds with high specificity to the TSH receptor but interacts minimally with the LH or the FSH receptor. Nonetheless, there can be subtle physiologic consequences of hormone cross-reactivity with other receptors. Very high levels of hCG during pregnancy stimulate the TSH receptor and increase TH levels, resulting in a compensatory decrease in TSH.

Insulin, insulin-like growth factor (IGF) type I, and IGF-II share structural similarities that are most apparent when precursor forms of the proteins are compared. In contrast to the high degree of specificity seen with the glycoprotein hormones, there is moderate cross-talk among the members of the insulin/IGF family. High concentrations of an IGF-II precursor produced by certain tumors (e.g., sarcomas) can cause hypoglycemia, partly because of binding to insulin and IGF-I receptors (Chap. 24). High concentrations of insulin also bind to the IGF-I receptor, perhaps accounting for some of the clinical manifestations seen in severe insulin resistance.

Another important example of receptor cross-talk is seen with PTH and parathyroid hormone–related peptide (PTHrP) (Chap. 27). PTH is produced by the parathyroid glands, whereas PTHrP is expressed at high levels during development and by a variety of tumors (Chap. 24). These hormones share amino acid sequence similarity, particularly in their amino-terminal regions. Both hormones bind to a single PTH receptor that is expressed in bone and kidney. Hypercalcemia and hypophosphatemia may therefore result from excessive production of either hormone, making it

TABLE 1-1

MEMBRANE RECEPTOR FAMILIES AND SIGNALING PATHWAYS

RECEPTORS	EFFECTORS	SIGNALING PATHWAYS
G Protein–Coupled Seven-Transmembrane (GPCR)		
β-Adrenergic LH, FSH, TSH Glucagon	$G_s\alpha$, adenylate cyclase	Stimulation of cyclic AMP production, protein kinase A
PTH, PTHrP ACTH, MSH GHRH, CRH	Ca^{2+} channels	Calmodulin, Ca^{2+}-dependent kinases
α-Adrenergic	$G_i\alpha$	Inhibition of cyclic AMP production
Somatostatin		Activation of K^+, Ca^{2+} channels
TRH, GnRH	G_q, G_{11}	Phospholipase C, diacylglycerol, IP_3, protein kinase C, voltage-dependent Ca^{2+} channels
Receptor Tyrosine Kinase		
Insulin, IGF-I	Tyrosine kinases, IRS	MAP kinases, PI 3-kinase; AKT, also known as protein kinase B, PKB
EGF, NGF	Tyrosine kinases, ras	Raf, MAP kinases, RSK
Cytokine Receptor–Linked Kinase		
GH, PRL	JAK, tyrosine kinases	STAT, MAP kinase, PI 3-kinase, IRS-1
Serine Kinase		
Activin, TGF-β, MIS	Serine kinase	Smads

Note: IP_3, inositol triphosphate; IRS, insulin receptor substrates; MAP, mitogen-activated protein; MSH, melanocyte-stimulating hormone; NGF, nerve growth factor; PI, phosphatylinositol; RSK, ribosomal S6 kinase; TGF-β, transforming growth factor β. For all other abbreviations, see text.

difficult to distinguish hyperparathyroidism from hypercalcemia of malignancy solely on the basis of serum chemistries. However, sensitive and specific assays for PTH and PTHrP now allow these disorders to be separated more readily.

Based on their specificities for DNA binding sites, the nuclear receptor family can be subdivided into type 1 receptors (GR, MR, AR, ER, PR) that bind steroids and type 2 receptors (TR, VDR, RAR, PPAR) that bind TH, vitamin D, retinoic acid, or lipid derivatives. Certain functional domains in nuclear receptors, such as the zinc finger DNA-binding domains, are highly conserved. However, selective amino acid differences within this domain confer DNA sequence specificity. The hormone-binding domains are more variable, providing great diversity in the array of small molecules that bind to different nuclear receptors. With few exceptions, hormone binding is highly specific for a single type of nuclear receptor. One exception involves the glucocorticoid and mineralocorticoid receptors. Because the mineralocorticoid receptor also binds glucocorticoids with high affinity, an enzyme (11β-hydroxysteroid dehydrogenase) located in renal tubular cells inactivates glucocorticoids, allowing selective responses to mineralocorticoids such as aldosterone. However, when very high glucocorticoid concentrations occur, as in Cushing's syndrome, the glucocorticoid degradation pathway becomes saturated, allowing excessive cortisol levels to exert mineralocorticoid effects (sodium retention, potassium wasting). This phenomenon is particularly pronounced in ectopic adrenocorticotropic hormone (ACTH) syndromes (Chap. 5). Another example of relaxed nuclear receptor specificity involves the estrogen receptor, which can bind an array of compounds, some of which share little structural similarity to the high-affinity ligand estradiol. This feature of the estrogen receptor makes it susceptible to activation by "environmental estrogens" such as resveratrol, octylphenol, and many other aromatic hydrocarbons. On the other hand, this lack of specificity provides an opportunity to synthesize a remarkable series of clinically useful antagonists (e.g., tamoxifen) and selective estrogen response modulators (SERMs) such as raloxifene. These compounds generate distinct conformations that alter receptor interactions with components of the transcription machinery, thereby conferring their unique actions.

HORMONE SYNTHESIS AND PROCESSING

The synthesis of peptide hormones and their receptors occurs through a classic pathway of gene expression: transcription → mRNA → protein → posttranslational protein processing → intracellular sorting, membrane integration, or secretion.

Many hormones are embedded within larger precursor polypeptides that are proteolytically processed to yield the biologically active hormone. Examples include proopiomelanocortin (POMC) → ACTH; proglucagon → glucagon; proinsulin → insulin; and pro-PTH → PTH, among others. In many cases, such as POMC and proglucagon, these precursors generate multiple biologically active peptides. It is provocative that hormone precursors are typically inactive, presumably adding an additional level of regulatory control. This is true not only for peptide hormones but also for certain steroids (testosterone → dihydrotestosterone) and thyroid hormone [L-thyroxine (T_4) → triiodothyronine (T_3)].

Hormone precursor processing is intimately linked to intracellular sorting pathways that transport proteins to appropriate vesicles and enzymes, resulting in specific cleavage steps, followed by protein folding and translocation to secretory vesicles. Hormones destined for secretion are translocated across the endoplasmic reticulum under the guidance of an amino-terminal signal sequence that is subsequently cleaved. Cell-surface receptors are inserted into the membrane via short segments of hydrophobic amino acids that remain embedded within the lipid bilayer. During translocation through the Golgi and endoplasmic reticulum, hormones and receptors are also subject to a variety of posttranslational modifications, such as glycosylation and phosphorylation, which can alter protein conformation, modify circulating half-life, and alter biologic activity.

Synthesis of most steroid hormones is based on modifications of the precursor, cholesterol. Multiple regulated enzymatic steps are required for the synthesis of testosterone (Chap. 8), estradiol (Chap. 10), cortisol (Chap. 5), and vitamin D (Chap. 25). This large number of synthetic steps predisposes to multiple genetic and acquired disorders of steroidogenesis.

Although endocrine genes contain regulatory DNA elements similar to those found in many other genes, their exquisite control by other hormones also necessitates the presence of specific hormone response elements. For example, the TSH genes are repressed directly by thyroid hormones acting through the thyroid hormone receptor (TR), a member of the nuclear receptor family. Steroidogenic enzyme gene expression requires specific transcription factors, such as steroidogenic factor-1 (SF-1), acting in conjunction with signals transmitted by trophic hormones (e.g., ACTH or LH). For some hormones, substantial regulation occurs at the level of translational efficiency. Insulin biosynthesis, while requiring ongoing gene transcription, is regulated primarily at the translational level in response to elevated levels of glucose or amino acids.

HORMONE SECRETION, TRANSPORT, AND DEGRADATION

The circulating level of a hormone is determined by its rate of secretion and its circulating half-life. After protein processing, peptide hormones (GnRH, insulin, GH) are stored in secretory granules. As these granules mature, they are poised beneath the plasma membrane for imminent release into the circulation. In most instances, the stimulus for hormone secretion is a releasing factor or neural signal that induces rapid changes in intracellular calcium concentrations, leading to secretory granule fusion with the plasma membrane and release of its contents into the extracellular environment and bloodstream. Steroid hormones, in contrast, diffuse into the circulation as they are synthesized. Thus, their secretory rates are closely aligned with rates of synthesis. For example, ACTH and LH induce steroidogenesis by stimulating the activity of *st*eroidogenic *a*cute *r*egulatory (StAR) protein (transports cholesterol into the mitochondrion) along with other rate-limiting steps (e.g., cholesterol side-chain cleavage enzyme, CYP11A1) in the steroidogenic pathway.

Hormone transport and degradation dictate the rapidity with which a hormonal signal decays. Some hormonal signals are evanescent (e.g., somatostatin), whereas others are longer-lived (e.g., TSH). Because somatostatin exerts effects in virtually every tissue, a short half-life allows its concentrations and actions to be controlled locally. Structural modifications that impair somatostatin degradation have been useful for generating long-acting therapeutic analogues, such as octreotide (Chap. 2). On the other hand, the actions of TSH are highly specific for the thyroid gland. Its prolonged half-life accounts for relatively constant serum levels, even though TSH is secreted in discrete pulses.

An understanding of circulating hormone half-life is important for achieving physiologic hormone replacement, as the frequency of dosing and the time required to reach steady state are intimately linked to rates of hormone decay. T_4, for example, has a circulating half-life of 7 days. Consequently, >1 month is required to reach a new steady state, but single daily doses are sufficient to achieve constant hormone levels. T_3, in contrast, has a half-life of 1 day. Its administration is associated with more dynamic serum levels and it must be administered two to three times per day. Similarly, synthetic glucocorticoids vary widely in their half-lives; those with longer half-lives (e.g., dexamethasone) are associated with greater suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Most protein hormones [e.g., ACTH, GH, prolactin (PRL), PTH, LH] have relatively short half-lives (<20 min), leading to sharp peaks of secretion and decay. The only accurate way to profile the pulse frequency and amplitude of these hormones is to measure levels in frequently sampled blood (every 10 min or less) over long durations (8–24 h). Because this is not practical in a clinical setting, an alternative strategy is to pool three to four samples drawn at about 30-min intervals, recognizing that pulsatile secretion makes it difficult to establish a narrow normal range. Rapid hormone decay is useful

in certain clinical settings. For example, the short half-life of PTH allows the use of intraoperative PTH determinations to confirm successful removal of an adenoma. This is particularly valuable diagnostically when there is a possibility of multicentric disease or parathyroid hyperplasia, as occurs with multiple endocrine neoplasia (MEN) or renal insufficiency.

Many hormones circulate in association with serum-binding proteins. Examples include (1) T_4 and T_3 binding to thyroxine-binding globulin (TBG), albumin, and thyroxine-binding prealbumin (TBPA); (2) cortisol binding to cortisol-binding globulin (CBG); (3) androgen and estrogen binding to sex hormone–binding globulin (SHBG) (also called testosterone-binding globulin, TeBG); (4) IGF-I and -II binding to multiple IGF-binding proteins (IGFBPs); (5) GH interactions with GH-binding protein (GHBP), a circulating fragment of the GH receptor extracellular domain; and (6) activin binding to follistatin. These interactions provide a hormonal reservoir, prevent otherwise rapid degradation of unbound hormones, restrict hormone access to certain sites (e.g., IGFBPs), and modulate the unbound, or "free," hormone concentrations. Although a variety of binding protein abnormalities have been identified, most have little clinical consequence, aside from creating diagnostic problems. For example, TBG deficiency can greatly reduce total TH levels, but the free concentrations of T_4 and T_3 remain normal. Liver disease and certain medications can also influence binding protein levels (e.g., estrogen increases TBG) or cause displacement of hormones from binding proteins (e.g., salsalate displaces T_4 from TBG). In general, only unbound hormone is available to interact with receptors and thereby elicit a biologic response. Short-term perturbations in binding proteins change the free hormone concentration, which in turn induces compensatory adaptations through feedback loops. SHBG changes in women are an exception to this self-correcting mechanism. When SHBG decreases because of insulin resistance or androgen excess, the unbound testosterone concentration is increased, potentially leading to hirsutism (Chap. 13). The increased unbound testosterone level does not result in an adequate compensatory feedback correction because estrogen, and not testosterone, is the primary regulator of the reproductive axis.

An additional exception to the unbound hormone hypothesis involves megalin, a member of the low-density lipoprotein (LDL) receptor family that serves as an endocytotic receptor for carrier-bound vitamins A and D, and SHBG-bound androgens and estrogens. Following internalization, the carrier proteins are degraded in lysosomes and release their bound ligands within the cells. Megalin deficiency in mice impairs androgen-dependent testis descent and estrogen-mediated vaginal opening, confirming a functional role in these steroid-dependent events.

HORMONE ACTION THROUGH RECEPTORS

Receptors for hormones are divided into two major classes—membrane and nuclear. *Membrane receptors* primarily bind peptide hormones and catecholamines. *Nuclear receptors* bind small molecules that can diffuse across the cell membrane, such as TH, steroids, and vitamin D. Certain general principles apply to hormone-receptor interactions, regardless of the class of receptor. Hormones bind to receptors with specificity and an affinity that generally coincides with the dynamic range of circulating hormone concentrations. Low concentrations of free hormone (usually 10^{-12} to 10^{-9} *M*) rapidly associate and dissociate from receptors in a bimolecular reaction, such that the occupancy of the receptor at any given moment is a function of hormone concentration and the receptor's affinity for the hormone. Receptor numbers vary greatly in different target tissues, providing one of the major determinants of specific cellular responses to circulating hormones. For example, ACTH receptors are located almost exclusively in the adrenal cortex, and FSH receptors are found only in the gonads. In contrast, insulin and TRs are widely distributed, reflecting the need for metabolic responses in all tissues.

MEMBRANE RECEPTORS

Membrane receptors for hormones can be divided into several major groups: (1) seven transmembrane GPCRs, (2) tyrosine kinase receptors, (3) cytokine receptors, and (4) serine kinase receptors (**Fig. 1-1**). The *seven transmembrane GPCR family* binds a remarkable array of hormones, including large proteins (e.g., LH, PTH), small peptides (e.g., TRH, somatostatin), catecholamines (epinephrine, dopamine), and even minerals (e.g., calcium). The extracellular domains of GPCRs vary widely in size and are the major binding site for large hormones. The transmembrane-spanning regions are composed of hydrophobic α-helical domains that traverse the lipid bilayer. Like some channels, these domains are thought to circularize and form a hydrophobic pocket into which certain small ligands fit. Hormone binding induces conformational changes in these domains, transducing structural changes to the intracellular domain, which is a docking site for G proteins.

The large family of *G proteins*, so named because they bind guanine nucleotides (GTP, GDP), provides great diversity for coupling receptors to different signaling pathways. G proteins form a heterotrimeric complex that is composed of various α and βγ subunits. The α subunit contains the guanine nucleotide–binding site and hydrolyzes GTP → GDP. The βγ subunits are tightly associated and modulate the activity of the α subunit, as

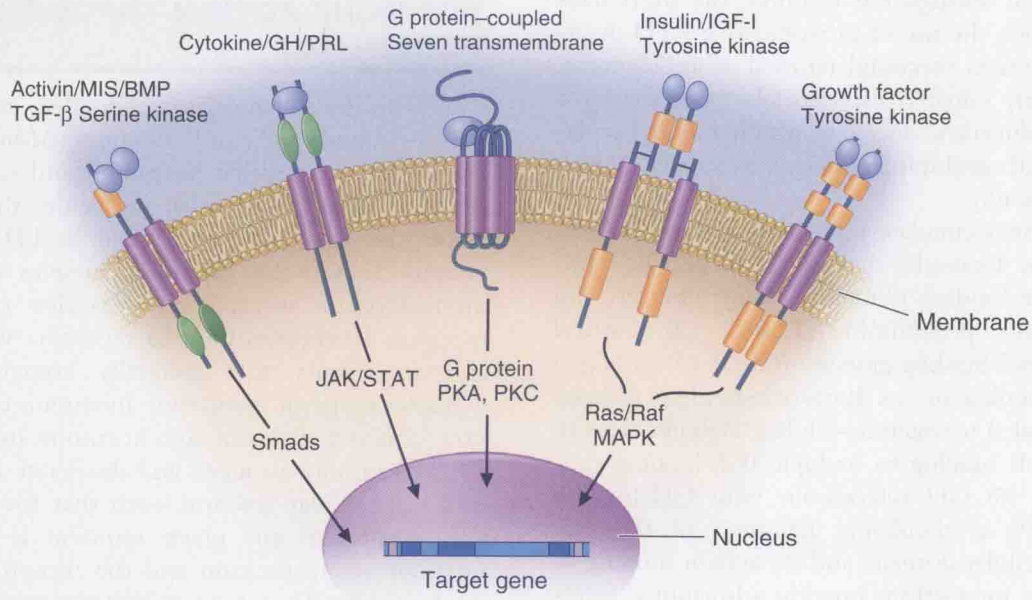

FIGURE 1-1

Membrane receptor signaling. MAPK, mitogen-activated protein kinase; PKA, -C, protein kinase A, C; TGF, transforming growth factor. For other abbreviations, see text.

well as mediating their own effector signaling pathways. G protein activity is regulated by a cycle that involves GTP hydrolysis and dynamic interactions between the α and βγ subunits. Hormone binding to the receptor induces GDP dissociation, allowing Gα to bind GTP and dissociate from the βγ complex. Under these conditions, the Gα subunit is activated and mediates signal transduction through various enzymes such as adenylate cyclase or phospholipase C. GTP hydrolysis to GDP allows reassociation with the βγ subunits and restores the inactive state. As described below, a variety of endocrinopathies result from G protein mutations or from mutations in receptors that modify their interactions with G proteins.

There are more than a dozen isoforms of the Gα subunit. $G_s\alpha$ stimulates, whereas $G_i\alpha$ inhibits, adenylate cyclase, an enzyme that generates the second messenger, cyclic AMP, leading to activation of protein kinase A (Table 1-1). G_q subunits couple to phospholipase C, generating diacylglycerol and inositol triphosphate, leading to activation of protein kinase C and the release of intracellular calcium.

The *tyrosine kinase receptors* transduce signals for insulin and a variety of growth factors, such as IGF-I, epidermal growth factor (EGF), nerve growth factor, platelet-derived growth factor, and fibroblast growth factor. The cysteine-rich extracellular ligand-binding domains contain growth factor–binding sites. After ligand binding, this class of receptors undergoes autophosphorylation, inducing interactions with intracellular adaptor proteins such as Shc and insulin receptor substrates. In the case of the insulin receptor, multiple kinases are activated, including the Raf-Ras-MAPK and the Akt/protein kinase B pathways. The tyrosine kinase receptors play a prominent role in cell growth and differentiation as well as in intermediary metabolism.

The GH and PRL receptors belong to the *cytokine receptor* family. Analogous to the tyrosine kinase receptors, ligand binding induces receptor interaction with intracellular kinases—the Janus kinases (JAKs), which phosphorylate members of the signal transduction and activators of transcription (STAT) family—as well as with other signaling pathways (Ras, PI3-K, MAPK). The activated STAT proteins translocate to the nucleus and stimulate expression of target genes.

The *serine kinase receptors* mediate the actions of activins, transforming growth factor β, müllerian-inhibiting substance (MIS, also known as anti-müllerian hormone, AMH), and bone morphogenic proteins (BMPs). This family of receptors (consisting of type I and II subunits) signals through proteins termed *smads* (fusion of terms for *Caenorhabditis elegans* sma + mammalian mad). Like the STAT proteins, the smads serve a dual role of transducing the receptor signal and acting as transcription factors. The pleomorphic actions of these growth factors dictate that they act primarily in a local (paracrine or autocrine) manner. Binding proteins, such as follistatin (which binds activin and other members of this family), function to inactivate the growth factors and restrict their distribution.

NUCLEAR RECEPTORS

The family of nuclear receptors has grown to nearly 100 members, many of which are still classified as orphan receptors because their ligands, if they exist, remain to be identified (Fig. 1-2). Otherwise, most nuclear receptors are classified based on the nature of their ligands. Though all nuclear receptors ultimately act to increase or decrease gene transcription, some (e.g., glucocorticoid receptor) reside primarily in the cytoplasm, whereas others (e.g., thyroid hormone receptor) are always located in the nucleus. After ligand binding, the cytoplasmically localized receptors translocate to the nucleus. There is growing evidence that certain nuclear receptors (e.g., glucocorticoid, estrogen) can also act at the membrane or in the cytoplasm to activate or repress signal transduction pathways, providing a mechanism for cross-talk between membrane and nuclear receptors.

The structures of nuclear receptors have been extensively studied, including by x-ray crystallography. The DNA-binding domain, consisting of two zinc fingers, contacts specific DNA recognition sequences in target genes. Most nuclear receptors bind to DNA as dimers. Consequently, each monomer recognizes an individual DNA motif, referred to as a "half-site." The steroid receptors, including the glucocorticoid, estrogen, progesterone, and androgen receptors, bind to DNA as homodimers. Consistent with this twofold symmetry, their DNA recognition half-sites are palindromic. The thyroid, retinoid, peroxisome proliferator–activated, and vitamin D receptors bind to DNA preferentially as heterodimers in combination with retinoid X receptors (RXRs). Their DNA half-sites are arranged as direct repeats. Receptor specificity for DNA sequences is determined by (1) the sequence of the half-site, (2) the orientation of the half-sites (palindromic, direct repeat), and (3) the spacing between the half-sites. For example, vitamin D, thyroid, and retinoid receptors recognize similar tandemly repeated half-sites (TAAGTCA), but these DNA repeats are spaced by three, four, and five nucleotides, respectively.

The carboxy-terminal hormone-binding domain mediates transcriptional control. For type 2 receptors, such as TR and retinoic acid receptor (RAR), co-repressor proteins bind to the receptor in the absence of ligand and silence gene transcription. Hormone binding induces conformational changes, triggering the release of co-repressors and inducing the recruitment of coactivators that stimulate transcription. Thus, these receptors are capable of mediating dramatic changes in the level of gene activity. Certain disease states are associated with defective regulation of these events. For example, mutations in the TR prevent co-repressor dissociation, resulting in a dominant form of hormone resistance (Chap. 4). In promyelocytic leukemia, fusion of RARα to other nuclear proteins causes aberrant gene silencing and prevents normal cellular differentiation. Treatment with retinoic acid reverses this repression and allows cellular differentiation and apoptosis to occur. Most type 1 steroid receptors interact weakly with co-repressors, but ligand binding still induces interactions with an array of coactivators. X-ray crystallography shows that various SERMs induce distinct estrogen receptor conformations. The tissue-specific responses caused by these agents in breast, bone, and uterus appear to reflect distinct interactions

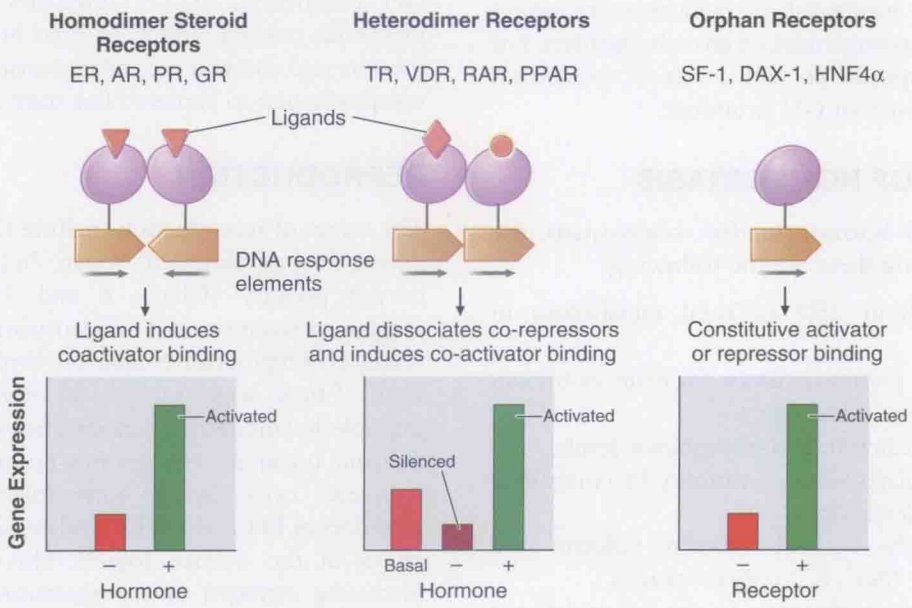

FIGURE 1-2

Nuclear receptor signaling. ER, estrogen receptor; AR, androgen receptor; PR, progesterone receptor; GR, glucocorticoid receptor; TR, thyroid hormone receptor; VDR, vitamin D receptor; RAR, retinoic acid receptor; PPAR, peroxisome proliferator activated receptor; SF-1, steroidogenic factor-1; DAX, *d*osage-sensitive sex reversal, *a*drenal hypoplasia congenita, *X* chromosome; HNF4α, hepatic nuclear factor 4α.

with coactivators. The receptor-coactivator complex stimulates gene transcription by several pathways, including (1) recruitment of enzymes (histone acetyl transferases) that modify chromatin structure, (2) interactions with additional transcription factors on the target gene, and (3) direct interactions with components of the general transcription apparatus to enhance the rate of RNA polymerase II–mediated transcription. Studies of nuclear receptor–mediated transcription show that these are dynamic events involving relatively rapid (e.g., 30–60 min) cycling of transcription complexes on any given target gene.

FUNCTIONS OF HORMONES

The functions of individual hormones are described in detail in subsequent chapters. Nevertheless, it is useful to illustrate how most biologic responses require integration of several different hormone pathways. The physiologic functions of hormones can be divided into three general areas: (1) growth and differentiation, (2) maintenance of homeostasis, and (3) reproduction.

GROWTH

Multiple hormones and nutritional factors mediate the complex phenomenon of growth (Chap. 2). Short stature may be caused by GH deficiency, hypothyroidism, Cushing's syndrome, precocious puberty, malnutrition, chronic illness, or genetic abnormalities that affect the epiphyseal growth plates (e.g., *FGFR3* or *SHOX* mutations). Many factors (GH, IGF-I, TH) stimulate growth, whereas others (sex steroids) lead to epiphyseal closure. Understanding these hormonal interactions is important in the diagnosis and management of growth disorders. For example, delaying exposure to high levels of sex steroids may enhance the efficacy of GH treatment.

MAINTENANCE OF HOMEOSTASIS

Though virtually all hormones affect homeostasis, the most important among these are the following:

1. TH—controls about 25% of basal metabolism in most tissues
2. Cortisol—exerts a permissive action for many hormones in addition to its own direct effects
3. PTH—regulates calcium and phosphorus levels
4. Vasopressin—regulates serum osmolality by controlling renal free-water clearance
5. Mineralocorticoids—control vascular volume and serum electrolyte (Na^+, K^+) concentrations
6. Insulin—maintains euglycemia in the fed and fasted states

The defense against hypoglycemia is an impressive example of integrated hormone action (Chap. 20). In response to the fasted state and falling blood glucose, insulin secretion is suppressed, resulting in decreased glucose uptake and enhanced glycogenolysis, lipolysis, proteolysis, and gluconeogenesis to mobilize fuel sources. If hypoglycemia develops (usually from insulin administration or sulfonylureas), an orchestrated counterregulatory response occurs—glucagon and epinephrine rapidly stimulate glycogenolysis and gluconeogenesis, whereas GH and cortisol act over several hours to raise glucose levels and antagonize insulin action.

Although free-water clearance is primarily controlled by vasopressin, cortisol and TH are also important for facilitating renal tubular responses to vasopressin (Chap. 3). PTH and vitamin D function in an interdependent manner to control calcium metabolism (Chap. 25). PTH stimulates renal synthesis of 1,25-dihydroxyvitamin D, which increases calcium absorption in the gastrointestinal tract and enhances PTH action in bone. Increased calcium, along with vitamin D, feeds back to suppress PTH, thereby maintaining calcium balance.

Depending on the severity of a given stress and whether it is acute or chronic, multiple endocrine and cytokine pathways are activated to mount an appropriate physiologic response. In severe acute stress such as trauma or shock, the sympathetic nervous system is activated and catecholamines are released, leading to increased cardiac output and a primed musculoskeletal system. Catecholamines also increase mean blood pressure and stimulate glucose production. Multiple stress-induced pathways converge on the hypothalamus, stimulating several hormones including vasopressin and corticotropin-releasing hormone (CRH). These hormones, in addition to cytokines (tumor necrosis factor α, IL-2, IL-6), increase ACTH and GH production. ACTH stimulates the adrenal gland, increasing cortisol, which in turn helps to sustain blood pressure and dampen the inflammatory response. Increased vasopressin acts to conserve free water.

REPRODUCTION

The stages of reproduction include (1) sex determination during fetal development (Chap. 7); (2) sexual maturation during puberty (Chaps. 8 and 10); (3) conception, pregnancy, lactation, and child-rearing (Chap. 10); and (4) cessation of reproductive capability at menopause (Chap. 12). Each of these stages involves an orchestrated interplay of multiple hormones, a phenomenon well illustrated by the dynamic hormonal changes that occur during each 28-day menstrual cycle. In the early follicular phase, pulsatile secretion of LH and FSH stimulates the progressive maturation of the ovarian follicle. This results in gradually increasing estrogen and progesterone levels, leading to enhanced pituitary sensitivity to GnRH, which, when combined with accelerated GnRH secretion, triggers the LH surge and rupture of the mature follicle. Inhibin, a protein produced by the granulosa cells, enhances follicular growth and feeds back to the pituitary to selectively