Paparella: Volume I: Basic Sciences and Related Principles

Section 8: General Medical Principles

Chapter 37: Endocrinology

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Since the work of Claude Bernard, it has been axiomatic that the internal environment is maintained in a constant state (Cannon's principle of homeostasis). Throughout the internal and external stresses of normal life, disease, or injury, the body returns to an appropriate state of equilibrium. It has been taught that the internal chemical processes are under the control of the anterior pituitary gland, which by secretion of trophic hormones regulates end-organ manufacture of steroids and thyroxine while more directly regulating other key metabolic processes by its output of growth hormone and other substances. This concept is outmoded since it is known that the pituitary has its own master regulator. The hypothalamus is the final common pathway between the brain and the pituitary.

Significant advances have been made recently in identifying and characterizing the pathways of neural control over the pituitary and its trophic hormones. Hormones are chemical substances synthesized in the body that exert regulatory effects on the target tissue. In general, the effect of hypothalamic hormones over the pituitary is stimulatory. Interruption of the neural pathways leading to the hypothalamus results in diminished secretion of the corresponding pituitary hormones, with the exception of prolactin, which increases with removal of hypothalamic control. The various hormones that have been identified that exert hypothalamic control over the pituitary include peptide chains, which contain from 3 to 44 amino acids, and dopamine. A thorough understanding of the interactions of these regulatory pathways is required of the head and neck surgeon.

The Pituitary Gland

The pituitary is a small structure weighing approximately 0.5 gm. It is located within the sphenoid bone at the base of the skull. Functionally the pituitary is divided into two anatomic sections, an anterior portion known as adenohypophysis and a posterior portion known as the neurohypophysis.

Current functional concepts of regulation of the anterior pituitary postulate control by a three-level system of brain, hypothalamus, and pituitary, utilizing a complex organization of feedback loops. A close association between the neural and endocrine systems is demonstrated in anterior pituitary control. Regulation of the six major hormones secreted by the anterior pituitary is subject to cortical control through several neurotransmitter compounds, including dopamine, norepinephrine, serotonin, acetylcholine, histamine, and gamma-aminobutyric acid.

Central nervous system transmission of the various neurotransmitter compounds occurs through axodendritic and axoaxonic connections to the hormone containing nerve fibers in the hypothalamus. Utilizing these neurotransmitter substances, the synapses provide control signals to at least 10 different types of neurons located in the median eminence of the

hypothalamus. This hypophyseotropic area contains discrete populations of unique hypothalamic neurons that are neurosecretory and produce a group of substances known as the hypothalamic regulating peptides. These neurosecretory neurons release their regulating peptides as neurosecretory granules that may be either facilitatory or inhibitory in type and are carried by the hypothalamic-hypophyseal portal capillaries to the anterior pituitary gland. These regulating peptides then influence anterior pituitary cells to synthesize and secrete the specific trophic hormones of the anterior pituitary (Table 1). Further regulation of the anterior pituitary occurs via feedback loops. In this way, peripheral hormones whose production is controlled by pituitary trophic hormones may influence the ultimate release of the pituitary trophic hormones via facilitative or inhibitory feedback at the level of the CNS monoaminergic neuron, the hypothalamic neurosecretory neuron, or the anterior pituitary trophic cell itself.

Table 1. Hypothalamic Regulatory Factors

Name	Structure
Thyrotropin-releasing hormone (TRH)	Tripeptide
Corticotropine-releasing hormone (CRH)	41 amino acid peptide
Luteinizing hormone-releasing hormone (LHRH)	Decapeptide
Growth hormone-releasing hormone (GHRH)	40 to 44 amino acid peptide
Growth hormone release-inhibiting hormone (Somatostatin)	14 amino acid peptide
Prolactin-releasing factor (PRF)	TRH, vasopressin, VIP
Prolactin release-inhibiting factor (PIF)	Dopamine.

Diseases of the Anterior Pituitary and Hypothalamus

Pituitary disease may be discretely anatomic or purely functional in type. A variety of disorders that may interfere with the sensitive neuroendocrine control of the anterior pituitary are being newly defined. Typically, discrete anatomic lesions are those most commonly sought. Vascular lesions in the form of ischemia to the anterior pituitary may occur either as the result of thrombosis or because of decreased circulation through the hypothalamic-hypophyseal portal circulation as a result of hypotension. Sheehan's syndrome is a form of ischemic necrosis of the anterior pituitary associated with postpartum hypotension. Post-traumatic hypopituitarism is a rarely described condition. However, recent evidence suggests that this condition may be a consequence of closed head trauma and is much more frequent that previously believed (Paxson and Brown, 1976; Brown and McMillin, 1977). In some cases, post-traumatic disorders of the pituitary gland are believed to be secondary to shearing of the pituitary stalk, especially in the case of panhypopituitarism in the setting of a basal skull fracture.

Tumors of the anterior pituitary, the hypothalamus, and the surrounding suprasellar area are among the lesions frequently under the care of the head and neck surgeon. These constitute a large variety of adenomas of the anterior pituitary trophic cells as well as craniopharyngioma and related cystic lesions. In addition, significant petitur destruction of the area may occur as a consequence of invasion by other CNS disorders, particularly pinealomas.

Infiltrative and inflammatory disorders affecting the anterior pituitary and hypothalamus include the various forms of histiocytosis X as well as sarcoidosis. Syndromes of granulomatous disorders include Hand-Schüller-Christian disease, characterized by polyuria, exophthalmos, and skull defects; Letterer-Siwe disease, a similar but more rapidly progressive form of disease; and eosinophilic granuloma, in which similar pathologic findings are present in isolated areas of bone. Symptoms of diabetes insipidus are present in approximately 50 per cent of patients with Hand-Schüller-Christian disease as well as growth failure, hypogonadism, and panhypopituitarism. Sarcoidosis, although relatively rare in the central nervous system, often affects the hypothalamus and pituitary. Symptoms of diabetes insipidus, galactorrhea secondary to hyperprolactinemia, anterior pituitary insufficiency, somnolence, and hyperphagia have been associated with sarcoidosis.

Radiation-induced hypothalamic dysfunction is occasionally seen after radiation therapy for intracranial neoplasms. Children are more likely to develop the disorder than adults. The delay in onset ranges from 1 to 10 years following therapy of at least 4000 rads to the hypothalamus or pituitary in the course of treatment for intracranial tumors and nasopharyngeal and maxillary sinus carcinomas.

Autoimmune disorders have been described as potential causes of functional pituitary impairment. Characterized by lymphocytic hypophysitis, the condition is seen occasionally in postpartum women who present with symptoms of an expanding pituitary mass lesion or with hypopituitarism. The pathologic lesion consists of parenchymal replacement of pituitary tissue with lymphoid follicles and may present in association with other autoimmune-mediated disorders such as lymphocytic thyroiditis, pernicious anemia, hypoparathyroidism, and adrenal insufficiency.

Congenital disorders of the anterior pituitary gland include cystic lesions resembling craniopharyngioma and syndromes of congenital hypopituitarism, which may be due to circulatory insufficiency during the birth process or to hypotension and related problems in the mother. Additional syndromes of congenital pituitary insufficiency associated with a small phallus and panhypopituitarism in the newborn with structural anomalies of the face are well documented. A syndrome of wide midface with relative hypertelorism, a wide nasal bridge, and absence of the pituitary gland has been described (Brown and Klain, 1978). Congenital hypopituitarism usually becomes manifested as an intractable form of hypoglycemia in the first few hours of life. In cases in which an incomplete form exists, hypoglycemia may be considerably more subtle and may not appear until the infant is several weeks or months of age.

Various functional disorders of the hypothalamus and pituitary gland are of interest to the otolaryngologist. Hypothalamic hypogonadism presenting with anosmia represents Kallmann's syndrome of olfactory-genital dysplasia. This may be seen with other associated deficits such as cranial nerve deafness and color blindness. Midline developmental defects can occur including cleft lip and palate as well as hypoplasia of the anterior commissure, olfactory bulb, and hypothalamus (Lieblich et al, 1982).

The neurohypophysis or posterior pituitary gland may exhibit two classic functional abnormalities. Neurogenic diabetes insipidus is characterized by partial or complete loss of the posterior pituitary hormone (ADH, vasopressin). ADH acts upon the distal convoluted

tubule of the kidney and the renal collecting ducts, facilitating reabsorption of water. In the absence of ADH, up to 15 per cent of the total glomerular filtrate is not reabsorbed, leading to significant polyuria. Associated with this fluid loss is polydipsia and, eventually, dehydration if fluid replacement is inadequate. The serum is extremely concentrated, with elevated serum osmolality and serum sodium levels. In addition, the high urine volume is extremely dilute, with low urine osmolality and specific gravity. Most commonly, diabetes insipidus occurs as an idiopathic syndrome and is frequently encountered postoperatively following neurosurgical procedures. In addition, it is commonly seen following head trauma. At least 95 per cent of the cases of postsurgical and post-traumatic diabetes insipidus are of a transient nature. The majority of patients with this condition exhibit significant polyuria and polydipsia with concomitant serum and urine changes, but this clinical picture tends to resolve within 2 weeks.

The syndrome of inappropriate ADH secretion (SIADH) is encountered less frequently than diabetes insipidus. This syndrome is related to an increased release of ADH directly from the hypothalamus or the neurohypophysis as well as increased sensitivity of the kidneys to normal circulating levels of the ADH. SIADH may be seen following neurosurgical procedures or head trauma. Pulmonary disease, particularly aspiration syndromes or disorders characterized by diminished pulmonary compliance, may cause release of ADH-like peptides into the circulation, producing a syndrome identical in its manifestation to SIADH of a neurogenic origin. Clinical signs involve circulatory volume overload with diminished urine output. Patients exhibit extremely dilute serum with diminution of serum osmolality and relative dilutional hyponatremia and hypochloremia. Urine output is significantly diminished, and the urine is highly concentrated, as measured by both increased urinary specific gravity and urine osmolality.

Diagnostic Studies of the Pituitary Gland and the Hypothalamus

Determination of pituitary function may be made by direct measurement of the pituitary trophic hormones. All the pituitary trophic hormones may be measured by radioimmunoassay, as may all the peripheral hormones released under pituitary control. In addition, specific radioimmunoassay for ADH is available.

Provocative stimulation studies for the pituitary trophic hormones are frequently carried out in order to duplicate physiologic circumstances and to indicate anterior pituitary reserve and dynamic drive.

The most frequently used provocative release studies for anterior pituitary function involve the thyrotropin-releasing hormone (TRH) test and a variety of provocative tests for growth hormone. TRH may also be used as a releasing substance for prolactin as well as for thyroid-stimulating hormone (TSH). Simultaneous determinations of prolactin provide further information with regard to integrity of the anterior pituitary gland. Growth hormone is stimulated by a variety of substances. The most frequently used are oral L-dopa and arginine administered intravenously. Intravenous insulin at doses of 0.05 to 0.1 unit per kg of body weight may also be used.

Recently, an anterior pituitary trophic hormone, beta-lipotropin, has been described. This molecule undergoes conversion within the pituitary gland and the peripheral circulation

to a variety of smaller substances. The most important by-products of this larger trophic hormone are a group of substances called the endorphins, which occupy endogenous morphine-like receptors within the central nervous system. These substances may play important roles with regard to dreaming, behavior, perception, and altered states of consciousness. The endorphin group of compounds can now be measured by radioimmunoassay and may be an additional important parameter of assessment of anterior pituitary function.

Evaluation of disorders of the posterior pituitary gland involves direct measurement of ADH with accompanying determinations of urine osmolality and specific gravity and serum osmolality. Water deprivation testing with determination of serial ADH levels and accompanying osmolalities may be helpful in determining the degree of insufficiency of the posterior pituitary gland.

Replacement Therapy in Hypopituitarism

Complete replacement therapy for deficits of anterior pituitary trophic hormones can be adequately and effectively provided. Most patients who need therapy have only partial deficits requiring minimal dose hormone replacement. However, in the case of complete destruction of the total anterior and posterior pituitary gland, all essential factors can be safely provided (Table 2).

Table 2. Hypopituitary Replacement Therapy

Trophic Hormone	Replacement	Dose
TSH	L-Thyroxine	100-200 microg/day (PO)
ACTH	Hydrocortisone or cortisone acetate	30 mg (20 mg PO every AM, 10 mg every PM)
LH	Male: Testosterone	200 mg IM (enanthate) every 10 to 17 days
	Female: Progesterone, estrogen	Provera-Premarin or sequential preparations
HGH	Recombinant HGH	0.1 mg/kg, 3 times/week
ADH	Pitressen tannate	5 to 10 U (IM) every 48 to 72 hours
	Aqueous Pitressin	Diagnostic purposes only
	DDAVP (nasal spray)	10 to 25 microg intranasally twice daily
	DDAVP (parenteral)	1 to 4 microg (IM) daily.

TSH deficiency may be compensated by replacement of thyroid hormone, using levothyroxine sodium in daily doses in the range of 150 microg/m^2/day. Deficiencies of adrenocorticotrophic hormone (ACTH) are treated with a variety of steroid preparations. Oral hydrocortisone preparations in the range of 15 to 20 mg/m^2/day may be given two or three times daily. Cortisone acetate may also be used at doses 20 to 25 per cent higher than those for hydrocortisone. Deficiencies of the gonadotropins are managed with exogenous sex hormone replacement. For males, testosterone preparations, such as testosterone enanthate or testosterone cyclopropionate, may be administered in doses of 100 to 200 mg intramuscularly every 2 to 4 weeks. Adequacy of dosage is determined by maintenance of secondary sex

characteristics and libido and adequacy of sexual performance and behavior. For females, gonadotropin deficiencies are replaced by providing estrogen and progesterone. This may be done using oral conjugated estrogens (Premarin) and medroxyprogesterone acetate (Provera) combinations or commercially available sequential oral contraceptives. In estrogen replacement, minimal low-dose estrogens should be used to avoid the complications of hyperestrogenation. Human growth hormone replacement is available but is restricted to the growing child in whom some benefit may be anticipated. Growth hormone is now available as a product of recombinant DNA, thereby avoiding the question of a transmissible agent in the prepared human product. It may be administered in doses of 0.5 microg, given by intramuscular injection three times per week.

Deficiencies of posterior pituitary function resulting in diabetes insipidus may be treated using ADH hormone preparations. A long-acting preparation (Pitressin tannate in oil) is available. This preparation may be given in doses of 1 to 5 units (usually 0.5 mL of suspension) intramuscularly. The duration of action varies, depending on the size of the dose administered and the size of the patient. Clinical responses vary from 18 to 36 hours after injection, with most patients requiring injections four to five times weekly. A shorter-acting preparation (aqueous Pitressin) is available for patients exhibiting transient syndromes of diabetes insipidus. This preparation is administered in doses of 1 to 5 units intramuscularly every 6 to 8 hours, depending on clinical response. Recently, a new therapeutic agent, 1-deamino-(8-D-arginine)-vasopressin (DDAVP), has become available. DDAVP is an ideal therapeutic agent for the management of diabetes insipidus. This is a highly purified, potent, and therapeutically consistent preparation that is not injectable. DDAVP is administered intranasally via a plastic catheter. The duration of antidiuretic effect following the initial dose of DDAVP is 20 to 24 hours. Subsequent doses last 8 to 12 hours. Patients with persistent diabetes insipidus may be managed on dosages of 5 to 10 microg of DDAVP administered twice daily (Uden and Brown, 1978; Brown and Uden, 1979).

The Thyroid Gland

Anatomy and Histology

The thyroid gland is one of the largest of the endocrine structures, with an average weight of approximately 20 gm in adult white Americans (Ingbar, 1985). The capacity for growth of the thyroid gland is great and its enlargement into goitrous structures weighing several hundred grams is not unusual.

The thyroid gland is made up of two lateral lobes with a connecting thinner structure between them known as the isthmus. In addition, a pyramidal lobe is often identifiable as a projection upward from the isthmus just lateral to the midline and most frequently on the left side; it is most discrete when the remainder of the gland is enlarged. The right lobe of the thyroid gland frequently has a richer blood supply than the left. Normally, it is the larger of the two lobes and has a tendency to increase in size to a greater degree in those disorders of the thyroid gland associated with a generalized increase in size.

Blood flow to the thyroid may be in the range of 4 to 6 ml/min/g of tissue, which is at least twice as great as blood flow to the kidney. In situations of diffuse toxicity and goiter with associated hyperthyroidism, blood flow as great as l L/min has been documented, since

increased vascularity causes a palpable thrill, or more commonly, the auscultatory bruit. This association of progressively increased vascularity with increased thyroid mass in situations of hyperactivity is important when considering thyroidectomy in patients with thyrotoxicosis. The remarkable absolute increase in thyroidal blood flow as well as the increase in the true size of vascular structures to the gland must be kept in mind at all times.

The thyroid gland is composed of multiple, closely packed, saclike structures referred to as follicles. Each of these follicles is filled with a clear protein colloid material that makes up the major constituent of thyroid tissue. The size of such follicles show great heterogeneity within the same gland, usually between 150 and 250 microns. The structure of the follicular epithelium varies depending on the degree of glandular activity and stimulation, tending to be columnar when most active and flattened when inactive. Twenty to forty such follicles may be anatomically defined by connective tissue structures to form discrete lobules, each supplied by a single artery. There may be considerable heterogeneity with regard to the anatomic structure and function between discrete and even neighboring lobules within the same thyroid gland.

In addition to the follicular cells, the thyroid tissue also contains perifollicular or C-cells. These cells are located within the medullary portion of the thyroid gland and produce a specific calcium-lowering polypeptide hormone known as calcitonin. The C-cells are found within the follicular epithelium and also within the interstitium of the gland but are never found bordering the follicular lumen. The importance of the calcitonin-producing cells is in regard to the behavior and clinical characteristics of medullary carcinoma of the thyroid, which appears to be derived exclusively from these cells. Recently, the C-cell has been shown to be part of a discrete system of cells arising from common embryologic tissue referred to as the neural crest. This system, known as amine precursor uptake and decarboxylation (APUD), is of great clinical significance (see section on MEN syndrome).

Thyroid Hormone Synthesis: Physiology and Biochemistry

The biosynthesis of the thyroid hormones occurs in three discrete sequential stages: (1) the active transport of iodine into the thyroid follicular cell; (2) the oxidation of these iodine molecules and their incorporation into tyrosine molecules, known as organification, to form iodothyronines within the thyroglobulin proper; and (3) the coupling of inactive iodotyrosine into hormonally active iodothyronines, specifically triiodothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). The hormonally active T3 and T4 molecules are then held in specific peptide linkages to form the substance thyroglobulin, which is the major component of colloid within the thyroid follicular cell.

The initial step of thyroid hormone synthesis is uptake by active transport of iodide into the thyroid follicular cell. In addition to iodide itself, other anions, specifically perchlorate and thiocyanate, may also be used and undergo uptake - a factor that is of both therapeutic and diagnostic importance in terms of functional thyroid testing. The second step involves the oxidation and actual organic binding of the iodide molecule onto tyrosine, forming the endocrinologically inactive monoiodotyrosine and diiodotyrosine. This is an extremely critical step in thyroid hormone biosynthesis. Specific defects in thyroid synthesis that, in turn, lead to functional hypothyroidism appear to be focused on this step. For example, the autoimmune thyroid disorders such as Hashimoto's thyroiditis, or chronic

lymphocytic thyroiditis, appear to be associated with specific antibody formation against the enzymes involved in the organification step. This immunologic attack on the enzyme machinery involved in organification underlies the eventual thyroid deficiency that occurs in patients with such conditions. The functional manipulation of this phase of thyroid hormone synthesis is critical to the understanding of specific thyroid function studies.

The release and secretion of the active thyroid hormones triiodothyronine and thyroxine from the intrafollicular thyroglobulin involve two additional biochemical steps: (1) the hydrolysis of the thyroglobulin by a thyroid protease enzyme and peptidase, which leads to the liberation of free iodinated amino acids; and (2) the release of these active iodothyronines into the circulation.

The ability of the thyroid gland to concentrate iodine is not unique, as this may occur in other tissues of endodermal origin. Most notable are the salivary glands and the gastric glands. Isotopic scanning and radionuclide counting of the thyroid gland must take into consideration that the salivary glands also take up and incorporate such isotopes.

Regulation of Thyroid Function: The Hypothalamic-Pituitary-Thyroid Complex

As is the case with most other endocrine tissues, recent evidence suggests a close functional relationship both anatomically and physiologically, between the thyroid and the pituitary glands. In addition, sophisticated regulatory control of the pituitary gland by higher cortical centers and the hypothalamus, in turn, influences the activity of the thyroid gland. Sophisticated autoregulatory control of thyroid function by the gland itself also plays an important role (Reichlin et al, 1972).

The functional sequence of regulatory control of the thyroid gland involves multiple levels as well as a complex system of long and short feedback loops. Initial input into centers of the higher cerebral cortex results in the transport of neuroinformation to the area of the hypothalamus. Specifically, discrete neurosecretory cells are found within the median eminence of the hypothalamus. Specific cells produce thyroid-releasing hormone (TRH), a tripeptide composed of glutamic acid, histidine, and proline. This hormone is released via the hypothalamic-pituitary portal circulation and transported to the anterior pituitary gland, where cells are stimulated by TRH both to synthesize and to release TSH. TSH is then released from the anterior pituitary into the general circulation, where it is transported to the thyroid gland. At the level of the thyroid cell, and specifically within the follicular cell complex, TSH exerts facilitative effects on all the previously mentioned steps in both thyroid hormone biosynthesis and thyroid hormone secretion. Recent evidence shows that the uptake of iodide by the thyroid gland is directly influenced by TSH stimulation, and perhaps more specifically, evidence also shows that the organification and binding of the iodide to form the active thyroid hormones T3 and T4 are TSH dependent. In addition, the hydrolysis of the thyroglobulin releasing T3 and T4 into the circulation is also influenced by TSH. Therefore, at multiple sites, the presence of increased amounts of TSH leads to increased thyroid hormone synthesis and secretion.

As the levels of T3 and T4 in the circulation increase, they eventually reach a level sufficient to maintain their required biologic effects. This results in decreased stimulation from the cortical centers to the hypothalamus as well as direct signals to the hypothalamus

to decrease the synthesis and secretion of TRH, producing decreased stimulation to the anterior pituitary, with resultant decreased synthesis and release of TSH. This process decreases T3 and T4 synthesis and secretion. As a result, intact thyroid gland function requires multiple levels of functional integrity at the central nervous system, hypothalamus, and pituitary levels as well as at the level of the gland itself.

These neuroendocrine principles involved in the regulation of thyroid gland function are important not only in understanding the mechanisms of various thyroid disorders but also in providing the underlying basis for additional function tests.

Thyroid Function Testing

Thyroid-Stimulating Hormone (TSH) Test

Recent developments in the laboratory assessment and interpretation of thyroid status have been chronicled in the literature. Tests that have been considered the standard for routine evaluation, although still used throughout the United States, are currently undergoing major changes. These changes are occurring in part owing to technological advances that allow more sensitive, rapid, and accurate evaluation of the thyroid endocrine axis. In addition, the medical-economic climate is such that pressure is brought to bear on obtaining a single convenient and inexpensive test for assessing thyroid status.

Formerly, the measurement of total T4, free T4, and T3 with evaluation of TSH response to intravenous TRH administration was required for evaluation of the thyroid hormone status of an individual. In the instance of normal hormonal balance, this test required multiple assays for the characterization of normal function. It has become increasingly evident that a sensitive assay of a serum TSH will permit the clinician to know at a glance whether or not thyroid hormone balance is present. Previous radioimmunoassays (RIAs) were relatively insensitive to the low levels of TSH seen in subclinical or clinical hyperthyroidism, and tedious serial dilutions were required to assay the high levels seen in primary hypothyroidism.

With the development of immunoradiometric assays (IRMAs), a markedly sensitive, fast, and convenient assay became available to delineate fairly clearly and accurately the status of a patient's thyroid function. Although RIAs were insensitive to the TSH levels present in 13 per cent of normal subjects, IRMAs were able to quantify 100 per cent of the TSH levels in normal control subjects. Specifically, RIAs have a working range of 0.5 to 15 microU/mL, and IRMAs are sensitive to a working range of 0.05 to 200 microU/mL (Ridgeway, 1988).

Because of expanded sensitivity of TSH quantitation by IRMAs, it is now possible to obtain accurate measurements in the initial TSH assay of serum from hypothyroid individuals. Hyperthyroid individuals will have low or not quantifiable TSH levels that, if performed by IRMA, will clearly suggest their hyperthyroid status. Unlike the results from previous assays, patients with hyperthyroidism are always distinguishable from euthyroid control subjects and, in IRMA assays, frequently have values below the detection limit. The enhanced ability to separate euthyroid control subjects from patients with hyperthyroidism suggests that the IRMA of TSH can accurately discriminate in a single test normal subjects from those with

either enhanced or depressed TSH secretion.

Conditions that enhance TSH secretion involve the entire spectrum of primary thyroid gland failure, including iodine deficiency, faulty hormone synthesis, and loss of functioning follicles. In addition to spontaneous or idiopathic causes, gland hypofunction following thyroid surgery can be expected to lead to an elevated TSH. It should be pointed out that 30 per cent of those patients receiving radioiodine therapy for treatment of thyroid disorders will have hypofunctioning thyroid tissue at 5 years. Suppression of TSH levels can be expected to result from clinical or subclinical hyperthyroidism, a hyperfunctioning thyroid nodule, multinodular goiter, overzealous thyroid replacement therapy, and medications including dopamine or glucocorticoid therapy. Isolated hypopituitary hypothyroidism is rare, with only a few case reports describing the entity in the literature. Secondary hypopituitarism is even rarer, occurring either in association with other hypothalamic syndromes or through isolated hypothalamic TRH insufficiency.

With the use of the IRMA for the measurement of TSH, a new approach to thyroid imbalance is now possible. Recent studies utilizing the sensitive thyrotropin immunoradiometric assay suggests that the TSH and the T4 assay provide the best initial screening laboratory tests for the evaluation of suspected thyroid imbalance (Surks et al, 1990). Current clinical uses of serum TSH measurement include diagnosis of primary hypothyroidism as well as hyperthyroidism, differentiation of primary versus secondary hypothyroidism, and evaluation of TSH reserve using the TRH stimulation test. Recently, the TSH assay has been used in assessing the adequacy of thyroid replacement (Hay, 1988). An algorithm has been offered in the literature to allow the rapid and economical assessment of thyroid hormone disorders with a minimum of testing (Toft, 1988).

Total Tetraiodothyronine Concentration (TT_4) Test

The currently available test for total thyroxine concentration measures iodothyronines; therefore, it is unaffected by contaminant iodide. The test measures both protein-bound thyroxine as well as free thyroxine (recall that it is the free thyroxine that is responsible for metabolic effects at the cellular level). Protein-bound thyroxine accounts for 99.97 per cent of the total T4. Wide fluctuations in the amount of protein-bound T4 occur, making a meaningful interpretation difficult without further tests to delineate the bound protein from the free T4.

Free Thyroxine (FT_4) Test

Free T4 measurement is an absolute measure of unbound hormone using a radioimmunoassay technique. This test can accurately delineate the thyroid status of an individual in the setting of altered protein binding.

Thyroxine-Binding Globulin (TBG) Test

In the setting of an abnormal total thyroid hormone level in the serum, this test can differentiate apparent hyperthyroidism or hypothyroidism from the setting of increased or decreased thyroid-binding protein. Factors that increase TBG include pregnancy, use of birth control pills, acute hepatitis, acute intermittent porphyria, and some medications (eg, Trilafon).

Decreased levels of thyroglobulin occur with the administration of androgens, high-dose glucocorticoids, and in settings of major illness and acromegaly.

T_3 Resin Uptake (T_3RU) Test

The T3RU assay is based on competition between available TBG-binding sites and a synthetic resin for added radioactive T3. It is an indirect measure of free T4 concentration. The free thyroxine index is a derived quantity that attempts to correct for the variations in thyroid hormone carrier. It is generally defined as a total T4 multiplied by the T3 uptake. If available binding sites are increased, such as in hypothyroidism and instances of increased thyroid-binding globulin, more radioactive T3 will fill them and, consequently, less will be taken up by the resin, giving a low T3RU. If available binding sites are decreased, as in hyperthyroidism and in settings of decreased TBG, less radioactive T3 can bind to them, more will be on the resin, and the T3RU will be high.

Total Triiodothyronine Concentration (TT_3) Test

Although is an excellent test of hyperthyroidism with good correlation with clinical status and degree of therapeutic control of hyperthyroidism, the same problems of protein binding that apply to total thyroxine also apply to the measurement of triiodothyronine. Of the total T3, 99.7 per cent is bound to protein carriers, with the biologically active free hormone comprising only 0.3 per cent of the total amount. The TT3 discriminates poorly between normal and hypothyroid individuals. This assay does provide a useful test in identifying surreptitious T3 ingestion.

Free Triiodothyronine (FT_3) Test

This is a sensitive radioimmunoassay that correlates well with the clinical status of an individual.

Protein-Bound Iodine (PBI) Test

This test provides a measure of all organic iodides in a serum sample. It includes T4, T3, and other iodothyronines as well as iatrogenic sources. This test is useful in diagnosing Hashimoto's thyroiditis as well as other organification defects. The PBI quantitatively exceeds the total T4 in serum by greater than 2 microg/dL.

Test for Antithyroid Antibodies

This test is useful in diagnosing autoimmune thyroid disorders (Graves' disease, Hashimoto's). Antimicrosomal serum antibodies are most useful in making the determination when they are positive in serum. Rarely, they can be elevated in pediatric patients.

Reverse T_3 (RT_3) Test

This test provides a measurement of an inactive structural variant of T3. The element is found only in the fetus and decreases within the first 7 days after birth. RT3 is the best screening test for neonatal hypothyroidism.

Thyrotropin-Releasing Hormone (TRH) Test

This test is an excellent tool for the assessment of the status of the pituitary-thyroid axis and involves the administration of TRH, usually as an intravenous bolus injection of TRH (7 microg/kg) in 1 mL of normal saline over 5 to 10 seconds. Blood is then collected for determination of TSH at 0, 15, 30, 45, 60, and 90 minutes. The peak TSH response is expected between 20 and 45 minutes. The application of the test is two-fold. First, it is used to determine the ability of the pituitary gland to respond to the hypothalamic peptide TRH. A normal pituitary gland releases TSH in response to TRH. Second, it is used to distinguish tertiary from secondary hypothyroidism.

T_3 or T_4 Suppression Test

This test is based on the principle that, in normal subjects, thyroid function is almost completely suppressible by exogenous thyroid hormone via its inhibitory effects on pituitary TSH secretion. In some patients with thyroid disease (eg, Graves' disease, some nodular goiters), thyroid function is not TSH dependent and hence is not TSH suppressible by exogenous thyroid hormone. The T3 or T4 suppression test is useful in confirming the hot nodule, as the autonomously functioning nodule is not suppressed by the lack of TSH stimulation but appears as a hyperfunctioning spot on the thyroid scan. Following a baseline 24-hour uptake 123I scan, 25 microg of T3 is administered for 8 days prior to repeating the thyroid scan. A normal response is defined as a greater than 50 per cent fall in the 24-hour uptake after 8 days of triiodothyronine therapy.

Radioactive Iodine Uptake (RAIU) Test

This test measures the percentage of a dose of orally administered 123I or 131I taken up by the thyroid gland over a fixed interval, usually 24 hours. In most cases, hyperthyroid patients have elevated 24-hour uptakes and hypothyroid patients have depressed uptakes compared with normals. The normal range for uptake is 8 to 30 per cent of the administered iodine after 24 hours. Hypothyroidism and hyperthyroidism appear in all three categories (increased, normal, and decreased); therefore, radioisotopic studies are rarely indicated in the initial workup of suspected thyroid dysfunction. The major clinical utility is in the evaluation of thyroid nodules (cold versus hot).

Radioisotope Scintiscanning

Radioisotope scintiscanning is useful in assessing the size, location, and functional status of thyroid nodules. Like the thyroid uptake scan, scintiscanning is performed after administration of an oral dose of ^{123}I or ^{131}I, and the patient's functional status determined by the relative uptake of isotope by a nodule. Nodules may appear as hot, cold, or warm, depending on the uptake of radioisotope within a given nodule. The majority of nodules that take up the radioactive iodides tend to be of a benign nature, whereas those that do not take up the radionuclides are referred to as cold and have a greater propensity for malignancy. Technetium 99m (Tc 99m) may be used to limit the radiation dose, particularly in children. If only morphology of the gland is of interest, Tc-99m scanning provides the necessary information with the minimum radiation exposure. Caution is advised in the interpretation of nodules on Tc-99m scans, because nodules that would be interpreted as cold on 123I or 131I

scans may appear as warm nodules on Tc-99m scans, limiting the clinical usefulness of Tc-99m scanning.

Specific considerations when ordering a thyroid scan are as follows: (1) Scanning should be done under basal conditions. Patients should not be on exogenous thyroid medications, which block uptake and suppress endogenous TSH, causing poor visualization of active thyroid tissue. (2) Scanning should be carried out from just above the base of the tongue down into the mediastinum. When attempting to identify aberrant thyroid tissue, it is critical that the entire pathways of downward migration of the thyroid be explored. (3) It is important to remember that other tissues are capable of trapping radioactive isotopes.

The specifics of scanning for the presence or absence of thyroid tissue as well as the position and presence of ectopic thyroid tissue are obvious. Identification of thyroid size and activity may vary with the experience of the observer, but scans are uniformly helpful in this regard. Certain thyroid diseases may show changes that are not universal but that are diagnostically helpful when present. Chronic lymphocytic thyroiditis appears in a spotty distribution throughout the gland. This disorder causes areas of variable activity within the gland, producing a characteristic "salt-and-pepper" appearance. Areas of diminished activity alternating with areas of normal or even accentuated activity are suggestive of chronic lymphocytic thyroiditis.

Perchlorate Discharge Test

The perchlorate discharge test is useful in instances in which an organification defect is suspected (Pendred's syndrome) or when considering Hashimoto's thyroiditis. The test is performed by giving a small dose of radioactive iodine, followed by an uptake scintiscan after 1 hour. Afterward, a dose of oral perchlorate ($KClO_4$) is given to inhibit further thyroid trapping and a repeat scintiscan is performed 1 hour later. In normal individuals, 85 to 90 per cent of the ^{131}I seen at the first scan should be present at the second scan 1 hour later because it will be organified and unaffected by the competitive perchlorate anion. A normal gland discharge no more than 10 to 15 per cent. This test is used in the diagnosis of congenital organification enzyme defects and the acquired immunologic forms of hypothyroidism. This test, together with the supportive evidence of a PBI and T_4 discrepancy, elevated antibody titers, and a clinical picture compatible with chronic lymphocyte thyroiditis, has superseded the need for biopsy in this disorder.

Ultrasound Thyroid Scanning

Ultrasound thyroid scanning is useful in establishing the nature of a palpable thyroid nodule as a cystic versus a solid lesion. Sensitive to lesions of about 0.5 cm in diameter, ultrasound can also provide a guide to the fine needle aspiration of small lesions.

Goiter Differential Diagnosis

The presence of thyroid enlargement (goiter) alone is not diagnostic and is present in hypothyroidism, hyperthyroidism, and in euthyroid individuals. Enlargement of the thyroid may be present as a result of tumors, vascular anomalies, benign accumulations of increased amounts of colloid within the follicular cell, abscesses, and other forms of acute or subacute

inflammation and infection of the gland (Table 3).

Some characteristics of the thyroid gland, particularly in its enlargement, may give helpful diagnostic clues. Thyroid enlargement in Graves' disease tends to be more uniform and symmetric. If asymmetry is present, the majority of patients usually have selective of the right lobe. The gland is soft, nontender, and mobile. A palpable thrill or bruit may be present. The gland may be smooth or irregular over its surface, but nodularity is rarely present.

Table 3. Differential Diagnosis of Goiter

Simple colloid (juvenile goiter)
Chronic lymphocytic thyroiditis
Graves' disease
Endemic iodine deficiency
Excessive exogenous iodine uptake or ingestion of goitrogens
Thyroid neoplasia
Toxic nodular goiter (Plummer's disease)
Subacute thyroiditis
Acute thyroiditis (suppurative, with abscess formation)
Post-traumatic intrathyroidal or adnexal hemorrhage.

In chronic lymphocytic thyroids, the gland is usually asymmetrically enlarged, again with selective enlargement of the right lobe. Typically, the isthmus is palpable and makes up a significant proportion of the enlarged thyroid mass. A pyramidal lobe extending from the superior surface of the thyroid isthmus is palpable. Such glands tend to be somewhat firm and rubbery. The surface may be smooth or may demonstrate a multinodular character. Discretely palpable anatomically defined nodules are not characteristic. The gland usually is not tender, but early in the course of the disease, there may be minimal pain or discomfort on palpation. In a large number of cases, anterior cervical lymphadenopathy may also be noted. Acute and subacute infections of the thyroid gland producing thyroiditis may be associated with an extremely tender thyroid.

Pain on swallowing and extreme tenderness on palpation suggest acute thyroiditis. The association of symptoms of systemic infection, as well as accompanying fever and an antecedent history of infection, provides important clues. Glands exhibiting such symptoms may also be warm to the touch and have a sensation of throbbing and hyperemia.

Neoplasms of the thyroid may be discretely palpable. Malignant lesions are fixed to the thyroid surface and usually are not mobile. They may be associated with fibrosis and tenderness. Firm, hard lymph nodes to the area of lymphatic drainage from the thyroid may be present. Discrete mucosal neuromas on the tongue and in the buccal mucosa may be an important clue to the presence of medullary carcinoma of the thyroid associated with the multiple endocrine neoplasia type III syndrome.

The presence of an enlarged thyroid gland or the appearance of a thyroid nodule is always an indication of underlying thyroid disease and should prompt further investigation.

Diagnostic Workup of the Thyroid Nodule

Having confirmed the presence of a nodule on physical examination, the selection of the appropriate diagnostic tests remains controversial. In the workup of the solitary thyroid nodule, there are a few statistics to guide the selection of appropriate diagnostic tests. Among these, 17 per cent of cold thyroid nodules are malignant. In addition, 9 per cent of hypofunctioning and normally functioning (warm) thyroid nodules are malignant. One should also recall that autonomously functioning hot nodules almost never are carcinomas; however, these constitute only 5 per cent of solitary nodules. At some centers, the palpable thyroid nodule is an immediate indication for the performance of a fine needle aspiration. This, however, is contingent on the availability of a highly trained pathologist with an interest in assessing cytology smears. The immediate aspiration precludes further radionuclide imaging and ultrasound studies for a period of several weeks following the nodule aspiration because the presence of a hematoma in the region of a nodule would make further tests uninterpretable. We believe FNA to be an excellent technique for assessing the cellularity of a nodule after the functioning status of the nodule has been established. An algorithm is offered for the workup of a solitary thyroid nodule.

Hypothyroidism

Hypothyroidism, or decreased function of the thyroid gland, can occur as a result of either (1) primary disease due to absence of the gland, surgical ablation, or destruction of the gland or (2) congenital absence or maldevelopment of the gland. In addition, secondary hypothyroidism may occur in decreased TSH stimulation to the thyroid (Table 4). Clinical hypothyroidism presents a variable spectrum of disorders ranging from mild thyroid deficiency to complete absence of thyroid function. The onset of hypothyroidism may be extremely insidious, and the typical clinical manifestations may take years to appear and may not be noticeable to others. This gradual development of the hypothyroid state is due not only to the possibly slow progression of the thyroid dysfunction but also to the equally slow appearance of the clinical manifestations after the thyroid failure has occurred. Of course, more rapid development of the hypothyroid state is seen on the acute withdrawal of replacement therapy, in secondary hypothyroidism, and in situations following surgical removal of the thyroid gland without adequate replacement therapy.

The symptoms of hypothyroidism, particularly the early ones, are highly variable and nonspecific. The clinical manifestations vary considerably with the age of the patient. The newborn infant with congenital hypothyroidism may present with the classic picture of athyrotic cretinism, characterized by edematous facies and enlarged tongue, high-pitched cry secondary to the laryngeal edema, generalized myxedema, and umbilical hernia, and muscular hypotonia. In addition, other signs of decreased systemic metabolism may become manifest as prolonged jaundice and decreased renal function. The manifestations in children may be similar to those in adult, but the child classically present with growth failure. Children in whom significant thyroid deficiency exists have progressive decline in growth chart measurements and show accompanying delays in skeletal maturation, as reflected by bone age x-ray determinations of epiphyseal maturation. Diminished school performance and mental and physical lethargy accompany growth failure as the predominant manifestations in childhood. In the adult, fatigue and lethargy are the most common manifestation, and difficulties in performing daily tasks with decreased work performance are quite common. Progressive constipation also occurs with great frequency. Cold sensitivity is often present, and menstrual disturbances are usual in the female. The voice may have a husky quality

caused by submucosal laryngeal edema. Periorbital edema may become manifest late in the course of the disease. As hypothyroidism progresses, coarsening of the body features may appear that is caused by changes in the mucopolysaccharide of connective tissues. This is most obvious in the face. Physical examination may demonstrate cold skin, particularly in the distal acral parts of the extremities; decreased sweating; thickening of the tongue; and decreased deep tendon reflexes, particularly a slowing of the return phase of the Achilles tendon reflex.

Table 4. Etiology of Hypothyroidism

A. Primary hypothyroidism
- 1. Postablative (postsurgical thyroidectomy)
- 2. Congenital hypothyroidism (nongoitrous)
  - a. Athyrotic
  - b. Defects due to maldescent
- 3. Endemic goiter (iodine deficiency)
- 4. Goiter due to antithyroid substances
  - a. Antithyroid drugs
  - b. Naturally occurring goitrogenic food substances
- 5. Iodine-induced goiter
- 6. Genetic defects in thyroid hormone biosynthesis
  - a. Iodide transport defect
  - b. Organification defect, i.e., defective organification with deafness (Pendred's syndrome)
  - c. Iodotyrosine coupling defect, i.e., defective coupling, associated with deafness (Hollander's syndrome)
  - d. Thyroid dehalogenase defect
- 7. Autoimmune thyroid deficiency (acquired biosynthetic defects), i.e., chronic lymphocytic thyroiditis (Hashimoto's thyroiditis)

B. Secondary hypothyroidism (decreased TSH)
- 1. Tumors (adenomas)
- 2. Congenital deficiencies of the anterior pituitary
- 3. Vascular disorders
  - a. Intrapituitary hemorrhage
  - b. Sheehan's syndrome
- 4. Craniopharyngioma.

Laboratory Studies Specific to Hypothyroidism

All forms of hypothyroidism are characterized by a decrease in the concentration of circulating hormones. Determination of serum T4 levels by radioimmunoassay provides a valuable indicator of chemical hypothyroidism. However, serum TSH values may provide an important indicator of the true state of hypothyroidism for two reasons. (1) The serum TSH values reflect changes in the thyroid state long before serum T4 level may be noted to be subnormal. Consequently, a rise in TSH levels above the normal range can reflect not only true hypothyroidism but early chemical hypothyroidism. (2) The serum TSH determination assists in the differentiation of primary thyroid failure, because elevations of the serum TSH concentration are present in this disorder. However, pituitary failure with clinical

manifestations of hypothyroidism, low serum T4 concentrations, and low-to-absent concentrations of serum TSH reflect anterior pituitary dysfunction. To assist further in the differentiation of primary and secondary hypothyroidism, the TRH stimulation test is used. Low serum T4 levels and accompanying low-to-absent TSH concentrations with failure of the serum TSH level to rise in response to a bolus of the intravenous TRH suggest a deficiency in the anterior pituitary gland. A positive response of serum TSH to TSH that is associated with low T4 and low basal TSH levels may suggest the possibility of underlying hypothalamic disease producing secondary pituitary insufficiency with tertiary hypothyroidism. Accordingly, additional studies of the central nervous system for a possible intracranial neoplasm are indicated.

Table 5. Symptoms of Hypothyroidism (Myxedema)

Symptoms	Incidence (%)	Symptoms	Incidence (%)
Weakness	99	Memory impairment	66
Dry skin	97	Constipation	61
Coarse skin	97	Gain in weight	59
Lethargy	91	Loss of hair	57
Slow speech	91	Pallor of lips	57
Edema of eyelids	90	Dyspnea	55
Sensation of cold	89	Peripheral edema	55
Decreased sweating	89	Hoarseness or aphonia	52
Cold skin	83	Anorexia	45
Thick tongue	82	Nerousness	35
Edema of face	79	Menorrhagia	32
Coarseness of hair	76	Palpitation	31
Pallor of skin	67	Deafness	30
		Precordial pain	25.

In primary hypothyroidism, serum cholesterol concentrations may also be increased, with values in excess of 300 mg/dL. However, in secondary and tertiary forms of hypothyroidism, hypercholesterolemia may not be present. The serum (PBI) determination is also helpful in assessing the hypothyroid state in that an elevated PBI level associated with a subnormal T4 concentration may suggest the presence of abnormal iodinated materials in the serum compatible with an organification defect. This, in turn, suggests a cause for the hypothyroidism. Other changes in the hypothyroid state include increased concentrations of serum enzymes such as creatinine phosphokinase (CPK), serum glutamic-oxaloacetic transaminase (SGT), and lactic dehydrogenase (LDH). In addition, an abnormally prolonged Achilles reflex time may be observed and may be measured by kinomometry.

Nuclear medicine studies, such as radioactive technetium and iodine scans, iodine 131 uptake, perchlorate washout, also play important diagnostic roles.

Electrocardiogram (EKG) changes include bradycardia and prolongation of conduction times. Changes in the ST segment and T-waves are typical in hypothyroidism. With long-standing hypothyroidism leading to clinical myxedema, dramatic changes in the myocardium may occur (cardiomyopathy). The performance of EKG is essential prior to providing any sort

of stress involving anesthesia or surgery. Of particular importance is the use of the EKG in determining the rate of replacement of thyroid hormone when treatment is initiated. If EKG changes or other clinical signs of cardiomyopathy are present, replacement therapy must be initiated extremely slowly so as to not precipitate congestive heart failure in an already decompensated myocardium.

Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)

By far the most common cause of goiter and hypothyroidism is autoimmune chronic lymphocytic thyroiditis, or Hashimoto's thyroiditis. Certainly Hashimoto's thyroiditis is the most common cause of sporadically appearing goiter in children and very likely also the most common cause in the adult population.

Cell-mediated immunity plays an important role in initiating the pathogenesis of Hashimoto's thyroiditis. There is an initial T-lymphocyte attack on thyroid tissue due to an initial viral insult with a common antigen association. The genetic predisposition toward autoimmune thyroiditis may be released, and the T-lymphocytes may attack thyroid tissue. Secondary humoral antibody changes follow the cellularly mediated pathogenesis. The result of this combined immunologic attack on thyroid tissue is a slow and progressive destruction of functionally active follicular thyroid tissue with eventual fibrosis and atrophy of the gland.

Hashimoto's thyroiditis is three to five times as common in females as in males. It has a bimodal incidence of occurrence. In the pediatric population, the average age of onset is 13 years. The disorder is rarely seen after 18 years of age until its second and higher peak occurrence between the ages of 30 and 50 years. In all age distributions, the female predominance persists. Approximately 70 per cent of patients are clinically euthyroid, with goiter being the basis of presentation. Twenty per cent of the patients are hypothyroid when first seen, and 10 per cent or less may present initially with transient thyrotoxicosis. In clinically euthyroid patients, careful laboratory evaluation reveals specific evidence compatible with impending hypothyroidism and demonstrable defects in thyroxine synthesis (specifically organification) as well as immunologic evidence for this condition.

It is important to emphasize that Hashimoto's thyroiditis may be associated with the development of additional autoimmune conditions. Other endocrinopathies may occur in association with Hashimoto's thyroiditis or may follow years later. Commonly observed associations are thyroiditis and diabetes as well as thyroiditis with either adrenal insufficiency or hypoparathyroidism. In addition, it may be associated with other systemic autoimmune diseases such as rheumatoid arthritis, pernicious anemia, and autoimmune disorders of the central and peripheral nervous systems. Once Hashimoto's thyroiditis is diagnosed, the patient and family are informed of the possibility of the patient's developing other autoimmune diseases. Laboratory studies of the patient with Hashimoto's thyroiditis reflect very clearly both the underlying immunologic abnormalities and the organification defect. Although the majority of patients present with normal serum T4 concentrations, most have impending hypothyroidism on the basis of elevated serum TSH levels. Since goiter is universally present, a Tc-99m thyroid scan is useful in demonstrating the increased thyroid morphology in Hashimoto's thyroiditis. Immunologic assessment for antithyroid antibodies (antimicrosomal antithyroid antibody) frequently demonstrates elevated titers. These laboratory studies usually provide sufficient confirmation of Hashimoto's thyroiditis. Other studies, specifically those

involving antithyroglobulin antibodies, are less helpful. Biopsy is unnecessary.

Clinical Manifestations. The clinical manifestations of Hashimoto's thyroiditis vary according to the degree of hypothyroidism present. Typical hypothyroidism becomes manifest initially in the minority of patients, and, as previously stated, goiter is the outstanding clinical characteristic of this condition. In a few patients, the disease may progress extremely rapidly, leading to an initial phase of mild symptomatic thyrotoxicosis. This condition is universally transient over several weeks to 2 months. On physical examination, the thyroid gland either may be smooth or may have a nodular consistency.

Both lobes of the gland are usually enlarged, with one lobe (usually the right) often being larger than the other. Enlargement of the pyramidal lobe and thyroid isthmus is extremely common. Compression of surrounding structures is extremely rare. In extremely rare neonatal goiters, severe tracheal compression with respiratory decompensation due to both the thyroidal mass and the surrounding edema of the cervical structures may indicate the need for tracheostomy as well as thyroidectomy. Goiters, when present, usually show little change after the appearance of the initial manifestations. Less than 20 per cent of untreated patients show subsequent further enlargement. Waxing and waning of the size of the gland is characteristic, even during treatment. With thyroid replacement, the gland initially may undergo significant involution, only to enlarge again later. The gland usually becomes fibrotic and eventually decreases in size.

Treatment. Replacement therapy should be initiated with appropriate doses of thyroid hormone. The predominant indicator for hormone replacement is an elevated serum TSH concentration. Therapy should be guided by serially following the serum TSH values. Levels of thyroid hormone replacement are required that keep the serum T4 level within the appropriate range and suppress the serum TSH concentration. As the disease progresses, and particularly in the growing pediatric patient, dosages must increase accordingly. Thyroid hormone replacement continues throughout life. Surgical intervention is indicated only for extrinsic compression of surrounding structures. Cosmetic procedures to reduce the size of the thyroid gland are probably not appropriate. Long-term follow-up for this condition is indicated for (1) appropriate adjustment of the thyroid dose in terms of progression of the disease, (2) observation for the development of associated systemic diseases, and (3) observation for thyroid neoplasia that may indicate the emergence of clinically overt thyroid malignancy, which is very rare. However, neoplasms, particularly of the papillary type, have been described.

Genetic Disorders of Thyroid Hormone Synthesis Associated with Deafness

Defective Organification and Deafness (Pendred's Syndrome). This condition is a variant of the usual congenital organification defect in which goiter is present along with deafness. Unlike the deafness commonly seen in severely hypothyroid individuals, which is usually of the conductive type and returns to normal with the administration of replacement therapy, the deafness in Pendred's syndrome is of the receptive type. This type of deafness likely results from the strong association of Pendred's syndrome with Mondini's cochlear malformation (Johnsen et al, 1987). Vestibular function is usually reported as normal. Goiter and decreased hearing usually becomes manifest in childhood. The thyroid abnormalities are usually minimal, and although goiter is present, patients are usually euthyroid or only mildly

hypothyroid. These conditions are familial, and a great deal of heterogeneity in presentation is observed between families (Bax, 1966).

The cause of this syndrome is somewhat controversial. The more frequent euthyroid state seen in affected patients makes the possibility of intrauterine hypothyroidism leading to abnormal development of the acoustic apparatus improbable. The possibility of the presence of a common toxic substance that influences both thyroid and auditory function has been proposed but has not been identified. Very likely a multigenetic focus underlies this defect, having effects on both the thyroid gland and the inner ear. Such genetic foci may also be involved in regulating the activity of the enzymes required for organification. Such peroxidase enzymes may also play an important role in the early development of the inner ear.

Pedigrees of families with Pendred's syndrome have established that this is an autosomal recessive defect. However, because of the multigenetic focus and heterogenous manifestations, great variance is seen within such families (Proctor, 1977). Approximately 7 per cent of congenitally deaf individuals have been found to have Pendred's syndrome.

Diagnosis of this condition is suggested in patients presenting with receptive hearing loss, goiter, and variable degrees of hypothyroidism. Confirmation is based on normal or low serum T4 concentrations and accompanying elevations of serum TSH. Other criteria compatible with the organification defect, such as an increased serum PBI level compared with the level of serum T4 and functional demonstrations of significant washout with Tc-99m studies, further confirm the diagnosis. Absence of elevated antithyroid antibody titers will differentiate this condition from Hashimoto's thyroiditis.

Defective Coupling and Deafness (Hollander's Syndrome). A family has been described in which goiter and deafness occurred in several family members in their late 20s. The patients were euthyroid with a normal serum T4 level. Studies of surgically removed thyroid tissue demonstrated a partial defect in the coupling mechanism in thyroxine biosynthesis (Hollander et al, 1964).

Disorders of Maldescent. Embryologic defects in the descent of the thyroid along its normal course of migration include lingual thyroid and aberrant thyroid gland, which can be found at any site in the thyroglossal duct tract from the foramen cecum to the mediastinum.

Medical Management of Hypothyroidism

The treatment of hypothyroidism depends on adequate replacement with thyroid hormone. Multiple preparations exist for replacing the thyroid hormones. The most commonly used is synthetic levothyroxine sodium (Synthroid). Various forms of desiccated whole thyroid remain on the market, but in recent years the lower cost of synthetic thyroid versus biologic preparations, as well as their greater purity and reliability, has made synthetic thyroid preparations the method of choice. Levothyroxine sodium is equivalent to thyroxine or T4. Various regimens of replacement are referred to in the literature, but doses of 100 microg/m^2 of Synthroid are the most commonly recommended initial therapy. Thyroid hormone is usually administered as a single dose on awakening in the morning. The half-life of

levothyroxine sodium is approximately 72 hours, making the administration of a single daily dose adequate for physiologic needs. Average replacement doses in the adolescent and adult are 150 microg/day. Titrating the dose of levothyroxine in an individual to a normal serum thyrotropin level is a very accurate means of ensuring the proper replacement.

Precautions that should be observed in thyroid hormone replacement are most apparent for patients with significant long-standing hypothyroidism and particularly for those with any cardiovascular abnormalities. In patients with severe hypertension, myxedematous heart disease unrelated to the hypothyroid state, or any situation in which cardiovascular dynamics potentially may be altered, caution is indicated. As a general rule in such situations, replacement should be begun at dosages of 25 to 35 per cent of the regular dosage requirement for the first week of treatment. If the patient tolerates such dosages adequately, the dosage may then be increased over 4 weeks to the full dosage, as tolerated.

Thyroid preparations of pure T3 (Cytomel) are also available. Since T3 is the active form of thyroid hormone and T4 requires deiodination (conversion to T3), it would seem that replacement with pure T3 preparations would be advantageous. However, the conversion of T4 (Synthroid) to T3 occurs rapidly and universally. Essentially, there are no reports of the inability to convert Synthroid to active T3. The utility of Cytomel and other pure T3 preparations is extremely limited and such forms of thyroid replacement should not be used routinely.

In postsurgical care in which thyroid hormone replacement is essential and the oral route cannot be used, parenteral preparations are available. Dosage equivalents are maintained for the parenteral preparations as well as the oral preparations. Such agents are administered daily. Depo preparations exist but are not recommended.

The major indicators of adequate thyroid hormone replacement are the clinical signs showing resolution of hypothyroidism, and in the young child, an adequate, recovered pattern of growth. Follow-up laboratory studies include the serum T4 determination, which should be maintained within the normal range, and the serum TSH determination, which may fall either within the normal range or be suppressed below normal. Using the sensitive new TSH assay, it may be possible to titrate the dose of thyroxine to a normal TSH level, thereby eliminating overtreatment (Toft, 1988). In the setting of thyroid replacement and subnormal TSH levels, it is important to carefully monitor the patient for signs of hyperthyroidism.

Surgical Implications of the Hypothyroid State

Hypothyroidism in patients who require surgical procedures usually creates no major problems if the diagnosis is known. Severe hypometabolic problems, hypothermia, hypovolemia, and difficulty in handling medication and anesthesia may be present. Patients with such conditions have decreased renal function with a decreased glomerular filtration rate. In addition, hepatic dysfunction and changes in hepatic enzyme levels may be present in patients with long-standing hypothyroidism. Problems in degradation and excretion of various analgesic medications as well as turnover rates of antibiotics and other substances may then occur. Such difficulties correlate with the degree and duration of untreated hypothyroidism. If possible, surgical procedures should be delayed until the patient is euthyroid.

Patients with known hypothyroidism who have been given adequate doses of thyroid replacement and are euthyroid have no special problems during surgery. It is imperative, however, that they continue to receive thyroxine on a regular basis via either the oral or the parenteral route. Evaluation of thyroid function just prior to surgery is essential.

Patients not previously known to he hypothyroid and particularly those with clinical myxedema require special consideration. In addition to the problems just mentioned, myxedema may lead to difficulties with wound healing, and biochemical changes caused by mucopolysaccharides of connective tissue may lead to additional wound complications. Cardiovascular complications must also be considered. Normochromic, normocytic anemia is common in long-standing hypothyroidism. In hypothyroidism of the autoimmune type, the possibility of concomitant adrenal insufficiency, diabetes mellitus, or hypoparathyroidism must be considered. The unrecognized presence of these conditions can severely complicate the operative and postoperative course in such patients. In the hypothyroid patient, the metabolic turnover of other hormones may be compromised. Consequently, it may become extremely difficult to assess the endocrine status in such patients until thyroid regulation is complete.

Thyrotoxicosis (Hyperthyroidism)

Thyrotoxicosis refers to the biochemical and physiologic consequences that result from excessive quantities of active thyroid hormone entering the circulation (Table 6). This process may occur under a variety of circumstances involving the endogenous release of increased amounts of thyroid hormones caused by overproduction by the thyroid itself, or it may be due to exogenous factors (thyrotoxicosis factitia) as a result of excessive ingestion of thyroid hormones.

Table 6. Symptoms and Signs of Thyrotoxicosis

Symptoms	Signs
Nervousness	Tachycardia
Increased sweating	Thyroid enlargement
Hypersensitivity to heat	Skin changes
Palpitation	Tremor
Fatigue	Bruit over thyroid gland
Weight loss	Eye signs
Tachycardia	Atrial fibrillation
Dyspnea	Splenomegaly
Weakness	Gynecomastia
Increased appetite	Liver palms.
Hyperdefecation	
Diarrhea	
Anorexia	
Constipation	
Weight gain	

Clinical Manifestations

A variety of changes are produced in the skin, including increased warmth and moisture. The hair is often very fine and breaks easily. Alopecia may occur, and the nails may be soft and breakable.

Eye abnormalities are extremely common in thyrotoxicosis. Most commonly, retraction of the upper lid is seen, demonstrated by a rim of white sclera between the lid and the limbus of the eye. Movements of the lids are often jerky and may be spasmodic. These eye abnormalities occur in all forms of thyrotoxicosis. However, the specific petitur ophthalmopathy is uniquely characteristic of thyrotoxicosis due to Graves' disease.

Cardiovascular manifestations in thyrotoxicosis are among the most dramatic and frequent consequences. Owing to the hypermetabolic state and the need to eliminate excessive body heat, increased circulatory demands occur. Cardiac output is increased, and peripheral vascular resistance is decreased, along with an increase in stroke volume and heart rate. Tachycardia is always present. Systolic pressure is significantly increased and diastolic pressure is decreased, producing a wide pulse pressure. Palpitation is often experienced, and systolic murmurs are frequently present. These signs usually resolve when a euthyroid state is restored. Cardiac arrhythmias are common in thyrotoxicosis and are usually supraventricular. Ten per cent of patients with thyrotoxicosis have atrial fibrillation.

Respiratory symptoms due to thyrotoxicosis become manifest most commonly by dyspnea that is usually not associated with heart failure. Vital capacity may be reduced, with weakness of the respiratory muscles. In addition, the hypermetabolic state may produce increases in oxygen utilization out of proportion to the rate of ventilation.

The gastrointestinal system is variably affected with increased appetite in patients with thyrotoxicosis and, depending on the balance of metabolic rate and dietary intake, weight loss or gain. Bowel motility may be affected, and although true diarrhea is rare, frequent bowel movements of formed stools commonly occur. Hepatic dysfunction may occur in those with thyrotoxicosis, particularly in long-standing and severe cases. Hepatomegaly is present in the most severe cases and jaundice, though rare, may occur.

Nervous system manifestations are almost invariably present. These commonly are exhibited as increased nervousness, emotional lability, behavior changes, and hyperactivity. Nervousness is characterized by extreme restlessness, shortness of attention span, and a need too be continually involved in various activities in spite of fatigue. Emotional instability is a prominent symptom. In advanced cases the severe behavioral manifestations may mimic severe manic-depressive psychosis and frank schizophrenia. Other nervous system changes may include fine, rhythmic tremors of the hands and tongue as well as the eyelids when tightly closed.

Alterations in renal function are rarely present in thyrotoxicosis. Minimal urinary tract symptoms occur, including mild polyuria that is often present initially and is associated with increased thirst and water intake.

Laboratory Studies Specific to Hyperthyroidism

With the advent of sensitive IRMAs for the measurement of TSH, the diagnosis of clinical or subclinical hyperthyroidism has been greatly simplified. The improved sensitivity of currently available tests allows the differentiation, with 100 per cent specificity, of thyrotoxic patients from normal subjects. This capacity suggests that serum TSH is the best initial test used in making the diagnosis of hyperthyroidism.

Serum T4 levels are elevated in 90 to 95 per cent of patients with thyrotoxicosis. Circulating T4 levels are increased as a result of increased thyroxine synthesis and release from the overactive thyroid gland. However, the predominant hormonal elevations are reflected in the determination of serum T3 levels by radioimmunoassay. Although the levels of serum T4 may be significantly elevated in this condition, the serum T3 levels most clearly reflect the degree of increased thyroidal activity due both to increased thyroid release of T3 and to increased peripheral conversion of T4 and T3. Five to ten per cent of patients with thyrotoxicosis have normal serum T4 levels. Such situations are termed isolated T3 thyrotoxicosis. On medical treatment, the serum T4 levels return to normal before serum T3 levels by as early as 4 to 8 weeks. The persistence of symptoms of thyrotoxicosis in the presence of normal serum T4 levels is clearly correlated with the persistent elevation of the serum T3 levels.

Antithyroid antibodies are also of assistance in the diagnosis of thyrotoxicosis specifically due to Graves' disease. Because this condition is an immunologically mediated thyroid disease, increased titers of humoral antithyroid antibodies occur. The same considerations with regard to specific antithyroid antibody tests that were discussed in association with Hashimoto's thyroiditis also apply in the immunologic evaluation of Graves' disease. Titers of 1:1600 to 1:6400 are commonly seen in Graves' disease.

Radioisotope scintillation scanning of the thyroid plays a role in evaluating thyrotoxicosis. Such studies provide information on the absolute size of the thyroid gland, which is increased in 97 per cent of patients with true thyrotoxicosis. Relative increased activity of the thyroid gland may also be determined by the rate of incorporation of radioisotopes by the thyroid gland. Delineation of masses due to multinodular goiter and toxic adenoma may be clearly defined with scans using radioactive iodine or Tc-99m. Thyroid scanning is extremely helpful in differentiating true thyroid disease from factitious hyperthyroidism. When thyrotoxicosis is induced by excessive exogenous thyroid hormone, the thyroid gland is uniformly diminished in size owing to the suppression of TSH.

An EKG is routinely performed on all patients with suspected or confirmed hyperthyroidism because recent medical regimens for the treatment of thyrotoxicosis have used beta-blocking agents such as propranolol. Therefore, an assessment of cardiovascular status is indicated prior to the administration of such drugs.

Ophthalmologic assessment is routine in patients with suspected or confirmed thyrotoxicosis. Baseline Hertel's exophthalmometry for detecting proptosis is indicated both to determine the presence of existing eye changes in suspected Graves' disease and as a baseline for following such patients. Visual acuity is determined, and a careful ophthalmologic assessment of other eye changes is further documented.

Hyperthyroid exophthalmos is a confusing and severe medical problem. The patient

should be fully evaluated and recognized to be euthyroid before surgery is undertaken. The indications for surgery include loss of visual acuity, exposure keratitis, corneal ulcer, pain in the eye, and occasionally pure cosmesis. A Hertel exophthalmometer is used to measure the eyes preoperatively and also intraoperatively to ensure that balance is achieved between the two eyes. The technique is discussed in a separate section on ophthalmology.

Radioactive iodine uptake studies are of minimal value in current evaluations of thyrotoxicosis. The use of this functional test has been superseded by the availability of the new TSH tests.

The TRH stimulation test may also be helpful in deciding when to terminate suppressive medical therapy or in determining whether or not a thyrotoxic state exists in rare cases in which equivocal serum T3 and T4 values exist.

Graves' Disease

The most common cause of excessive thyroid hormone production is Graves' disease. Less common causes include toxic adenoma of the thyroid and the hyperthyroid phase of chronic lymphocyte thyroiditis.

Graves' disease is currently considered a humoral immune disorder resulting from a defect of immune surveillance. This permits a mutated clone of thyroid-directed lymphocytes to survive and interact with an antigen on the thyroid cell membrane. The result is the production of a thyroid-stimulating immunoglobulin directed against the TSH receptor (Volpe, 1976). This thyroid-stimulating immunoglobulin then attaches to the TSH receptor on the thyroid cell membrane, which results in stimulation of the thyroid cell similar to that that would occur with TSH. The end result is an immunologically mediated increase in production of thyroid hormones.

Since this condition is an autoimmune disorder, future therapy will be directed toward alleviating the underlying immune process. Present treatment for Graves' disease is directed toward the control of excessive thyroid hormone production. This may be accomplished either by suppression of thyroid hormone synthesis by using antithyroid drugs or by destruction of thyroid tissue by means of radioactive iodine or thyroidectomy. In addition, less specific forms of therapy are also used, and most recently, the sympathetic blocking agent propranolol has been used to provide relief of symptoms in this condition.

Methods of Treatment

Thyroidectomy. Surgery for Graves' disease should be reserved for selected patients in whom successful remission with drug therapy is not possible and for young children or adolescents for whom radioactive iodine treatment is contraindicated. Thyroidectomy in the pediatric age group has been restricted to those patients in whom noncompliance to antithyroid medication has been adequately demonstrated or to a small number of patients in whom toxic reactions to antithyroid drugs make their continued use unacceptable. It is essential that patients being considered for surgery be made euthyroid by means of drug therapy for at least 4 weeks prior to surgery. The utilization of nonspecific agents such as propranolol is highly recommended during the month previous to surgery and throughout the

operative and immediate postoperative period. Dosages of propranolol of 1 to 2 mg/kg/day, broken down to be administered three times a day, have been adequate.

The use of iodine (Lugol's solution) as a means of reducing vascularity of the thyroid gland and preparing patients for surgery has not been universally accepted. Earlier indications for its use predate the availability of propranolol and antithyroid medications. Those patients with cardiac disease who require digitalization and antiarrhythmic agents should be euthyroid and well controlled prior to entering the operating room.

Although the complications of thyroidectomy are minimal in most centers, these sequelae are well defined and well documented. The major complications include postoperative hypoparathyroidism that is either transient or permanent, hemorrhage, damage to the recurrent laryngeal nerves, and risks of anesthesia. Only hypoparathyroidism is considered a likely complication. Postoperative hypothyroidism is not considered to be a complication but almost an essential desired result. Therefore, significant thyroid tissue should be removed, with the residual left in place only to the extent that the parathyroid glands will be identified. If enough thyroid tissue remains, the patient does not develop hypothyroidism and is at risk for later reactivation of clinical Graves' disease. However, patients and their families are told that hypothyroidism will likely occur sooner or later in the postoperative course. In a report on a large series, the incidence of postoperative hypothyroidism following subtotal thyroidectomy was 40 per cent in the first 18 months, with an additional 10 per cent developing late hypothyroidism in the decade following surgery (Hedley et al, 1983).

Hypothyroidism may be subtle in those patients in whom it begins many years postoperatively. Such situations appear to be due to functional remnants of thyroid eventually undergoing immune destruction. The basic antithyroid immunoglobulin attack persists in the remnants and eventually leads to destruction of thyroid tissue in a disease process similar to chronic lymphocytic thyroiditis. Acute hypothyroidism after surgery develops due to total resection of functional thyroid tissue.

Postoperative hypoparathyroidism occurs in 1 to 2 per cent of patients following subtotal thyroidectomy. Many investigators report that up to 10 per cent of the patients may have subtle forms of hypoparathyroidism, which become manifest during calcium deficiency and periods of severe stress. Transient hypoparathyroidism lasting from 8 to 48 hours may occur in up to 50 per cent of patients following subtotal thyroidectomy. This appears to be somewhat more common in the pediatric population. Paralysis of the vocal cords due to recurrent laryngeal nerve injury may occur in up to 5 per cent of patients, although the incidence approaches zero with an experienced surgeon. This condition is usually unilateral. In most cases, it produces alterations in the characteristics of the voice and may result in chronic hoarseness. Bilateral recurrent laryngeal nerve paralysis leads to airway obstruction, although vocal function is good, and may require a tracheostomy.

Statistics regarding the postoperative persistence of hyperthyroidism vary but probably average about 5 per cent. The recurrence of Graves' disease in the postoperative gland is a function of the amount of thyroid tissue removed initially. The incidence of this recurrence is probably between 5 and 10 per cent, although it appears that immunologic destruction of persistent thyroid remnants is more likely with consequent hypothyroidism than is recurrence of active hyperthyroidism.

Radioactive Iodine Therapy. The retention of iodine in significant amounts is the unique function of the thyroid gland. This factor makes the use of therapeutic radioactive iodine extremely appealing and suggests that the thyroid is the ideal organ for such therapy (Volpe et al, 1960). Iodine 131, a predominantly beta-emitting isotope, has a half-life of 8 days. Less than 10 per cent of the radiation from this source is of the gamma type. Because beta emissions travel only small distances within the thyroid gland, the administration of this isotope has a minimum effect on surrounding structures. This allows for the application of considerable doses of radiation without threatening tissues other than the thyroid itself. The principle of iodine 131 radiation treatment is that only some cells are destroyed and others are left intact. Consequently, the absolute synthesis of thyroid hormone is reduced. The advantages of this treatment are its convenience and the fact that it can generally be administered to the patient as a single dose without necessitating admission to the hospital. Surgical complications and the burden of regularly taking medication are eliminated.

However, the specific dose of radiation necessary to selectively destroy thyroid cells is somewhat arbitrary. Clinical effects are first noted 1 month following treatment, and improvement follows gradually thereafter. Associated with these effects is a progressive diminution in the size of the goiter. Approximately 80 per cent of patients so treated establish euthyroid or hypothyroid status after a single dose. Second and third doses may be required in the remaining patients.

The most important side effect with this radioactive iodine treatment is hypothyroidism. The incidence of this complication varies, but in most centers, it is between 20 and 70 per cent. Between 20 and 30 per cent of patients become hypothyroid during the first year following therapy, and this incidence increases to 50 to 70 per cent of patients in the first 10 years following treatment. Since the condition may be progressive over a long period of time as greater amounts of thyroid tissue become less active, progressive increases in exogenous thyroid dosage may be needed.

Although other complications remain primarily theoretical, they have resulted in contraindication of radioactive iodine therapy in a large number of centers and have caused exclusion of its use in pediatric and adolescent patients. These potential complications include leukemia, genetic mutations, and an increased incidence of carcinoma of the thyroid. Studies related to determining the incidence of these complications have not yet clearly demonstrated that any of these effects are related to radioactive iodine therapy. However, such risks may be real, and the use of radioactive iodine therapy has been restricted.

Antithyroid Drug Treatment. At the present time, two specific antithyroidal agents, propylthiouracil (PTU) and methimazole (Tapazole), are used in the treatment of Graves' disease. Propylthiouracil has been the drug of choice, particularly in the pediatric patient, for controlling Graves' disease. This drug appears to act by inhibiting critical enzyme systems involved in thyroxine synthesis, thereby reducing the amount of thyroid hormone released from the gland. It also acts peripherally in inhibiting the conversion of T4 and T3. Methimazole appears to exert its effect exclusively by blocking thyroid hormone synthesis within the gland.

A recommended initiating dose for propylthiouracil is 6 to 7 mg/kg of body weight/day, and the drug is administered every 8 hours. In both cases, the duration of action

of the medications is 8 to 10 hours. Patients are followed at 2-week intervals with serum T4 and T3 determinations by radioimmunoassay. Dosages of propylthiouracil are maintained at 6 to 7 mg/kg/day until the serum T3 level returns to normal values. At that time, the dosage is reduced to one-half of the initiating dose. Following complete clinical remission of symptoms, the dose is slowly and progressively diminished for up to 3 years, at which time drug therapy is discontinued, and clinical and laboratory responses are followed. Another program recommends that single doses of propylthiouracil in the range of 0.5 to 1. 5 mg/kg/day is often enough to maintain a euthyroid state.

The goiter may enlarge during this type of therapy, and this enlargement may be due to progression of the underlying autoimmune process, which is not ameliorated or significantly affected by such drug therapy. Likewise, the exophthalmos may progress or recede independently of the patient's thyroid status or response to antithyroid medication. Complications of drug therapy include agranulocytosis, which occurs in approximately 0.5 per cent of patients. This complication appears to be an idiosyncratic type of reaction; however, the incidence tends to be reduced with maintenance of lower doses of propylthiouracil and methimazole. This complication develops rather quickly and cannot be foreseen by performing frequent routine white blood cell counts. Clinical manifestations that may suggest the presence of the condition include severe pharyngitis with accompanying fever as well as rashes. If patients develop any of these symptoms, the medication should be discontinued immediately and a white blood cell performed. This type of agranulocytosis is usually reversible, and if detected in the acute phase, it may be of only minimal clinical significance. Other side effects reported include joint pains, muscle pains, jaundice, fever, hepatitis, neuritis, loss of taste sensation, toxic psychoses, lymphadenopathy, loss of hair pigmentation, and a lupus-like syndrome.

Parathyroid Hormone and Calcium Metabolism

The regulation of calcium metabolism in the body is formally under the control of two hormones. Until 1960, the only identified internal regulator of serum calcium was parathyroid hormone. This was first discovered in 1925 by Collip, who extracted the active principle from bovine parathyroid glands. This hormone has since been discovered to be intimately involved in the regulation of calcium metabolism by its effects on bone, kidney, and gastrointestinal absorption. The other agent long recognized to play a basic role in mobilizing calcium is vitamin D. Its role, however, appeared permissive and not regulatory. However, it is now known that the vitamin and the hormone interact closely with a more recently discovered hormone produced by the C-cells of the thyroid gland and named thyrocalcitonin (TCT). The action of this latter hormone appears to be that of inhibiting bone resorption, in contrast to that of parathyroid hormone, which stimulates resorption. TCT appears to have a burst effect in preventing hypercalcemia. Thus, TCT, which appears to be the regulator, acts synergistically with phosphate, which is the enhancer.

Usually, there are two to six parathyroid glands, although four is the more common number. In the adult, each of these glands, usually in close approximation to the thyroid gland, is 5 x 3 mm in size and weighs approximately 35 mg. The microscopic anatomy of these glands indicates that oxyphil cells appear at about the time of puberty. These cells, as well as the fat cells that appear in the stroma in late childhood, increase in number until they occupy 50 per cent of the volume of the gland. There are two types of chief cells that

comprise cords, sheets, and acini in a loose areolar stroma. The light chief cell, an inactive cell, has abundant glycogen. The dark chief cell, an active cell, has a less well-defined cell membrane and shows some glycogen. The oxyphil cell normally has no significant role in production of parathyroid hormone (PTH), whereas the ultrastructure of the active form of the chief cell indicates that this is the producer of parathyroid hormone.

PTH contains 84 amino acids and the amino terminal 34 residue has full biologic activity measured in vivo and in vitro. Deletion of two-thirds of the carboxyl terminal end is allowed. This is similar to ACTH.

Proparathyroid hormone, the precursor of PTH, is found in the glandular tissue but only rarely in serum samples. It has a 6- to 20-peptide sequence at the amino terminal.

Clinical detection of PTH by radioimmunoassay shows that the plasma contains hormonal fragments as well as intact 84-amino-acid PTH. The dominant fragment in serum is the carboxyl terminal fragment. This is the inactive fragment, and therefore, much of the assayable amino acid circulating hormone is biologically inactive. Three generally useful amino acid assays have been described, one for the N-terminal PTH, one for the carboxyl terminal PTH, and one specific for the midportion of the molecule.

In 1941, Albright showed that low serum calcium levels produced parathyroid hyperplasia. PTH hyperfunction in vitamin D deficiency has been noted and is due to decreased serum calcium levels, which are, in turn, secondary to decreased calcium absorption. The negative feedback hypothesis formulated in 1955 by McClean has held true and indicates that this gland, like the pancreas, is not under the control of the master pituitary gland. Further studies have suggested that calcium affects both parathyroid hormone synthesis and secretion, whereas magnesium ion concentrations affect only secretion. At the cellular level, proparathyroid hormone is created at the ribosomes and converted in the endoplasmic reticulum to PTH. A low calcium diet increases the conversion efficiency without increasing the synthesis of proparathyroid hormone. Ectopic peptide formation by derepression in a tumor cell can produce hypercalcemia without evidence of bony metastasis. Frequently, a patient with multiglandular parathyroid hyperplasia or adenomas actively secretes both proparathyroid hormone and intact PTH.

The two primary actions of PTH are (1) inhibition of phosphate resorption by the renal tubule and (2) resorption of phosphate and calcium from the bone by stimulating the activity of the osteoclasts. The two secondary actions are (1) increased calcium absorption from the gastrointestinal tract and (2) action of the renal tubule that enhances calcium resorption. Specifically, PTH acts on the proximal tubule to activate cyclic adenosine monophosphate (cAMP) and to inhibit sodium, phosphate, and calcium reabsorption. In the distal tubule, this hormone further inhibits phosphate reabsorption but increases calcium reabsorption. These two renal sites of action of PTH result in its phosphaturic and anticalciuric effects and an increase in cAMP secretion. This latter finding is another mechanism used in the chemical detection of hyperparathyroidism.

In all of its functions, vitamin D is actively involved with PTH, particularly after hydroxylation in the liver and further hydroxylation in the kidney to the metabolically active form 1.25-dihydrocholecalciferol. Calcium absorption from the gut is independent of

phosphate serum calcium ion concentration. The mechanism is activated by PTH and leads to increased activity of vitamin D by increasing the rate of hydroxylation to the active form. PTH also stimulates hydroxylase activity, which produces increased calcium absorption. However, this activity is delayed more than 24 hours after PTH enters the bloodstream; therefore, supplemental parenteral calcium ion may be needed in acutely hypoparathyroid or hypocalcemic patients.

There is little lag time before PTH activity on the target cell ceases. The large calcium pool in bone allows the body homeostasis for wide ranges and durations.

The C-terminal residue is normal in hypercalcemia of metastatic bone cancer and other nonparathyroid hormone causes of hypercalcemia.

Hyperparathyroidism

Primary hyperparathyroidism is a disorder of mineral metabolism characterized by a defect in the normal feedback control of parathyroid hormone secretion by the plasma calcium concentration. Secondary hyperparathyroidism is a disorder characterized by a primary disruption of mineral homeostasis leading to a compensatory increase in parathyroid gland function and size. Hyperparathyroidism is the most common disorder of the gland and is due to adenoma 88 per cent of the time, hyperplasia 11 per cent of the time, and carcinoma 1 to 2 per cent of the time. Hypercalcemia, on the other hand, is most frequently caused by malignant disease that is usually unrelented to the parathyroid glands and is most frequently due to osteolytic metastases. Other nonparathyroid causes for hypercalcemia include sarcoidosis, milk alkaline syndrome, adrenal insufficiency, and prolonged bed rest. OccasiÁnally, metabolically active nonparathyroid neoplasms have been the source of the hypercalcemia. In general, excess parathyroid hormone secretion produces increased phosphaturia and hypocalciuria accompanied by hypercalcemia and hyperchloremic acidosis. The renal synthesis of vitamin D increases intestinal absorption and acts with the parathyroid hormone to decalcify bone.

Hyperparathyroidism is frequently detected clinically by the presence of renal calculi, vague gastrointestinal symptoms, or skeletal pain. Acute or severe disease causes central nervous system (CNS) symptoms. The EKG shows a decreased Q-T interval. Typically, the serum calcium concentration is elevated and the serum phosphate level is abnormally low. The alkaline phosphatase level is elevated only in the presence of bone disease. Subperiosteal absorption of bone is associated with the condition, as well as peptic ulcer disease and epulis of the jaw.

The differential diagnosis is reviewed for each patient because neck and mediastinal exploration is mandatory if other causes for the hypercalcemia are excluded by routine studies. The biochemical battery for detection of this disorder is discussed later.

Hypovitaminosis D (greater than 50,000 units per day) produces hypercalcemia with hyperphosphatemia, which together with blood samples showing normal levels of PTH, differentiates this condition from primary hyperparathyroidism. Hypercalcemia due to bony metastasis is identified by an abnormal radiograph or scan in conjunction with an increased alkaline phosphatase level as well as the usual complaint of bone pain in a patient with

metastatic carcinoma. Pseudohyperparathyroidism has been described since 1937 and is usually due to secretion of a polypeptide hormone from the primary tumor. The ectopic hormone is frequently indistinguishable from normal parathyroid hormone. However, careful biochemical study may distinguish this ectopic hormone-producing tumor from primary benign hyperplasia of the parathyroid glands.

The routine differential findings are as follows: A serum chloride level below 102 mEq/L is usual in primary hyperparathyroidism but infrequent in pseudohyperparathyroidism. Similarly, subperiosteal bone destruction and renal calculi are less frequently found in pseudohyperparathyroidism. This bone destruction is most frequently due to lung and renal tumors, whereas hypercalcemia due to bony metastasis is most frequently seen with breast cancer. Measuring levels of C-terminal fragment PTH (or inactive PTH (iPTH)) in proportion to the serum calcium levels aids in differentiation. This ratio is found to be greater in pseudohyperparathyroidism than in primary hyperparathyroidism. Therefore, the C-terminal fragment is the best differential diagnostic agent. Venous blood from the tumor region may be measured for intact PTH and the values compared with those of neck vein blood. This will frequently indicate the source of the PTH. The tumor assay for PTH is most definitive in its diagnosis.

It is important to differentiate primary and pseudohyperparathyroidism in patients with a thoracic or abdominal cancer because synchronous parathyroid disease may occur. The hypercalcemia must be treated directly by removal of the overproducing tissue, whether this is lung cancer or hyperplastic parathyroid tissue. In pseudohyperparathyroidism, the parathyroid tissue is normal and is not hyperplastic. This situation has thwarted the hypothesis that the lesion is on the parathyroid glands. If chemical and venous catheter studies are inconclusive, neck exploration is indicated to detect adenoma in treated renal or lung cancer patients whose course is expected to be protracted. Removal of a primary secreting malignancy of the lung or kidney as well as eradicating all evidence of metastases returns the calcium metabolism to normal. Recurrence of calcium imbalance suggests regrowth of the tumor or the presence of a growth on the parathyroid gland.

Acute hypercalcemia is almost always due to metastatic disease. Its treatment is urgent, since rapid death may occur. Much of the treatment requires overcoming the effects of hypercalcemia. This includes hydration as well as salt loading to oppose the dehydration due to the gastrointestinal symptoms and the renal effects of hypercalcemia, such as stones and concentrated urine. Preparations used include the diuretic furosemide as well as steroids, which are most effective in metastatic bone disease and are almost always ineffective in hyperparathyroidism. Increasing phosphate and milk in the diet decreases calcium absorption from the gut. Mithramycin chemotherapy as a single dose of 25 microg/kg has been used successfully against tumors. This chemotherapeutic antibiotic inhibits DNA-dependent RNA synthesis, and its effects, which last 1 week, may be due to PTH antagonism. Removing the producing tissue, if possible, is obviously the best treatment.

Syndromes of multiple endocrine neoplasia (MEN) of otolaryngologic interest involve the thyroid and parathyroid glands. The embryologic derivation of many of the central and peripheral neuroendocrine cells determines their humoral capacities. Cytochemical characteristics common to many of the neuroendocrine cells have led to the APUD concept. This acronym refers to a few of the many common characteristics in their cells, namely,

*a*mine *p*recursor *u*ptake and *d*ecarboxylation, leading to amine and polypeptide synthesis. This concept and the embryology on which it is based suggest that the multiple endocrine adenopathies are due to endocrine tumors derived from a common stem cell that originates in the neural crest. The cells, which secrete peptides and amines, migrate to endocrine organs and include the C-cells of the thyroid gland (calcitonin) and the adrenomedullary cells. Parathyroid cells seem to be derived from neuroplacodes. The close association of this origin with the origins of the other glands may explain the ubiquity of parathyroid abnormality in the MEN syndromes.

Although some tumors become manifest as isolated endocrinopathies such as gastrinomas of the pancreas in Zollinger-Ellison syndrome or isolated medullary carcinoma of the thyroid (MCT), they may more usually be seen in a familial pattern or as multiple tumors that form Wermer's MEN I and Sipple's MEN II syndromes. Both syndromes are inherited in an autosomal dominant pattern with deep penetrance. The Wermer syndrome includes parathyroid lesions 90 per cent of the time as well as islet cell, pituitary, and adrenal cortical lesions and, occasionally, thyroid and ovarian neoplasia. The Sipple syndrome (MEN II) includes MCT, parathyroid lesions of hyperplastic adenoma or carcinoma, and pheochromocytoma, which is usually bilateral. This syndrome is diagnosed by family history, by the presence of a bilateral MCT (in both thyroid lobes), or by multiple neoplasia. If the Sipple syndrome is suspected, a full workup is needed for patients with increased serum calcium levels. This workup should include determination of the thyrocalcitonin level, either baseline or pentagastrin stimulated. Interestingly, the medullary carcinoma of the thyroid, an integral part of MEN II, is frequently polyhumoral, and the gland may produce TCT, secretin, and other polypeptides. However, patients with MCT are not hypocalcemic despite TCT secretion and, in fact, are occasionally hypercalcemic because of the PTH secreted as part of the syndrome. A variant, MEN III, occurs sporadically. It includes MCT, pheochromocytomas, mucosal neuromas, and marfanoid features but usually does not involve the parathyroid glands. This rare variant is aggressive and lethal but, fortunately, rare.

Rickets and Vitamin-D-Dependent Rickets

Renal failure produces secondary hyperparathyroidism through relative vitamin D deficiency, which renders the bones unresponsive to normal PTH levels. This produces hypercalcemia and increases PTH. The hyperactive gland may become autonomous and requires exploration of the neck after renal dysfunction is stabilized by dialysis or transplantation.

Hypocalcemia

Hypocalcemia is a frequent and urgent problem for the physician who gives primary attention to the head and neck. The most usual case of decreased PTH is surgical injury. Radiation rarely affects these glands. The idiopathic variety is unusual, occasionally familial, and rarely seen in syndromes such as DiGeorge's syndrome, in which abnormal cellular immunity and thymus aplasia accompany the findings.

The acute hypoparathyroidism produces tetany in 70 per cent of patients, causing a positive Chvostek sign (facial twitch, particularly over the upper lip in response to a finger tap at the facial nerve trunk). Trousseau's sign is seen when the sphygmomanometer is left

in place, subsequently causing greater than systolic pressure for at least 3 minutes. A positive sign produces carpopedal spasm. Metabolic problems that cause these symptoms, such as hyperventilation, hypocalcemia alkalosis, and rickets, must be excluded. Laryngeal spasm (stridor) is frequently seen in acute hypocalcemia, particularly in children. Following major cancer surgery of the neck, patients are usually not at risk for this complication, since they have a tracheostomy in place. The dangerous tetanic triad of muscle cramps, laryngeal stridor, and convulsions is due to spontaneous discharge of motor nerves at a serum calcium concentration below 7 mg/dl. Treatment of acute hypothyroidism and hypocalcemia is directed toward elevating the serum calcium level above 9 mg/dl.

The best form of treatment is pure PTH administration, but this frequently has a 24-hour delayed effect. The current treatment of choice, if the need is urgent, is parenteral calcium infusion. The normal daily calcium intake is 1000 mg, and 600 mg accumulates from intestinal secretion. Of this total, 700 mg is absorbed and 900 mg is excreted in the feces. The extracellular fluid contains 900 mg in ionic balance with 11000 mg intracellularly and 10 kg in bone. A total of 100 mg/day is excreted in the urine, thus maintaining homeostasis. Therefore, the object in maintaining the acutely ill patient who is unable to equilibrate calcium metabolism is to ensure that at least 100 mg/day reaches the extracellular fluid. The total of 100 mg/day of calcium that is lost in the urine must be replaced by parenteral administration. Any excess calciuria must similarly be replaced to maintain homeostasis, since bone mobilization of calcium does not occur well in the absence of parathyroid hormone.

Ten per cent calcium gluconate solution has 9 mg of calcium per milliliter. Ten milliliters of this solution given by slow injection (less than 1 ml/min) to prevent cardiac syncope replaces an average 24-hour excretory loss. This is usually sufficient daily replacement until hormone or vitamin therapy becomes effective or the patient recovers function. The serum calcium level is determined every 12 hours as a blood test to allow modification of calcium therapy. Oral calcium supplement is needed if the acute problem does not resolve. This supplement can be given by mouth or by nasogastric tube. Usually twice the standard 1000-mg daily intake is administered. Calcium gluconate is not a gastrointestinal irritant as compared with calcium chloride and is more palatable than calcium lactate. Daily oral doses of 15 gm of calcium gluconate are sufficient. Calcium gluconate, 15 ml given three times a day, also supplies 1 gm of free calcium and can be placed as a liquid in the nasogastric tube or gastrostomy. By using meat-based formula in tube feedings, phosphate is limited, since it inhibits calcium uptake from the gut.

A dose of 25.000 to 50.000 units a day of vitamin D_2 is used, and since this requires a latency period before its effect on intestinal absorption occurs, the daily dose should not be increased unless no response is seen after 2 weeks. Overzealously increasing the dose of vitamin D produces toxicity. The aim of therapy should be support of the serum calcium level by direct infusion or by oral calcium rather than excess vitamin D. If this is not done, an exaggerated sensitivity to vitamin D may result, producing vitamin intoxication syndrome. The usual long-term dose of vitamin D, which may be life-long, is 1.25 to 2.5 mg (15.000 units per day). When given as dihydrotachysterol, 4 to 5 mg per day is used.

Lifelong monitoring must be planned to detect recovery of glandular function in secondary hyperparathyroidism. Furthermore, following thyroid surgery, calciferol and its calcium-lowering effects are lost, increasing the danger of hypercalcemia. The loss of thyroid

hormone effect on the inhibition of calcium uptake from the gastrointestinal tract is also recognized.

Chronic hypercalcemia, which produces soft tissue calcification, particularly in the kidney and basal ganglia of the brain, must be prevented by monitoring of serum calcium and phosphate levels.

Pseudohypoparathyroidism is a rare genetic disease that is an X-linked dominant disorder with variable penetrance. Clinically, patients with this condition fail to respond to the administration of PTH. These persons are short and round-faced and have brachydactyly of the metacarpals and metatarsals caused by premature epiphyseal closure. The brachydactyly appears due to end-organ resistance to PTH. These people are differentiated from previously described groups by the presence of PTH in the blood. Pseudopseudohypoparathyroidism represents incomplete penetrance of the trait. The patient's physical appearance is abnormal, but the metabolic defect is not present.

The Adrenal Gland

Divided into cortex and medulla, the paired adrenal glands weigh 5 to 8 gm each in normal adults. The cortical adrenal portion comprises approximately 90 per cent of the glands and is derived from mesoderm, whereas the medulla arises from neuroectoderm. Hormones are released from the adrenal gland in response to an applied environmental stress. Stimulation can result in the cerebral cortex sympathetically mediating the release of catecholamines from the adrenal medulla or can result in the release of hypothalamically mediated anterior pituitary hormone ACTH from basophilic cells that is then transported hematogenously to the adrenal medulla, causing the release of various steroid products.

The Adrenal Cortex

Through multiple enzymatic steps, the adrenal cortex synthesizes approximately 30 steroid products from the initial substrate, cholesterol. These products fall into one of five principal groups including corticosteroids, mineralocorticosteroids, androgens, estrogens, and progestogens. Of primary interest in surgical otolaryngology are maintenance of homeostasis of salt and water balance and adequate response to overwhelming stresses, as required to combat the process of infection and while undergoing surgery.

The Mineralocorticoids. The essential characteristic of mineralocorticoid hormones is the regulation of salt and water homeostasis. Mineralocorticoids, including aldosterone, control salt and water excretion through renal effects on sodium and potassium excretion. Acting at the renal tubule, aldosterone activates sodium resorption or potassium excretion through specific enzyme activation at the serosal or luminal surface of the tubule. Inadequate production of mineralocorticoids results in the retention of potassium by the renal tubules and excessive excretion of sodium, with hypotension, weakness, and diminished circulatory volume. Elevations in potassium as a result of inadequate mineralocorticoid activity may result in cardiac arrhythmia, possibly resulting in shock and death.

The Glucocorticoids. Glucocorticoids are steroid hormones that help regulate protein, lipid, and carbohydrate metabolism. While stimulating gluconeogenesis in the liver, they also

diminish the peripheral utilization of glucose, fostering the formation of glycogen in the liver. In addition to metabolic regulation, glucocorticoids also have erythropoietic effects, increasing the circulating red blood cell mass. A frequently observed effect is seen in the increase in circulating leukocytes with glucocorticoid elevations, whether caused by exogenously administered steroids or adrenal cortical release of hormone. Interestingly, only the granulocytes seem to be significantly affected, with minimal effects seen on circulating T and B lymphocytes. The effects mediating calcium metabolism have been appreciated with acknowledgment of the significant contribution of exogenous glucocorticoids toward the development of osteoporosis.

Glucocorticoids have been used in otolaryngology because for a multitude of disorders because of their significant antiinflammatory effects. Otologic uses have included the treatment of sudden idiopathic sensorineural hearing loss, Cogan's syndrome (nonsyphilitic interstitial keratitis, sudden sensorineural hearing loss (SNHL), and vestibular symptoms), luetic deafness, and whenever an autoimmune mechanism for hearing loss can be invoked. First reported by McCabe (1979), the syndrome of autoimmune sensorineural hearing loss is characterized by progressive bilateral sensorineural hearing loss, unsteadiness, an increased sedimentation rate, and a positive lymphocyte inhibition assay using an inner-ear antigen. In cases of Bell's palsy, the administration of steroids may have some benefit, if they are initiated early in the course of the disease. Topical steroids are of some help in limiting the amount of inflammation and subsequent granulation tissue in ear infections.

Rhinologic uses of steroids include the treatment of allergic rhinitis in the form of intranasally administered beclomethasone or flunisolide. The topically administered forms of these compounds have also been shown to be effective in reducing the recurrence of intranasal polyps without any demonstrable systemic side effects from their use. Topical intranasal steroids may be of some benefit in weaning patients with rhinitis medicamentosa from a decongestant, if used concurrently with the decongestant spray for several days prior to stopping it.

Corticosteroids have been used in the airway management in croup, supraglottitis, acute tonsillitis, infectious mononucleosis with tonsillar enlargement, and peritonsillar abscess. Perioperative steroids have been used in tonsillectomy, palatopharyngoplasty, procedures for the base of the tongue, and endoscopic laryngeal surgery. Steroids have been advocated following facial trauma as well as events involving laryngeal trauma, whether caused by external sources or intubation procedures. Steroids can also be used to ameliorate the swelling anticipated following extubation in difficult cases.

When doubt exists as to whether to prepare a patient before surgery by giving exogenous cortisone, it is always safer to prepare preoperatively than to risk the onset of shock during or after surgery. The few contraindications to cortisone therapy are active tuberculosis, psychosis, and active peptic ulcer. Relative contraindications may be severe diabetes, acute viral or bacterial infection, congestive heart failure, or uremia. However, if these medical conditions are known and treated vigorously at the time steroids are given, the degree of risk is lessened.

Prednisone, prednisolone, methylprednisolone (Medrol), triamcinolone (Aristocort), Decadron, and others are synthetic derivations of cortisone or hydrocortisone. These

substances have potent glucocorticoid and anti-inflammatory qualities but few mineralocorticoid traits, thus minimizing salt and water retention by the patient. Although rarely necessary, more potent mineralocorticoid effects can be obtained with the use of corticosterone (Table 7).

Table 7. Relative Potencies of Equivalent Doses of Corticosteroids

Compound	Relative Anti-Inflammatory Potency	Relative Sodium-Retaining Potency	Approximate Equivalent Dose (mg)
Cortisol	1	1	20
Cortisone	4	0.8	25
Prednisone	4	0.8	5
Prednisolone	4	0.8	5
Methylprednisolone	5	0.5	4
Corticosterone	0.35	15	-
Triamcinolone	5	0	4
Paramethasone	10	0	2
Betamethasone	25	0	0.75
Dexamethasone	25	0	0.75