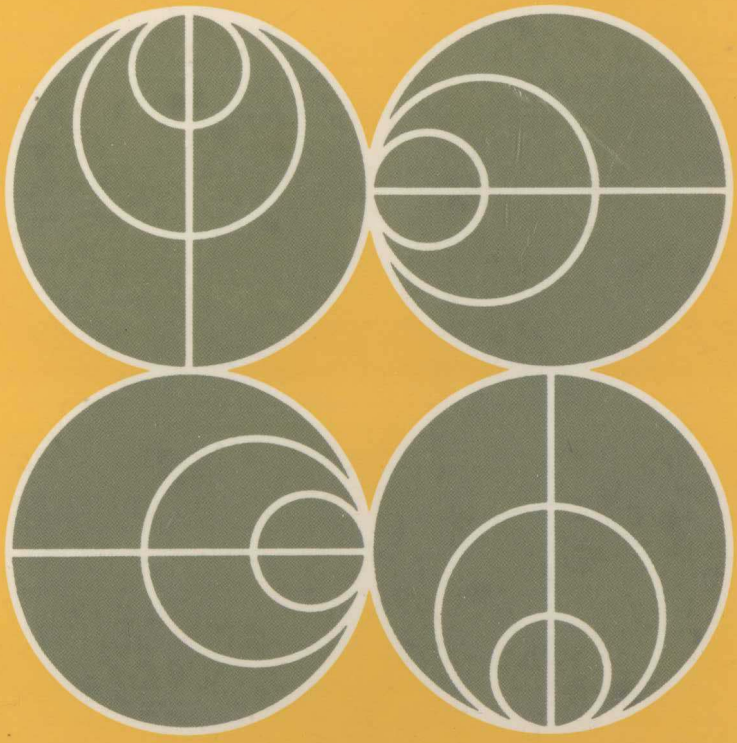
Endocrinology

A logical approach for clinicians

2nd Edition

WILLIAM JUBIZ



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ENDOCRINOLOGY
A Logical Approach for Clinicians

Second Edition

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PREFACE

The last five years have seen an explosion of new knowledge in the field of endocrinology, necessitating extensive reworking of the first edition. This new information has been incorporated without violating the principles of clarity and concision which govern the writing of the book. As in the previous edition, my intent has been to present a practical pathophysiologic approach to basic endocrine problems rather than to cover every aspect of endocrinology in detail. The book is designed as an introductory text for medical students and for housestaff, and clinicians who wish to review their general knowledge of endocrine diagnosis and management.

For the second edition, all material has been thoroughly revised and updated. Some chapters have been completely reorganized, and the information on laboratory procedures and hormone therapy—previously presented independently in separate chapters—is now integrated in the sections dealing with the corresponding gland. To further enhance the usefulness of the book as a learning tool, case studies have been added at the end of each chapter to enable the student to test his/her ability to apply basic concepts in a clinical context. Finally, I have attempted to instill in the reader an awareness of the increasing cost of medical care by focusing on the importance of ordering tests wisely and, where appropriate, recommending a specific therapeutic approach.

I would like to express my gratitude to Dr. William Odell and Dr. Dana Wilson for reading some of the chapters and offering invaluable suggestions, Julian Maack for artistic help with the illustrations, and especially Gwenevere Shaw who carried the burden of typing the entire manuscript with patience and dedication.

William Jubiz, M.D.

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CHAPTER
ONE

BASIC CONCEPTS IN ENDOCRINOLOGY

NATURE OF HORMONES

Hormones, a group of chemical messengers manufactured by the endocrine glands, regulate the function of many vital organs. Chemically, hormones fall into four categories: *peptides*, secreted predominantly by the anterior pituitary; *steroids*, from the adrenal cortex and the gonads; *iodothyronines*, from the thyroid gland; and *catecholamines*, which are produced by the adrenal medulla. There are fundamental differences in the synthesis, physical state in the circulation, life span, metabolism, and mechanism of action of these four hormonal groups. Peptides are synthesized from large precursors (prohormones) and stored in substantial quantities in the gland of origin. They are soluble in aqueous solvents, circulate in unbound form, have a very short half-life (a span of minutes), and undergo no substantial peripheral transformation to increase biologic activity before exerting their effects at the target organ. Peptides act in the plasma membrane by binding to specific receptors and stimulating the synthesis of cyclic adenosine monophosphate (cAMP). In contrast, the synthesis of steroids involves a series of enzymatic reactions from a common precursor, cholesterol. Glandular storage of steroids is minimal. They are soluble in nonaqueous solvents, circulate predominantly bound to plasma proteins, have a longer half-life than peptides (a span of hours), and undergo peripheral transformations that may increase their biologic activity. Steroids enter the target cells, bind to a cytoplasmic receptor, and act in the nucleus by stimulating the synthesis of messenger ribonucleic acid (mRNA). Iodothyronines are similar to the steroid hormones in many respects. They are synthesized in the thyroid gland from iodine and the amino acid tyrosine. Iodothyronines, unlike steroids, are stored in substantial

quantities in the gland of origin, and their half-life is longer than that of steroids (a span of days). Likewise, catecholamines share many of the properties of peptide hormones. However, synthesis of catecholamines, like that of steroids and iodothyronines, involves a series of enzymatic reactions. The precursor is the amino acid phenylalanine.

ORGANIZATION OF THE ENDOCRINE SYSTEM

The endocrine system consists of several components which are responsible for secreting a hormone, delivering it to the target cells, and allowing the expression of a physiologic function. In the secretory cells of the endocrine glands, biologically active hormones are synthesized and released into the bloodstream to meet body demands. This secretion is controlled by stimulatory and inhibitory forces which originate in the target cells or another gland. Delivery of the hormone to the effector cells requires recognition of the chemical signal by these cells and modification of their activity. After the biologic effect takes place, the hormone is degraded to prevent continued action. Finally, the secretory cells must receive notification that the mission has been completed so that hormone secretion will stop.

Hormone secretion → delivery to target cells →
hormone recognition by receptors in target cells →
biologic effect → hormone degradation →
signal from target cells to stop further hormone secretion (*feedback*)

Hypothalamic Control of Pituitary Function

We have learned that the hypothalamus plays an important role in hormone regulation by secreting a series of small peptides which stimulate or inhibit the synthesis and release of hormones by the anterior pituitary. Traditionally, these hypothalamic peptides have been known as releasing factors. However, since current knowledge indicates that hypothalamic peptides affect not only hormone release but also secretion, such a designation is erroneous. It might be better to refer to the hypothalamic peptides as hypophysiotropic hormones. The neurons that secrete the hypothalamic peptides are located in the ventromedial nucleus nearby the median eminence. Secretion of these peptides is intimately related to the release of neurotransmitters by neurosecretory cells which are located in the same anatomical area. Many neurotransmitters have been identified in the central nervous system (CNS), but the best known are the catecholamines dopamine and norepinephrine and the indoleamine serotonin. Other substances, such as acetylcholine, histamine, melatonin, and gamma-aminobutyric acid (GABA), have been implicated as neurotransmitters but their exact role is unclear. The axons of the hypothalamic secretory neurons anastomose with the vascular system which transports the hypothalamic peptides to the pituitary (Fig. 1-1). Several hypothalamic

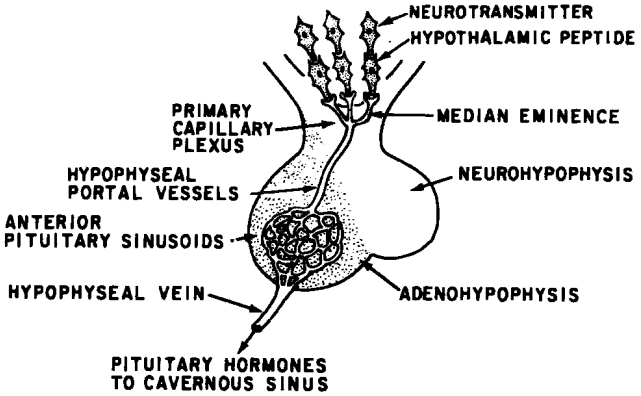

Figure 1-1 Physiologic anatomy of the hypothalamic-pituitary axis.

hypophysiotrophic hormones have been characterized and synthesized (Fig. 1-2). The corticotropin-releasing hormone (CRH), isolated from ovine hypothalami, contains 41 amino acids, which include the sequence of angiotensinogen. CRH stimulates the synthesis and release of corticotropin (ACTH) by the anterior pituitary. Thyrotropin-releasing hormone (TRH) is a tripeptide which controls the secretion of thyrotropin (TSH). The gonadotropin-releasing hormone (GnRH), or luteinizing hormone-releasing hormone (LHRH), is a decapeptide that stimulates pituitary secretion of luteinizing hormone (LH) and to a lesser extent that of follicle-stimulating hormone (FSH). Growth-hormone (somatotropin) secretion appears to be under dual control from a growth-hormone-releasing hormone

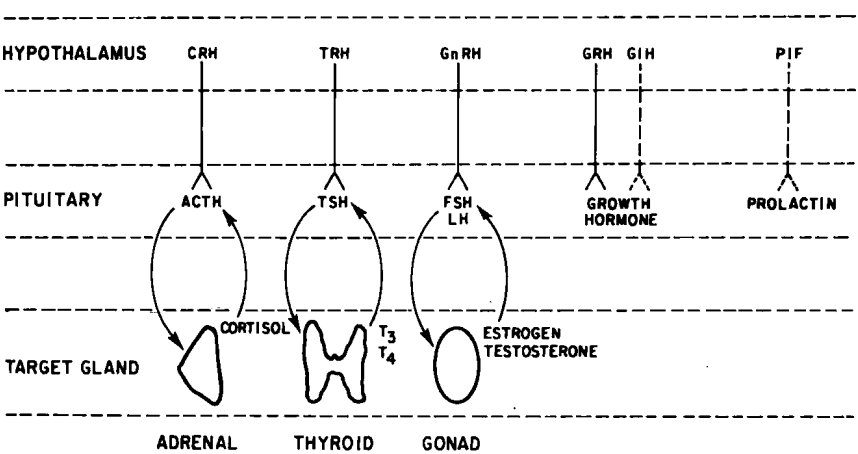

Figure 1-2 Control of anterior pituitary function by the hypothalamus and by hormones from the target glands.

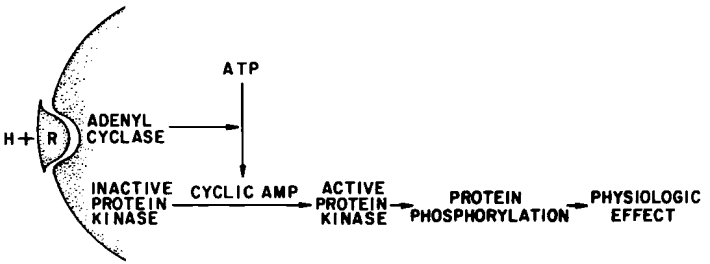

Figure 1-3 The cellular mechanism of action of peptide hormones. H = hormone, R = receptor, ATP = adenosine triphosphate.

(GRH) and an inhibiting hormone [growth-hormone-inhibiting hormone (GIH), or somatotropin release-inhibiting factor (SRIF) (somatostatin)]. GRH was originally isolated from a pancreatic tumor in a patient with acromegaly. It is a 44-amino-acid peptide which has full biologic activity in vitro and in vivo. Subsequently, other less potent smaller peptides have been characterized. GIH, a tetradecapeptide, inhibits growth hormone secretion from the anterior pituitary. The peptide is found not only in the hypothalamus but also in other parts of the brain, in the pancreas, and in the gastrointestinal tract. Besides inhibiting growth hormone secretion, GIH also inhibits insulin and glucagon secretion; gastrointestinal secretion of water, bicarbonate, pancreatic enzymes, gastric acid, and gastrin; and glucose absorption and calcium transport. Because of the nonspecificity of these effects, there are doubts concerning the physiologic role of somatostatin as a growth-hormone-inhibiting factor. Prolactin secretion appears to be under the control of a prolactin-inhibiting factor (PIF) which has not been characterized but which many feel is dopamine itself.

Endocrine Systems Independent of the Hypothalamic-Pituitary Axis

Other endocrine systems, such as the parathyroids and the pancreas, are independent of the hypothalamic-pituitary axis. Calcium and glucose, respectively, constitute the major regulatory factors. Hypocalcemia stimulates and hypercalcemia suppresses parathyroid hormone (PTH) secretion, whereas hyperglycemia stimulates and hypoglycemia decreases insulin secretion.

HORMONE ACTION

Peptides and Catecholamines

The action at the cellular level of hormones in this category starts with binding of the hormone to a high-affinity and specific plasma membrane receptor (Fig. 1-3). Combination of the hormone with the receptor initiates a transmembrane message which activates the enzyme adenyl cyclase, located at the

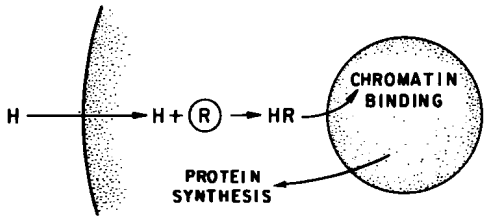

Figure 1-4 The cellular mechanism of action of steroid hormones. H = hormone, R = receptor, HR = hormone-receptor complex.

inner surface of the plasma membrane. A protein couples the receptor to the adenyl cyclase system. The cyclase catalyzes the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP), a soluble second messenger which diffuses through the cell, where it activates protein kinase, an enzyme that phosphorylates proteins, especially enzymes, and regulates their activity.

Steroids and Iodothyronines

Steroids cross the plasma membrane and bind to a cytoplasmic receptor. The hormone-receptor complex is then translocated into the nucleus, where a second binding to a chromatin receptor takes place (Fig. 1-4). Then, synthesis of messenger RNA and protein results. In contrast to steroid hormones, there is no cytoplasmic receptor for triiodothyronine (T_3), the physiologic thyroid hormone. Transfer of triiodothyronine across the plasma membrane is facilitated by an incompletely characterized system. Receptor binding takes place in the nuclear chromatin and the results are stimulation of mRNA and protein synthesis. Additional binding—of potential physiologic significance—of triiodothyronine to the mitochondria has been recognized.

Phospholipids and Hormone Action

In recent years, it has become clear that phospholipids serve as important mediators of hormone action. Several hormones have been shown to increase the synthesis of phosphatidic acid and/or the hydrolysis of phosphatidylinositol. As shown in Fig. 1-5, hormone binding to plasma membrane receptors activates phospholipase-C, which leads to hydrolysis of phosphatidylinositol and generation of diglycerides and phosphatidic acid. Phosphatidic acid is an endogenous ionophore which stimulates calcium mobilization from internal and external sources. Activation of cytosolic phospholipase-C by intracellular calcium results in phosphatidylinositol hydrolysis with subsequent formation of diglyceride and phosphatidic acid. Intracellular calcium and diglyceride evoke biologic responses such as exocytic secretion and hormone release. In addition, diglyceride activates calcium-dependent protein kinases, leading to stimulation of protein synthesis.

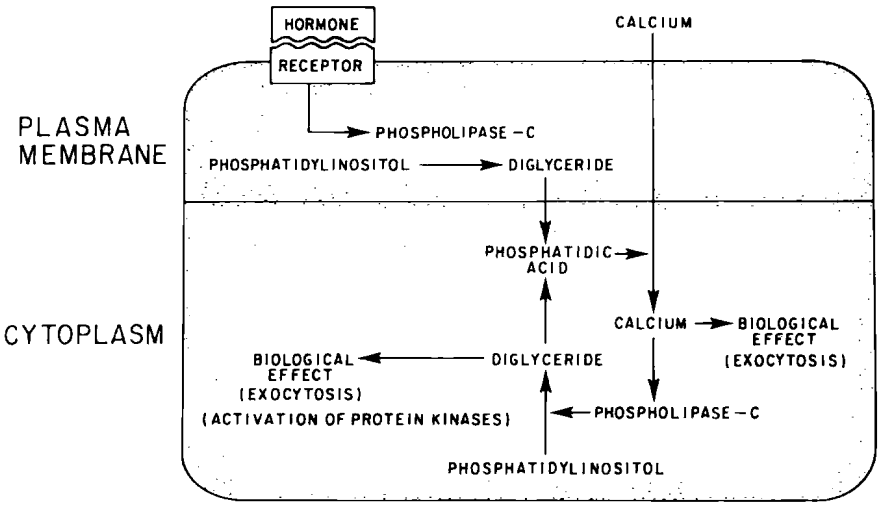

Figure 1-5 Phospholipids as intracellular mediators of hormone action. Phosphatidic acid functions as an endogenous ionophore which stimulates intracellular calcium entry. Calcium and diglyceride evoke biologic effects such as exocytosis and activation of calcium-dependent protein kinases.

Recently, it has become apparent that secretion vesicles, besides being involved in the storage and transport of hormones, play an active role in the regulation of hormone secretion. They contain binding sites for peptide hormones, are capable of converting ATP into cAMP, and possess cAMP-stimulated protein kinase activity. During exocytosis, secretion vesicles transfer the receptor and effector units to the plasma membrane for hormone action.

THE NATURE OF ENDOCRINE DISORDERS

Endocrine syndromes result from excessive or insufficient production of one or more hormones or from lack of tissue response to normal circulating concentrations of hormones (hormone resistance, end-organ unresponsiveness). The characteristic clinical manifestations of these syndromes represent the accentuation or absence of the hormone's physiologic actions. The following signs and symptoms, which are frequently seen in patients with endocrine diseases, serve to emphasize this point. Weight changes, either gains or losses, are an expression of the hormonal effects on metabolic processes, so-called anabolism and catabolism. Skin, hair, and nail changes can be part of an increased catabolic state. Blood pressure is regulated by hormones, particularly cortisol, aldosterone, and catecholamines. Excess production of these hormones in patients with Cushing's syndrome, primary aldosteronism, and pheochromocytoma is associated with hypertension. On the other hand, hypotension is seen in patients with cortisol

deficiency, hypoaldosteronism, or sympathetic dysfunction. Hormones affect energy and muscle function. Their deficiency may lead to weakness and tiredness. Since the female menstrual cycle is greatly influenced by gonadotropins, estrogen, and other hormones, menstrual irregularities are common manifestations of endocrine dysfunction.

The syndromes of hormone deficiency are caused by destruction or atrophy of an endocrine gland, whereas the syndromes of hormone excess result from gland enlargement or the presence of a tumor. Hormone-secreting tumors leading to syndromes of hyperfunction are autonomous, meaning that the hormone overproduction is not suppressed by the normal feedback mechanism.

PHYSIOLOGIC BASIS OF ENDOCRINE TESTING

Two types of tests are used to evaluate patients with symptoms suggesting endocrine dysfunction. *Screening tests* serve to suggest the existence of or rule out an endocrine abnormality, whereas *definitive (diagnostic) tests* are performed to establish the exact location of the abnormality. In general, screening tests measure the concentration in the blood of a hormone secreted by a particular gland. For example, to test for thyroid hyperfunction or hypofunction, serum thyroxine concentration is measured. Abnormally high concentrations indicate hyperthyroidism; abnormally low concentrations indicate hypothyroidism.

Once an abnormality has been established in a particular gland it is essential to use further diagnostic tests to determine whether the problem resides there or elsewhere. Some of these tests utilize the concepts of *feedback* (useful in diagnosing syndromes of hormone deficiency) and *autonomy* (helpful in diagnosing syndromes of hormone excess).

Feedback This concept is best demonstrated by means of the following example. ACTH from the anterior pituitary regulates the secretion of cortisol by the adrenals and, in turn, cortisol controls the secretion of ACTH (Fig. 1-6). In normal subjects, a fall in circulating cortisol causes an increase in plasma ACTH and vice versa. In patients with adrenal insufficiency, cortisol is not produced. Plasma ACTH concentrations are high if the problem resides in the adrenals (primary adrenal insufficiency) or low if the pituitary is damaged, and thus unable to respond (secondary adrenal insufficiency).

Autonomy The concept of autonomy (see Fig. 1-7) in diagnostic testing is illustrated when one demonstrates that a mechanism which normally controls secretion of a particular hormone fails to suppress excess production of that hormone. Some examples are:

1. Patients with acromegaly continue to produce growth hormone in excess despite hyperglycemia, which usually inhibits secretion of that hormone.

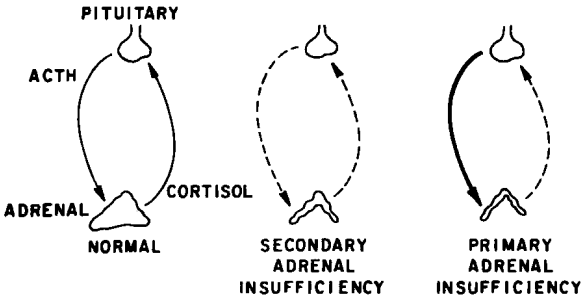

Figure 1-6 The concept of feedback: ACTH stimulates the secretion of cortisol by the adrenals and cortisol inhibits ACTH secretion. Plasma cortisol concentration is decreased in patients with secondary (ACTH deficiency) or primary adrenal insufficiency. Lack of ACTH inhibition by cortisol accounts for the high plasma ACTH concentrations in patients with primary adrenal insufficiency.

2. In patients with pituitary tumors secreting ACTH, elevated circulating cortisol concentrations fail to suppress ACTH overproduction.
3. Patients with primary hyperparathyroidism continue to overproduce PTH despite hypercalcemia, which suppresses PTH secretion in normal individuals.

QUESTIONS

1. What are the major differences between peptide hormones (e.g. corticotropin) and steroids (e.g. cortisol) with regard to mechanism of synthesis, state in the circulation, and mechanism of action?

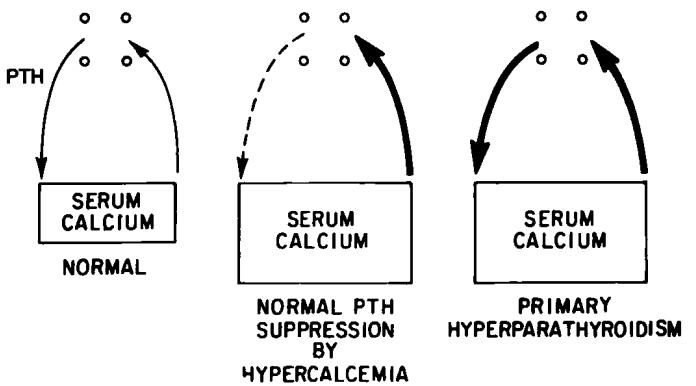

Figure 1-7 The concept of autonomy: Serum calcium controls the secretion of parathyroid hormone (PTH) by the parathyroid glands. In normal subjects, hypercalcemia (increased size of serum calcium rectangle and thick arrows) suppresses PTH secretion (dashed arrow). In patients with primary hyperparathyroidism caused by a parathyroid adenoma secreting PTH in excess (thick arrow), overproduction of the hormone continues despite hypercalcemia.

2. Delineate the components of the endocrine system beginning and finishing with hormone secretion.
3. Describe the hypothalamic control of pituitary function.
4. A 45-year-old male with typical symptoms of hypothyroidism has a low serum thyroxine (T_4) concentration. How do you proceed to investigate the site of the abnormality?

ANSWERS

1.

	Peptide Hormones	Steroids
Synthesis	From prohormones and stored in gland of origin	From cholesterol involving several enzymes. Minimal storage
State in the circulation	Unbound, very short half-life (minutes), no peripheral transformation to increase biologic activity	Bound, longer half-life (hours), peripheral transformation may increase biologic activity
Mechanism of action	Binding to plasma membrane receptors and stimulation of cyclic adenosine monophosphate (cAMP)	Binding to cytoplasmic and nuclear receptor and stimulation of messenger ribonucleic acid (mRNA) and protein synthesis

2. Hormone secretion → delivery to target cells → hormone recognition by receptors in target cells → biologic effect → hormone degradation → signal from target cells to stop further hormone secretion.
3. Hypothalamic peptides stimulate or inhibit the synthesis and release of anterior pituitary hormones. Corticotropin (ACTH): Corticotropin-releasing hormone (CRH) stimulates secretion. Thyrotropin (TSH): Thyrotropin-releasing hormone (TRH) stimulates secretion. Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH): Gonadotropin-releasing hormone (GnRH) stimulates secretion. Growth hormone: Growth-hormone-releasing hormone (GRH) stimulates secretion. Growth-hormone-inhibiting hormone (GIH) inhibits secretion. Prolactin: Prolactin-inhibiting factor (PIF) inhibits secretion.
4. First measure serum TSH concentration. If high, the problem resides in the thyroid; if low, the abnormality is in the hypothalamus or the pituitary gland. A normal TSH response to TRH implies a deficiency of the peptide and thus a hypothalamic defect. No TSH response to TRH is very suggestive of pituitary damage.