ESSENTIAL ENDOCRINOLOGY

A Primer for Nonspecialists

C. R. Kannan, M.D.

ESSENTIAL ENDOCRINOLOGY

A Primer for Nonspecialists

C. R. Kannan, M.D.

Chairman
Division of Endocrinology and Metabolism
Department of Medicine
Cook County Hospital
and Clinical Associate Professor of Medicine
University of Illinois at Chicago
Chicago, Illinois

PLENUM MEDICAL BOOK COMPANY
New York and London

Library of Congress Cataloging in Publication Data

Kannan, C. R. (Charkravarthy R.), 1943–
Essential endocrinology.

Includes bibliographies and index.
1. Endocrinology—Outlines, syllabi, etc. 2. Endocrinology—Handbooks, manuals, etc. I. Title. [DNLM: 1. Endocrine Diseases. WK 100 K16e]
RC648.K35 1986 612'.4 86-4925
ISBN 0-306-42172-0

Preface

This work, *Essential Endocrinology: A Primer for Nonspecialists*, is written with dual purposes in mind: first, to provide a framework of basic endocrinology and diabetology to the medical student, and second, to provide a quick, concise, and handy "guide" to the junior residents in their early years of training who wish to obtain a working knowledge about endocrine disorders that affect their patients. One of the outstanding advantages of being a teacher of endocrinology to students and junior residents is that it bestows a perspective from a unique vantage point. Books written for the junior members of our profession have suffered from extremes of caliber, ranging from excellence beyond their comprehension to insufferable mediocrity. Textbooks in endocrinology that are simple enough to cover the principles of that speciality and yet comprehensive enough without treading into controversial quicksand are few and far between. This book is aimed at filling that gap and is written with no other criterion than simplifying a complex subject matter. From this touchstone, the work has never really departed.

A decade of experience as a teacher and physician in the field of endocrinology has impressed on me that the process of "simplification" rests on four basic principles: an understanding of endocrine concepts, the application of these concepts to the understanding of diseases, the transference of knowledge to clinical situations, and the integration of the patient with the laboratory, the ultimate testing ground where clinical diagnoses stand or fall. A brief overview of the method in the making of this text seems appropriate.

An understanding of endocrine concepts is the common thread that is woven throughout the book. Each part begins by emphasizing the basic anatomic and physiological considerations that govern the proper functioning of each gland. The importance of understanding physiology is fostered by my firm belief that unless normal physiology is understood, disease states cannot be completely understood, nor can laboratory tests be clearly interpreted. Endocrine concepts can be divided into three classes: "core concepts" (concepts that are so vital that failure to understand these concepts precludes

further comprehension), "primary concepts" (which include basic dogma that has been passed down in every edition of every standard textbook), and "current concepts" (concepts that are believed to be true given the "state-of-the-art" information of the times). This last category of concepts is somewhat controversial, often enigmatic, and always intriguing. This text, at the risk of being labeled simplistic, has strived to focus on the "core concepts" and "primary concepts" that have stood the tests of time and weathered many a storm of controversy.

The controversial concepts have been kept to a minimum, since they matter very little to the student of basics, although they have enormous impact in stimulating the mind of the student who has mastered the basics. For instance, the beginner who is learning about insulin should first know the core concepts about that hormone: the source, the actions as they pertain to glucose transport, adipose tissue, and the liver, etc. After these are understood, the "primary concepts" constitute the regulation of the synthesis and release of the hormone as well as the major factors that modify these phenomena and the role of the hormone in maintaining glucose homeostasis. The "current concepts" in this context would be the speculative hypotheses on the possible mediators that express insulin action. Although the student will find all three types of concepts discussed, the proportion of core concepts and primary concepts far exceeds that of controversial concepts. This has been done deliberately to avoid overwhelming the student physician with trivia or confusing concepts. A list of references provided at the end of each section should satisfy the appetite of those who want more.

The second cornerstone of simplification is the application of the above-mentioned concepts to the understanding of diseases. This is done in the following manner: the book has been divided into nine sections: the pituitary gland (adenohypophysis and neurohypophysis), the thyroid gland, the parathyroids, the adrenal glands, the testes, the ovaries, the disorders of sexual differentiation, diabetes, and a section on miscellany. Each section involving individual endocrine organs, begins with a discussion of salient anatomy and physiology, followed by laboratory methods of testing glandular function; disorders involving hyperfunction, hypofunction, and other specific diseases affecting each gland are subsequently discussed. The inevitable physical limitations to what can be compressed between the boards of a book force every author to decide how much space to devote to each topic. The decision to devote maximal allotment to the pituitary gland, the thyroid gland, and diabetes is based on three facts: first, the pituitary, by virtue of the numerous hormones that it secretes, forces the author (and the reader) on a long sojourn with several detours; second, thyroid disorders are the most frequent ones that find a place in the general internist's practice (as well as in the Board Examination); third, diabetes is a subspeciality within a subspeciality demanding attention (and space) by its commonality and far-reaching effects that penetrate every discipline of internal medicine.

Unlike the standard treatises in endocrinology and diabetes, this book does not have the space to tell all, which is why the focus is at all times aimed

at being direct, simple, uncomplicated, and above all, on clinically oriented topics. For the reader who thirsts for more, the concise but comprehensive references at the end of each section or the standard voluminous textbooks in endocrinology would prove quite quenching. The incorporation of important concepts into diseases has been accomplished by juxtaposing the principles with the clinically established facts. Several tables have been used to indicate to the reader the reasons and logic underlying endocrine phenomena. Several of these tables are "thumbnail sketches" of entire paragraphs and are meant to serve as "instant replays" of the more detailed paragraphs in the text. This is especially so in the chapters on the gonads and sexual differentiation, topics that are justifiably perceived to be particularly difficult ones to comprehend.

Having conveyed the importance of endocrine concepts and their incorporation in the understanding of diseases, the third facet in the process of simplifying clinical endocrinology is the transference of knowledge to clinical situations. This is particularly important for the student physician, who must learn to think of symptoms rather than "disease labels." Whenever possible, the reader is provided with tables that correlate symptoms and signs of a certain disease with other disorders that cause identical symptoms or signs. The section on diagnostic studies in each chapter provides further correlations between established facts and several relevant diseases.

Finally, integration of the endocrine laboratory with the clinical presentations constitutes the fourth, and perhaps the conclusive, ingredient in the diagnostic process. This is approached in this book by providing the reader with two interconnected perspectives. First, at the beginning of each section, a chapter is devoted to testing function of a specific gland with particular reference to the important tests employed to assess functional integrity of the gland. Second, under individual diseases, the principles behind each test used, the indications for performing the tests (or study), and, more importantly, what the tests can and cannot reveal are outlined. Although it is true that endocrine studies do not always conclusively "make or break" a clinical diagnosis, in the interest of clarity, the student is shielded from these uncertainties. For the same reason, therapeutics of endocrine disorders is also dealt with in noncontroversial terms. In most instances, the therapeutic principles are broadly outlined. These principles do not include the beleaguering heterogeneity in patient responses.

Limitation on space, curiously enough, is a double-edged sword; on one hand, it impedes the amount an author wishes to offer (and all authors initially write more than what they intended), but on the other hand, when the time comes to "trim" (or edit), the limitations enforce focus on vital issues and reduce redundancy. Like most authors I have participated in both processes, and during the painful process of self-editing, the only determinant of what stays and what goes is the relevance and importance of the subject to the medical student and junior house staff. The constant questions, "Can a student afford to not know this fact?" and "Is this a core concept?" have dominated the editing process. For example, several paragraphs on human thyroid stim-

ulators (a topic close to the author's heart) were sacrificed to make room for principles underlying the T_3 resin uptake test—a basic core concept that needed expounding. The final product is a work trimmed to the bare essentials.

From the aforementioned, it should become evident that the student who sets out to learn the fundamentals of endocrinology and diabetes and goes to the well with this purpose will not come away dry. For the student who wishes to wander the academic vistas of molecular or research endocrinology, this book is but a window to that world. If either goal is accomplished, this book would have served its purpose. This work is meant to be a guide, not a reference work; a short story, not a novel; a song, and not a symphony.

ACKNOWLEDGMENT. The support and well wishes of several friends have made this work possible. The single authorship of the book notwithstanding, I have heavily relied on a "little help from my friends." Most notably, I am deeply grateful to Ms. Gayla Blake who has played several crucial roles as a supporter, as a typist, and as a graphic illustrator. Her incessant zeal has had a galvanizing effect on the making of this book. I am deeply indebted to my medical editor, Mrs. Janice Stern, and the entire staff of the Plenum Publishing Corporation. It is indeed my good fortune to have a publishing house that takes great pride in enhancing an author's work. Finally, without the patience and fortitude of my wife Molly and son Ashley, this work would not have been accomplished.

C. R. Kannan, M.D.

Cook County Hospital
Chicago, Illinois

Contents

An Introduction to Endocrinology 1

Part I. The Pituitary Gland

Chapter 1. The Anatomy of the Pituitary Gland 13
Chapter 2. Physiology: The Secretion, Regulatory Control, and Actions of Pituitary Hormones 17
Chapter 3. Testing Pituitary Function 31
Chapter 4. Pituitary Hyperfunction 43
Chapter 5. Pituitary Hypofunction 65
Chapter 6. The Empty Sella Syndrome 83
Chapter 7. Pituitary Tumors 87
Chapter 8. The Neurohypophysis: The Regulatory Control and Actions of Vasopressin 91
Chapter 9. Diabetes Insipidus 97
Chapter 10. Syndrome of Inappropriate ADH Secretion 105

Part II. The Thyroid Gland

Chapter 11. The Anatomy of the Thyroid Gland 117
Chapter 12. Physiology: The Secretion, Regulatory Control, and Actions of the Thyroid Hormones 119
Chapter 13. Testing Thyroid Function 123
Chapter 14. Thyroid Hyperfunction 133
Chapter 15. Thyroid Hypofunction 151
Chapter 16. The Thyroidites 161
Chapter 17. Thyroid Nodules 171
Chapter 18. Thyroid Cancer 179

Part III. The Parathyroids

Chapter 19. Anatomy of the Parathyroids 189
Chapter 20. Physiology: The Control, Regulation, and Actions of Parathyroid Hormone 191
Chapter 21. Hypercalcemia 201
Chapter 22. Primary Hyperparathyroidism 207
Chapter 23. Hypocalcemia 215
Chapter 24. Hypoparathyroidism 223

Part IV. The Adrenal Glands

Chapter 25. Anatomy of the Adrenal Glands 233
Chapter 26. Physiology: The Secretion, Regulatory Control, and Actions of the Adrenal Steroids 235
Chapter 27. Testing Adrenocortical Function 239
Chapter 28. Hyperfunction of the Adrenal Cortex 249
Chapter 29. Hypofunction of the Adrenals 265
Chapter 30. Tumors of the Adrenal Glands 273
Chapter 31. The Adrenal Medulla and Pheochromocytoma 279

Part V. The Testes

Chapter 32. Anatomy of the Testes 289
Chapter 33. Physiology of Testicular Function 291
Chapter 34. Testing Testicular Function 297
Chapter 35. Precocious Puberty in the Male 303
Chapter 36. Testicular Hypofunction 307

Part VI. The Ovaries

Chapter 37. Anatomy of the Ovaries 325
Chapter 38. Physiology of Ovarian Function 327
Chapter 39. Testing Ovarian Function 333
Chapter 40. Precocious Puberty in the Female 339
Chapter 41. Ovarian Failure 345

Part VII. Disorders of Sexual Differentiation

Chapter 42. Embryology of Sexual Differentiation 357
Chapter 43. Syndromes of Disordered Sexual Differentiation 363

Part VIII. Diabetes and Glucose Intolerance

Chapter 44. Physiology: The Synthesis, Release, and Actions of Insulin 375
Chapter 45. The Definition, Classification, and Etiology of Diabetes ... 381
Chapter 46. The Clinical Features of Diabetes 393
Chapter 47. Diagnostic Studies in Diabetes Mellitus 399
Chapter 48. Metabolic Decompensations in the Diabetic 407
Chapter 49. Chronic Complications of Diabetes 425
Chapter 50. The Treatment of Diabetes 449

Part IX. Miscellany

Chapter 51. Islet Cell Tumors 475
Chapter 52. Multiple Endocrine Adenomatosis 505
Chapter 53. Carcinoid Tumors 517

Index 525

An Introduction to Endocrinology

1. Background

Endocrinology is the study of hormones. The term *hormone* is derived from the Greek word *harmao* (I excite) and was used by the legendary physiologist E. H. Starling in his Croonian lectures at the Royal College of Physicians in 1905. He proposed, with remarkable prophecy, that these substances are secreted by one organ and are transported by the bloodstream ("ductless transport") to other organs at distant sites, on which they exert their diverse effects. It was further speculated at that time, again with remarkable accuracy, that these "chemical messengers" had a rather rapid onset of action and excited their target organs even in extremely small quantities. Since then, endocrinology has evolved into an extremely sophisticated branch of internal medicine. A brief historical review of the events that have bridged the past and the present is pertinent, since it illustrates how the echoes of the past have been profoundly visionary.

Although the science of "hormonology" had its origins at the turn of this century, the existence of hormones was suspected as early as the 16th century. In 1690, Fredrick Ruysch, the celebrated Dutch anatomist, suggested that the thyroid gland "poured important substances into the bloodstream." Historians of medicine regard Theophile Bordeu as the founder of endocrinology. This famous French physician from Montpellier (which was the citadel of research in the 17th century) wrote in his masterpiece, *Recherches sur les Maladies Chroniques* (*Research on Chronic Diseases*), that several parts of the body gave off "emanations" that had profound effects on other parts of the body. His concepts, however, remained as speculations that lacked experimental proof.

In 1849, two events occurred that were destined to affect the concept of hormones forever. First, Arnold Berthold reported the first documented experimental evidence of hormonal deficiency; he demonstrated that castration

of the rooster resulted in atrophy of its comb and that such atrophy can be prevented if the testes are transplanted to another part of the rooster's body. He proposed that an "internal secretion" from the testes prevented the atrophy of the rooster's comb. The second event was a much more celebrated and memorable one; on a gray afternoon in the autumn of 1849, Thomas Addison read to an audience of the London Medical Society about his 11 patients with a fatal condition. All of these cases were characterized by "anemia, increasing weakness, feebleness of the heart, a smoky pigmentation and disease of the suprarenal glands at autopsy." Thus, the first link between a disease entity and a diseased gland was established. This condition, which Addison termed "melasma suprarenale," was renamed Addison's disease (by his friend Trosseau). In 1855, Claude Bernard introduced the tern "internal secretion" ("*secretion interne*"), and the science of endocrinology took off at a very high pitch. Between 1860 and 1900, the existence and functions of the thyroid, pituitary, adrenals, gonads, parathyroids, and even the islets of Langerhans had become established with reasonable clarity.

The discoveries in this century have unraveled several secrets and mysteries of hormonal disorders. The most exciting discovery of the 1920s (and perhaps the century) was the discovery and chemical synthesis of insulin by the collaborative efforts of Banting, Best, Macleod, and Collip. The major breakthroughs of the 1930s were the characterization of the catecholamines and the synthesis of desoxycorticosterone; the concept of neurotransmitters was born in this decade, and yet the surface of Pandora's box had only been scratched; more was to come. The 1940s witnessed a lull in endocrine research, when the world went to war. Yet this period saw the systematic description of various endocrine disorders. Fuller Albright described, for the first time, three important concepts that were to revolutionize endocrine thought: he showed that the bone disease of hyperparathyroidism disappeared on removal of the parathyroid adenoma; he proposed that tumors can ectopically secrete a parathormonelike substance; and he introduced the concept of target organ resistance by describing pseudohypoparathyroidism. These concepts, taken for granted today, were conceived by the sheer genius of intellect at a time when laboratory proof for such phenomena were, at best, rudimentary. Also in the 1940s two therapeutic events occurred quietly in widely separated parts of the globe: a French scientist accidentally discovered an oral hypoglycemic agent, and in Boston radioactive iodine was administered for the first time to a thyrotoxic patient.

The 1950s and 1960s filled the pages of endocrine literature with the description of several new hypersecretory and hyposecretory syndromes. Gut hormones, prostaglandins, and calcitonin became new members in the "hormone club." Sutherland's concept that the actions of several hormones are mediated by that omnipotent second messenger cyclic AMP revolutionized the understanding of syndromes of target organ resistance. But the event that singlehandedly catapulted endocrinology into an extremely sophisticated sphere was the emergence of the radioimmunoassay. This tool permitted

measurement of practically every hormone in blood, conferring a sacrosanct status to the endocrine laboratory.

The 1970s and 1980s have witnessed a whole new realm of hypothalamic releasing factors that have had an enormous impact on diagnosis and therapy. The "high-tech" era has permeated endocrinology with marvels such as high-resolution computerized tomographic scans (which see everything), selective catheterization techiques (that can reach anywhere), sophisticated insulin-delivery pumps (that can be worn anywhere), and microsurgery. This remarkably dynamic subspeciality is still growing. Before embarking on a systematic description of disorders that involve the individual glands, it is important to outline some basic principles common to all endocrine glands. The focus is on four areas: hormonal secretion, hormonal feedback regulation, hormonal circulation, and hormonal action.

2. Hormonal Secretion

The secretory cells of the endocrine glands actively secrete, store, and release hormones. These cells are endowed with complicated synthetic machinery, histologically represented by an intense granular cytoplasm. Many hormones (ACTH, insulin, etc.) are synthesized as prohormones that are biologically inactive. Several enzyme systems within the cytoplasm are responsible for cleaving these prohormones at proper sites, converting them into active hormones. Very little is known regarding basal secretion of hormones by endocrine glands. Basal secretion is defined as the secretory activity of the endocrine gland in the absence of provocative or suppressive factors. It is believed that basal secretion of hormone by endocrine cells is under neuroregulatory control. The "bursts" of secretory activity of certain hormones (prolactin, growth hormone, etc.) and the diurnal rhythm of several hormones, particularly ACTH, are perhaps mediated by neuroregulation from the cortex or hypothalamus.

In contrast to the basal secretory rate of hormones, the stimulated output of endocrine glands has been studied extensively. Both physiological and chemical factors stimulate increased hormonal output. It is believed that hormones are stored within endocrine cells in two pools: a labile preformed pool, which is the moiety that is immediately released in response to provocative stimuli, and a synthetic pool, from which new hormone is actively synthesized, packaged, and released in response to continuous or chronic stimulation. The provocative factors that cause increased hormonal output can be hormonal, chemical, or neural or can be the circulating levels of certain metabolites. Examples of these four categories of provocative factors are outlined in Table 1 for growth hormone as an example.

There are several mechanisms by which trophic factors stimulate hormonal output, but the most dominant and frequent mechanism is the stimulation of membrane-bound adenylate cyclase, which catalyzes the conversion

TABLE 1
Provocative Stimuli for Growth Hormone Release

Type of stimulus	Example
Hormonal	Growth hormone-releasing hormone
Chemical	L-Dopa serotonin
Neural	α-Adrenergic stimulation
Metabolites	Hypoglycemia

of ATP to cyclic AMP. This is the mechanism that governs the trophic effect of TSH on the thyroid, the trophic effect of ACTH on the adrenal cortex, etc. This simplistic concept becomes more complex when one evaluates the role of metabolites in controlling hormone release. For instance, the mechanism of glucose-mediated insulin release belongs in this category and is discussed in Chapter 44. The magnitude of response of the same endocrine cell to different stimuli can have an impressive range. For instance, the response of prolactin release from the lactotroph can be quite variable, depending on the stimulus employed; stimulation of the nipple causes a much more brisk and profound increase in serum prolactin than chemical stimuli such as chlorpromazine or metoclopramide.

Suppressive factors are those that inhibit the release of glandular secretions. These factors are important in the day-to-day maintenance of constant hormonal levels and in avoiding hypersecretion. These suppressive factors, again, can be hormonal, chemical, neural, or metabolites themselves. Table 2 illustrates the variety of suppressive factors with growth hormone again used as an example.

Understanding the stimulatory and suppressive factors that govern the release of each hormone has tremendous diagnostic impact. The dictum, "when hypofunction is suspected the gland should be tested by stimlation, and when hyperfunction is suspected the gland should be tested by suppression," is a basic endocrine dogma. Table 3 outlines the multitude of provocative and suppressive factors for some of the frequently tested hormones.

TABLE 2
Suppressive Factors for Growth Hormone Release

Type of suppressive factor	Example
Hormonal	Somatostatin
Chemical	Chlorpromazine, progesterone, serotonin antagonist
Neural	β-Adrenergic stimulation
Metabolites	Hyperglycemia

TABLE 3
Provocative and Suppressive Factors That Affect Hormone Release

Hormone	Provocative factors	Suppressive factors
ACTH	Hypoglycemia, stress, CRF	Cortisol
TSH	TRH	Thyroid hormones
Growth hormone	Hypoglycemia, stress, dopamine, sleep, GHRH	Glucose, somatostatin
Prolactin	Stimulation of nipple or areola, chlorpromazine, TRH, sleep	Dopamine and dopamine agonists
LH, FSH	GnRH (gonadoptropin-releasing hormone)	Sex steroids
Thyroid hormone	TSH	
Cortisol	ACTH	
Aldosterone	Renin–angiotensin system, ACTH, hyperkalemia	Volume expansion, hypokalemia
Catecholamines	Stress, hypoglycemia	
Sex steroids	LH, FSH	
Insulin	Hyperglycemia, amino acids	Hypoglycemia
Glucagon	Hypoglycemia, amino acids	Hyperglycemia
PTH	Hypocalcemia	Hypercalcemia

3. Feedback Regulation

The term *feedback regulation* (or feedback loop) refers to the delicate relationship between ambient concentrations of the target gland hormone and its respective trophic hormone. With the notable exception of the parathyroids and pancreatic islet cells, almost all other endocrine glands participate in feedback loops involving the hypothalami pituitary unit. Thus, the functions of the thyroid, adrenal cortices, testes, and ovaries are modulated and fine-tuned by an intimate servo feedback mechanism involving the hypothalamic–pituitary unit. The term *negative feedback* implies a reciprocal relationship between target gland hormone and its trophic hormone; i.e., an increase in the concentration of target gland hormone will result in suppression of its spective trophic hormone, whereas decreasing concentrations of target gland hormone cause an increase in its respective trophic hormone level. Such is the relationship between the thyroid hormones and thyrotropin (TSH), glucocorticoids and cotricotropin (ACTH), as well as between testosterone and luteinzing hormone (LH). The effects of estrogens on the hypothalamic–pituitary unit in normal females is dichotomous, consisting of both negative and positive feedback regulatory mechanisms. The term *positive feedback* implies a linear relationship between target gland hormone and its trophic hormone; i.e., an increase in the circulating levels of target gland hormone results in stimulating its respective trophic hormone. The most illustrative physiological example of positive feedback between hormones is the "LH

surge" that occurs during the midmenstrual cycle caused by a progressive increase in circulating concentrations of 17 β-estradiol. Notably, this response is restricted only to females.

Feedback loops have also been categorized as "long," "short," and "ultrashort" feedback loops (Table 4):

1. *Long feedback loops* are exemplified by the feedback regulation between the hypothalamus and glucocorticoids or gonadal steroids. In the case of cortisol and testosterone, this feedback loop is exclusively a negative feedback loop, whereas in the case of 17β-estradiol this long feedback loop is both negative as well as positive under different circumstances.
2. *Short feedback loops* denote the servo feedback relationship between the pituitary gland and the hormones secreted by several of its target glands. The most impressive example of such a short feedback loop is the relationship between the pituitary TSH and the thyroid hormones. A similar situation is seen between ACTH and cortisol as well as between LH and gonadal steroids. Cortisol and the gonadal steroids feed back on both the hypothalamus (long negative feedback) as well as the pituitary (short negative feedback), whereas the thyroid hor-

TABLE 4
The Feedback Regulatory Loops

Type of loop	Target gland hormone	Trophic hormone
I. Long feedback		
A. Negative feedback	Cortisol	CRH[a]
	Testosterone or 17β-estradiol	GnRH[b]
B. Positive feedback	17β-Estradiol	GnRH
II. Short feedback		
A. Negative feedback	Thyroid hormones	TSH
	Testosterone or 17β-estradiol	LH
	Cortisol	ACTH
B. Positive feedback	None	None
III. Ultrashort feedback		
A. Negative feedback	ACTH	CRH
	?TSH	TRH
B. Positive feedback	Growth hormone	Somatostatin
	Prolactin	Hypothalamic PIF[c] (dopamine)

[a] CRH, corticotropin-releasing hormone.
[b] GnRH, gonadotropin-releasing hormone.
[c] PIF, prolactin inhibitory factor.

mones predominantly exert their negative feedback effect on the pituitary gland (short negative feedback loop).

3. The term *ultrashort feedback* refers to the intimate relationship between the pituitary gland and its hypothalamic master. These loops can be negative or positive. Thus, a negative ultrashort feedback loop exists between ACTH and corticotropin-releasing hormone (CRH) of the hypothalamus. A similar loop perhaps also exists between TSH and TRH. In contrast, a positive ultrashort feedback loop operates between growth hormone and somatostatin and perhaps between prolactin and hypothalamic dopamine.

4. Hormonal Circulation

In general, there are three major types of hormones secreted by endocrine glands, steroid hormones, polypeptide hormones, and amino acid (or short peptide) hormones. The steroid hormones (exemplified by cortisol, testosterone, estradiol, and aldosterone) circulate in blood bound to carrier proteins. The bound hormone is biologically inactive, and their circulating levels in plasma can be altered by quantitative or qualitative alterations in their respective carrier proteins. These carrier proteins are usually globulins (cortisol-binding globulin, sex-hormone-binding globulin, etc.) and are synthesized by the liver. An important concept to understand is that although the bound moiety of hormone is biologically inactive, it maintains equilibrium with its free, biologically active counterpart, for it is from this "reservoir" of bound hormone that the body draws up free hormone as and when the need arises. Generally, the bound hormone levels parallel the free hormone levels as long as there are no abnormalities in the binding proteins. The bound hormones circulate longer in plasma and are infinitely easier to measure than the free hormones.

The polypeptide hormones (exemplified by growth hormone, ACTH, PTH, and insulin) circulate in blood as such and are characterized by an extremely short half-life, usually in minutes. Some polypeptide hormones (insulin, PTH, ACTH, etc.) are derived from longer (or larger) precursor molecules with longer half-lives.

The third class of hormones, amino acid (or short peptide) hormones, are represented by thyroid hormones and catecholamines. There is extreme variability among these hormones in terms of their half-lives in the circulation. For instance, thyroxine circulates bound to several binding proteins (thyroxine-binding globulin, thyroxine-binding prealbumin, and albumin) and has a long half-life, whereas catecholamines circulate as such with an extraordinarily short half-life. Even among thyroxine and triiodothyronine, two seemingly identical iodoproteins, significant differences exist in binding, transport, and half-life.

The ambient level of a given hormone depends on two major factors, the production rate by the gland and the metabolic clearance rate of the