K. J. Lee: Essential Otolaryngology and Head and Neck Surgery (IIIrd Ed)

Chapter 21: Thyroid and Parathyroid

The Thyroid Gland

Although the thyroid gland is located superficially and is accessible for physical examination, knowledge of its physiologic role was slow to develop. Wharton, who gave the name thyroid to the gland because of its resemblance to an oblong shield, fancied that the gland was present to give a round contour to the neck. Fancier still was the view of Vercellone, who described the gland as a bag of worms, the eggs of which, and occasionally the adult worms, entered the esophagus for digestive purposes. Cower considered the thyroid gland to be part of the lymphatic system. As late as 1884, the thyroid gland was considered a vascular shunt cushioning the brain against sudden increases in blood flow.

In 1827, attempts were made to identify thyroid function by its ablation in animals. Since parathyroid glands were not yet identified, death resulting from tetany was wrongly attributed to the thyroid. Production of tetany from parathyroid removal in 1898 clinched the separate roles of parathyroid and thyroid. Discovery of calcitonin in 1962, established a link between calcium metabolism and the thyroid.

In 1896, the association between iodine and the thyroid was recognized. Kendal, in 1915, extracted L-thyroxine and elucidated its chemical structure in 1026. Thyroxine was considered to be the active hormone until triiodothyronine was discovered in 1926 by Gross and Pitt Rivers.

Graves has been credited as having recognized the association between hyperthyroidism and diffuse enlargement of the gland. DeQuervain, Hashimoto, and Riedel have drawn attention to thyroiditis, an autoimmune disorder.

Development of surgical treatment for thyroid disorders is a fascinating story. Albucasis, a Baghdad surgeon, is credited with the performance of thyroidectomy in 1000 AD. Since then, although several others attempted thyroidectomy, it was only in the latter part of the 19 century that thyroidectomy became an accepted modality of treatment. Theodore Kocher, by his meticulous technique and careful observation, established subtotal thyroidectomy as a safe procedure for treating hyperthyroidism. In the USA, the work of Halsted, the Mayo brothers, Crile, and Lahey, established thyroidectomy as a safe, acceptable procedure for managing thyroid disorders.

Anatomy

The thyroid gland, which in normal adults weighs 15-25 g, is a bilobed structure connected by an isthmus which lies anterior to the second, third, and fourth tracheal cartilages. Anteriorly, the gland is covered by skin, subcutaneous tissue, platysma, deep cervical fascia, strap muscles, and the anterior layer of deep cervical fascia. Posteriorly, the gland is related to the trachea and esophagus; laterally, to the great neurovascular bundle of the neck.

The gland is richly supplied with blood by the paired superior and inferior thyroid arteries. The former is a branch of the external carotid artery, and the latter a branch of the thyrocervical trunk of the subclavian artery. In addition, the isthmus in some instances is supplied by the unpaired thyroidea ima, a branch of the aortic arch or the innominate artery. Superior, middle, and inferior thyroid veins drain the blood into the internal jugular and brachiocephalic veins.

Pretracheal and mediastinal nodes drain the isthmus and the medial aspect of the thyroid lobes. The remainder of the gland drains into the deep cervical chain of lymph nodes situated along the internal jugular vein.

The relationship between the gland and the superior and recurrent laryngeal nerves is of surgical importance. The superior laryngeal nerve, arising in the neck as a branch of the vagus nerve, divides into an external motor branch and an internal sensory branch. The external branch innervates the cricothyroid muscle which tenses the vocal cord. The internal branch supplies the laryngeal mucosa after passing through the thyrohyoid membrane. Because of its proximity to the superior thyroid vessels, the external branch is vulnerable to injury during ligation of these vessels.

The recurrent laryngeal nerve arises in the mediastinum as a branch of the vagus nerve. Because of the changes occurring in the embryologic development of the primitive aortic arches, the course of the recurrent laryngeal nerves is different on the two sides. On the right, the fifth and sixth arches disappear and the recurrent laryngeal nerve loops around the fourth arch, which subsequently becomes the subclavian artery. When the origin of the subclavian artery is anomalous, the right recurrent laryngeal nerve will no longer be "recurrent", but arises at a higher level in the neck and passes directly into the larynx. Although a rare occurrence, anyone operating on the thyroid gland should be aware of this anomaly. The left recurrent laryngeal nerve loops around the sixth arch, which subsequently becomes the aortic arch. Both the recurrent laryngeal nerves pass upward in the tracheoesophageal groove to enter the larynx.

Microscopically, the thyroid gland consists of follicles lined by cells, which produce thyroid hormone. In addition to the follicular cells, the gland contains parafollicular or C cells, which produce calcitonin.

Embryology

At the junction of the copula and tuberculum impar, during the fourth week of fetal life, a median diverticulum develops from the pharyngeal endoderm. The diverticulum elongates and descends to occupy a position anterolateral to the trachea and esophagus. While the distal portion of the sinus tract develops into the isthmus and thyroid gland, the portion between the floor of the mouth and the isthmus disappears. Failure of such a disappearance results in the formation of a thyroglossal duct cyst. During its descent, the sinus tract remains in close contact with the ventral aspect of the hyoid bone. Because of this embrylogic relationship, unless the midportion of the hyoid bone is resected while excising thyroglossal duct cyst, elements of the thyroglossal duct are incompletely removed and result in a recurrence.

The thyroid gland occupies an ectopic location when the descent of the tract is interrupted or altered. The ectopic locations include the base of the tongue, mediastinum, pericardial sac, trachea, and esophagus. A radioisotope scan is helpful in localizing the gland. Cosmetic deformity and pressure symptoms produced by an ectopic gland may be relieved by administering exogenous thyroid hormone thereby decreasing the size of the gland. Operative removal will be necessary if thyroid suppression fails to relieve the symptoms or when a neoplasm cannot be excluded.

Physiology

Thyroid hormone is necessary for normal development in a maturing animal. In the adult, it plays an important role in maintaining metabolic stability. Both thyroxine (T4) and triiodothyronine (T3) stimulate calorigenesis, potentiate epinephrine, and lower serum cholesterol. At the cellular level, thyroid hormone is believed to mediate its action by its effect on both the mitochondria and the nucleus.

Kinetics of Thyroid Hormone

Iodine metabolism is intimately related to that of thyroid hormone. Normal adults on an average require 80 mg of iodine per day. Seafoods are the natural sources of dietary iodine. In the United States, the dietary intake is as high as 500 mg because of iodization of salt and flour. The ingested iodide is readily absorbed from the gastrointestinal tract and enters the iodide pool, which includes iodide derived from peripheral deiodinization of iodothyronine and nonhormonal iodide, which has leaked from the thyroid gland, in addition to the absorbed iodide. From this iodide pool, iodide exits via two routes: transportation into the thyroid gland and excretion through the kidneys. Iodide transportation into the thyroid cell is an active, energy-dependent process. Since other anions such as perchlorate, pertechnetate, and thiocyanate also are transported through the same mechanism, they act as competitive inhibitors of iodide uptake.

Within the cell, the iodide is oxidized and becomes bound to tyrosyl residues of thyroglobulin. Coupling of two monoiodotyrosyl molecules produces diiodotyrosine which when coupled produce thyroxine (T4). Coupling of a monoiodotyrosine molecule with a diiodotyrosine molecule or removal of a monoiodotyrosine from T4 produces triidotyrosine (T3). Removal of iodine from the inner ring produces what is called reverse T3 (rT3), a triiodothyrosine which is physiologically inert.

The thyroid hormones are stored within the follicles bound to thyroglobulin. Prior to its release into the circulation, the thyroglobulin is taken up by the cell and by proteolytic degradation, T4 and T3 are formed and diffuse into the circulation.

About 80-100 mg of T4 is produced daily, exclusively within the thyroid gland. The half-life of T4 in circulation is 6-7 days and about 10% is degraded daily. However, the rate of degradation is influenced by serum binding as well as tissue factors. The rate of degradation is increased when there is deficiency of thyroid-binding globulin (TBG) and the reverse effect is seen with TBG excess. Regardless of the changes in TBG concentration, the total amount of T4 degraded remains normal, whereas, with hypo- or hyperthyroidism, the total amount degraded decreases or increases, respectively. T4 is metabolized by

monodeiodination to form T3 which is several times more potent than T4, or to form rT3, which is physiologically inert. Conversion of T4 to T3 or rT3 is not a random process. T4 is preferentially converted to rT3 during starvation.

Of the 20-30 mg of T3 daily produced, 80% is derived from extrathyroidal deiodinization of T4 and the remainder from the thyroid gland. T3, unlike T4, has a short half-life of 30 hours.

Once released from the gland, T4 and T3 are transported in blood bound to plasma proteins. Under normal conditions, 80% of T4 is bound to TBG, 15% to thyroid binding prealbumin (TBPA), and the remainder to serum albumin. As far as T3 is concerned, 90% of it is bound to TBG, 5% to TBPA, and another 5% to serum albumin. Physiologically active hormone is that portion which is unbound and represents 0.05% of total serum T4 (about 2 ng/dL) and about 0-2 ng/dL of T3. The binding proteins act as reservoirs for storing hormone and help in bufferig the free hormone level.

Secretion of thyroid hormone is regulated by thyroid-stimulating hormone (TSH) of the anterior pituitary. Thyroid-stimulating hormone secretion is sensitive to serum thyroid hormone concentration. A decrease in serum thyroid hormone stimulates TSH secretion and the reverse is true with elevated serum thyroid hormone level. Secretion of TSH is, in turn, influenced by thyrotropin-releasing hormone (TRH) of the hypothalamus.

Thyroid Function Tests

Of the many thyroid function tests available, each one measures some aspect of the kinetics of thyroid hormone and, as such, there is no one ideal thyroid function test. Basically, one need to determine the functional status of the thyroid gland viz. hypo-, eu-, or hyperthyroidism, and if an abnormality is present, the mechanism of the underlying abnormality.

Measurement of the Thyroid Hormone in Serum

Determination of the levels of thyroid hormones is widely used because of its convenience. Serum T4 concentration is measured by radioimmunoassay and the normal is from 5-12 mg/dL. Serum concentration of T4 is affected by two factors: altered secretion by the thyroid gland and serum-binding capacity. An abnormal T4 determination fails to differentiate between the two. For instance, T4 may be misleadingly high in a euthyroid patient because of an increase in the serum concentration of binding proteins. The significance of altered T4 concentration cannot be interpreted without a simultaneous measurement of serum-binding capacity.

T3 Resin Uptake (T3 RU)

This test measures the number of unoccupied protein-binding sites for T4. The test is performed by mixing radio-labelled T3 with the test serum and then adding a resin. Measurement of radioactivity in the added resin measures the amount of T3 bound to the resin. Therefore, when there are many binding sites available for T3, the radioactivity of the added resin will be low and vice versa. Normally, the unoccupied protein-binding sites take

up 45-75% of the radiolabelled T3 and the resin takes up 25-55% (see Figure 21-1). It is to be remembered that T3 RU is not a measure of serum T3 level.

Binding sites for T4 may be decreased and T3 RU high due to any of the following conditions: (1) when binding sites are occupied by T4 as in hyperthyroidism; (2) when serum-binding sites are occupied by other ligands such as salicylates and clofibrate; (3) when serum-binding sites are decreased secondary to inhibition of TBG synthesis.

A low T3 RU, which indicates an increase in the available sites for T4 binding, occurs under two conditions: (1) when fewer binding sites are occupied as in hypothyroidism; (2) when TBG formation is increased (Table 21-1).

Concordant changes in T4 and T3 RU values indicate a secretory change whereas discordant values indicate a problem with binding proteins.

Table 21-1. Conditions Which Affect TBG Concentrations

1. Decreased TBG Concentrartion

Androgenic steroids
Glucocorticoids
Active acromegaly
Major systemic illnesses
Genetic determination

2. Increased TBG Concentration

Estrogens and hyperestrogenic state
Pregnancy
Neonatal period
Oral contraceptives
Biliary cirrhosis
Genetic determination
Acute intermittent porphyria.

Free Thyroxine (FT4)

Determination of free or unbound T4 measures the physiologically active portion of the hormone and is helpful in eliminating the difficulty in interpreting altered T4 values secondary to changes in binding protein concentration. Free thyroxine can be measured using membrane dialysis and the normal value is 0.4-3 mg/dL. This test is not readily available, takes a prolonged time for completion, and the artifacts induced by defects in dialysis membrane, bacterial overgrowth, and contaminants in radiolabelled T4 have limited its usefulness.

Calculated Estimates of Free Thyroxine Level

Because of the cumbersome nature of measuring the FT4 level, a variety of mathematic calculations are employed to derive the same information. The fre T4 index (FTI) is one such. It is the product of total T4 concentration and either T3 RU or the inverse of T3 resin ratio. Although FTI correlates well with the directly measured FT4 in most instances, it may be inaccurate when TBG concentration is markedly changed.

Serum Triiodothyronine Concentration (T3)

Like T4, T3 is measured by radioimmunoassay. The normal value is 70-200 mg/dL. Unlike T4, T3 is depressed in many nonthyroidal diseases. In T3 thyrotoxicosis, T3 is elevated without elevation of T4.

Thyroxine-Binding Globulin (TBG)

The normal value is 1-3 mg/dL. The concentration of TBG can be measured by radioimmunoassay, but the measurement offers little advantage over T3 RU in assaying total serum-binding capacity.

Serum TSH

This is a useful determination to confirm hypothyroidism when T4 and T3 RU are equivocal. In normal subjects, TSH rarely exceeds 10 microIU/mL and is nearly always greater thanb 20 microIU/mL in primary hypothyroid patients. A low T4, T3 RU, and lowered TSH is indicative of hypothyroidism secondary to a pituitary or hypothalamic disorder. Since the presently available methods of assay cannot differentiate between normal and low values, TSH determination is not helpful in confirming hyperthyroidism.

Pituitary-Thyroid Regulation

In normal subjects, administration of TRH is promptly followed by elevation of TSH. Because of TSH suppression in hyperthyroid patients, response to TRH is impaired or absent. Such a response indicates thyroid autonomy. The test is easy to perform. TSH is measured before, 15 and 30 minutes after administration of 400-500 mg of TRH.

Antithyroglobulin and Antithyroid Microsomal Antibodies

In autoimmune thyroiditis, these antibodies are elevated and are helpful in confirming the diagnosis.

Radionuclide Tests

With radioactive iodine and pertechnetate, not only can the uptake of the material from the gland be measured, but also the gland can be scanned to obtain anatomical details delineating areas of altered uptake. Scanning is also of value in detecting ectopic thyroid tissue. Pertechnetate is the preferred agent as it delivers less radiation than iodine.

Normal radioiodine uptake is 5-15% at 2-4 hours and 10-30% at the end of 24 hours aftet the administration of the isotope. A low uptake in an otherwise hyperthyroid patient is indicative of factitious hyperthyroidism or thyroiditis.

Sonography

By this noninvasive modality, it is possible to differentiate solid from cystic lesions of the thyroid gland. However, sonography cannot differentiate between benign and malignant lesions.

Biopsy

Tissue for histologic examination can be obtained by cytologic aspiration or using a Vim Silverman needle or one of its modifications. The risk of hemorrhage or of spreading tumor is minimal. It is important to realize that a negative biopsy does not necessarily exclude malignancy.

Diseases of the Thyroid Gland

Hypothyroidism

Hypothyroidism occurs more commonly in females. Cretinism refers to hypothyroidism in infants and, unless recognized early and promptly treated, retardation of physical as well as mental growth occurs. Hypothyroidism may be due to iodine deficiency in the diet or to enzymatic defects, which impair hormonogenesis within the thyroid gland. It also may result from surgical or radiation ablation of the gland, and overzealous treatment of thyrotoxicosis and pituitary or hypothalamic dysfunction.

Hypothyroidism is characterized by slow cerebration, impaired memory, brittle hair, dry thick skin, and in some cases, frank psychosis. The tongue is thick and the voice coarse. Reflexes are prolonged. Bradycardia is often present. Abdominal distention, secondary to constipation and ileus, can occur.

Treatment consists of thyroid hormone replacement.

Hyperthyroidism

The clinical and biochemical syndrome resulting from exposure of tissues to excessive amounts of thyroid hormone consitutes hyperthyroidism. The causes of hyperthyroidism include:

1. Graves' disease.
2. Thyroiditis.
3. Exogenous hyperthyroidism:
a. Iatrogenic.
b. Factitious.
c. Iodine-induced.
4. Uninodular toxic goiter.

5. Multinodular toxic goiter.
6. Thyroid carcinoma.
7. TSH excess:
a. Pituitary thyrotropin.
b. Trophoblastic tumors.

Of the above causes of hyperthyroidism, Graves' disease and multinodular toxic goiter are the most frequent. Hyperthyroidism may be mild or severe, transient or permanent, and the diagnosis obvious or difficult. It is important to identify the cause of hyperthyroidism because the natural history and the treatment varies depending on the etiologic factor.

Since thyroid hormone affects every organ system, hyperthyroidism manifests with multisystem abnormalities. The typical patient is nervous with fine muscular tremors and increased sweating. Heat intolerance, palpitation, increased appetite with weight loss, muscle weakness, and amenorrhea often are present.

Graves' Disease

Components of this syndrome include: (1) hyperthyroidism; (2) diffuse thyroid enlargement; (3) infiltrative ophthalmopathy; (4) infiltrative dermopathy (clubbing of fingers and localized myxedema).

Graves' disease is considered an autoimmune disorder. Thyroid-stimulating autoantibodies belonging to IgG fraction have been detected. The cause of extrathyroidal manifestations of Graves' disease is not known.

Management. Three options are available for managing patients with Graves' disease. These are drug therapy, ablation of the thyroid gland with radioactive iodine, or surgery. The three modalities of treatment are not mutually exclusive and in some instances more than one modality is employed to render the patient euthyroid.

Drug Therapy. Available drugs include: (1) iodine; (2) thionamides (propylthiouracil); (3) monovalent anions (perchlorate); (4) monovalent cations (lithium); and (5) beta-adrenergic blockers.

Iodine, the earliest used antithyroid drug, has only a transient effect in suppressing hormonogenesis. Within 2 weeks of continued iodine administration, the gland "escapes" and the symptoms recur. It is now primarily used in the preoperative preparation to render the gland less vascular and less friable.

Lithium and perchlorate are too toxic for routine use and are infrequently employed.

The most frequently used drugs are propylthiouracil and methimazole. The former has the added advantage of blocking peripheral conversion of T4 to T3. Since the duration of action of these drugs is short, the drug has to be administered three times a day. Adverse reactions to drugs occur in 3-5% of the patients and include drug fever, nausea, diarrhea, and vomiting. Bone marrow suppression and resulting agranulocytosis, the most serious

complications, are reversible if detected early and the drug is discontinued. Since methimazol causes a scalp defect in the fetus, the drug is contraindicated during pregnancy.

The incidence of permanent remission following drug therapy is gradually decreasing as compared with earlier reported series. The decline is probably related to increased dietary iodine intake. The most favorable prognostic factors for permanent remission include T3 thyrotoxicosis, a gland enlarged to less than twice the normal size, and serum hormone levels not greater than 50% above the upper limits of normal. Chances for permanent remission are as good following short-term therapy and discontinuation of the drug after attainment of euthyroid status as after continued therapy for a year of more.

Propranolol, a beta blocker, unlike other antithyroid agents, does not suppress hormonogenesis, but blocks the action of the hormone at peripheral sites. Because of its effectiveness, safety, and absence of adverse effects, the drug has in recent years been used with increasing frequency. The dose of the drug is titrated to relieve the symptoms. Beta blockers are best utilized as adjuncts to antithyroid drugs until circulating hormone level is rendered normal.

Treatment with Radioactive Iodine. Low cost, painlessness, absence of risks of an operation and its associated complications have great appeal for the use of radioactive iodine treatment. The disadvantage of this therapy includes a high occurrence (30-70%) of hypothyroidism, an incidence not influenced by the use of frequent smaller doses as opposed to a large single dose administration.

Surgical Treatment. Until the introduction of antithyroid drugs and radioactive iodine for treating hyperthyroidism, the only effective method of treatment was subtotal thyroidectomy. Properly done, the mortality for this procedure is near zero; the incidence of vocal cord paralysis is less than 0.5%. Subtotal thyroidectomy renders the patient euthyroid more expeditiously than either antithyroid drugs or radioactive iodine. The risk of recurrent hyperthyroidism is 3% and of hypothyroidism at the end of 5 years, 5-10%.

For the operation to be safe, the patient preoperatively should be rendered euthyroid either with antithyroid drugs or beta blockers. Overtreatment is preferable to undertreatment in preventing postoperative thyroid storm.

Opinion differs as to the ideal modality of treatment. Treatment selection should be individualized. An important consideration is the age of the patient. Pregnancy is an absolute contraindication for radioactive iodine usage. Since the long-term effects of radioactive iodine on genetic mutations is not known with certainty, radioactive iodine is, in most instances, reserved for patients over the age of 35 years. For those with shortened life expectancy due to concomitant medical disorders, and in those requiring a second neck exploration, radioactive iodine treatment is the preferred method.

Subtotal thyroidectomy is preferred for younger patients of child-bearing age; in patients in whom antithyroid drugs, despite prolonged use, have failre to induce a remission; in those intolerant of antithyroid drugs; in those fearful of radiation effects in any form; and in noncompliers of drug administration instructions.

Drug therapy is indicated in preoperative preparation. It also is indicated in young patients since a permanent remission may be induced. For drug therapy to be successful, the patient should be willing to take the medication regularly over a prolonged period and be available for follow-up visits.

Solitary Cold Nodule

The problem with the solitary cold nodule is to determine its nature: benign or malignant. The reported incidence of malignancy in cold nodules varies. A higher incidence is reported in surgical series compared to medical series. The risk factors include: age less than 20 years; male sex; solid nature of the nodule; and cystic lesions larger than 4 cm in diameter. Excepting medullary carcinoma, there are no clinical or laboratory features to differentiate benign from malignant nodules. Sonography, biopsy, aspiration cytology, while helpful in the diagnosis, are not infallible. Therefore, the decision to operate should take into consideration clinical facts.

"Hot" Nodule

Malignant transformation of a hot nodule is rare. Failure of a hot nodule to regress on thyroid suppression, or a chnage from a hot nodule to a cold nodule, needs surgical exploration to exclude malignancy. An autonomous nodule is treated with radioactive iodine or by surgical excision.

Nontoxic Nodular Goiter

The pathogenesis of nontoxic goiter is related to repeated episodes of thyroid hormone deficiency resulting in TSH secretion followed by hyperplasia of the gland. Alternating hyperplasia and involution occurring over a prolonged period causes nodularity. The nontoxic multinodular goiter may either be endemic or sporadic. The former occurs in geographic areas where dietary iodine intake is deficient. The cause of sporadic goiter is not well understood, but is believed to result from ingestion of excess fluoride or calcium which displaces iodine. It also has been observed to be associated with drinking of poluted water contaminated with Escherichia coli. The role of naturally occurring goitrogens in producing the goiter in humans is yet to be elucidated. Faulty utilization of iodine in homonogenesis may be responsible in some instances.

The symptoms depend on the size and location of the goiter. It may be asymptomatic. Mediastinal goiter may produce pressure symptoms on the trachea and esophagus. Large cervical goiters are cosmetically objectionable.

Treatment involves attempts at reducing the size of the gland by TSH suppression with exogenous thyroid hormones. Operative intervention is indicated for cosmetic reasons, to exclude malignancy, and to relieve pressure symptoms. Thyrotoxicosis resulting from hypersecretion of an autosomal nodule is treated with either radioactive iodine or surgical excision.

Thyroiditis

There are five categories of inflammatory thyroid conditions: (1) acute suppurative, (2) subacute (granulomatous disease), (3) Hashimoto's disease, (4) Riedel's struma, and (5) nonspecific inflammation. Although in many instances accurate categorization is not possible, its lack does not adversely affect surgical treatment.

Indications for surgical treatment include cosmetic deformity, suspicion of carcinoma, and for relief of pressure symptoms.

Malignant Lesions of the Thyroid Gland

There are two functionally distinct endocrine cells in the thyroid gland: follicular cells and parafollicular or C cells. The former, which secretes thyroid hormone, is the cell of origin for papillary, follicular, and anaplastic carcinoma. The parafollicular cell, a derivative of the neural crest and secretor of thyrocalcitonin, is the cell of origin for medullary carcinoma. Papillary and follicular carcinoma are well differentiated with a relatively good prognosis compared with the poorly differentiated anaplastic carcinoma. The place of medullary carcinoma in its degree of malignancy, falls between the well-differentiated papillary and follicular carcinoma and the poorly differentied anaplastic carcinoma.

Papillary carcinoma, the most frequent of the thyroid cancers, is unencapsulated and multifocal in origin. It spreads via the lymphatics; hematogenous spread is infrequent. Age, sex, and the extent of tumor spread influence the prognosis. A favorable prognosis is noted in patients younger than 40 years of age, in premenopausal women, and when the tumor is within the confines of the gland. A worse prognosis is associated more with local tissue invasion than with lymphatic spread.

Unlike papillary carcinoma, follicular carcinoma is typically solitary and encapsulated. It preferentially metastasizes by the hematogenous route to involve the bones and lung.

The highly malignant anaplastic carcinoma may be composed of either large or small cells. By the time the patient seeks medical attention, the tumor, in most instances, proves nonresectable by the extent of its spread.

Medullary carcinoma is the only thyroid carcinoma which is familial. It occurs, as a component of type II multiple endocrine adenopathy. Therefore, a diagnosis of medullary carcinoma warrants a search for pheochromocytoma and parathyroid adenoma.

Treatment. The modalities available for treating thyroid cancer include: surgery, radioactive iodine, suppression of TSH secretion by exogenous thyroid hormone, external radiation, and chemotherapy.

1. Surgery. Both the extent of thyroid resection and cervical node dissection needed for managing well-differentiated thyroid cancer is controversial. Total thyroidectomy is recommended by some to remove all foci of malignancy within the gland. An added advantage of total thyroidectomy is that it avoids the need for a subsequent second exploration and its associated complications when a remnant left behind by lesser procedures

requires subsequent excision to enhance radioactive iodine uptake by metastatic foci. Those opposing total thyroidectomy point out the lack of correlation between histologic malignancy and biologic behavior, as good a result from lesser resection as from total thyroidectomy, and the increased risk of injury to recurrent laryngeal nerves and parathyroid glands associated with total thyroidectomy. In view of the controversy, a reasonable approach is to perform a total lobectomy on the side of the lesion and near total thyroidectomy on the opposite side, and to reserve total thyroidectomy for patients with distant metastasis.

Anaplastic carcinoma, because of its extent of local invasion, is generally unresectable. A biopsy of the lesion to confirm its nature is all that can be done. In the rare instance, when the tumor is resectable, total thyroidectomy is performed. In sporadic medullary carcinoma, unilateral lobectomy is adequate when the tumor is confined to the gland. The familial form requires total thyroidectomy because of the high incidence of bilateral involvement.

The high incidence of microscopic metastatic involvement in normal-looking cervical node lead to the advocacy of prophylactic neck dissection. However, the incidence of subsequent nodal recurrence in patients with normal-looking glands is a low 3%. Therefore, prophylactic neck dissection is not favored in the treatment of well-differentiated cancer. Furthermore, delay in removing the involved nodes does not appear to jeopardize the chance for cure. In anaplastic carcinoma, neck dissection is considered only if the primary lesion is resectable. Node dissection is indicated in medullary carcinoma because of the high incidence of lymphatic metastases. Mediastinal dissection is undertaken in patients having well-differentiated carcinoma with metastasis to central compartment cervical nodes.

2. Radioactive iodine: Total thyroid ablation results in elevation of serum TSH levels. With elevated TSH concentration metastatic foci are stimulated to trap iodine and then radioactive iodine is administered with the hope that the metastatic foci concentrate enough iodine to receive a lethal dose of radiation. The success of the treatment depends on the ability of the metastatic lesions to trap iodine. Metastatic lesions from anaplastic and medullary carcinoma do not trap iodine in sufficient concentration to be therapeutically effective.

3. TSH suppression: The observation that the thyroid is dependent on pituitary TSH for its growth and development lead to the assumption that TSH suppression is beneficial in retarding the growth of well-differentiated cancers. For this purpose, L-thyroxine is administered in doses just short of producing early signs of toxicity.

4. External radiation: In some patients, palliation may be provided in relieving symptoms referable to metastatic, invasive, or incompletely excised lesions using external radiation.

5. Chemotherapy: In general, results with chemotherapeutic agents are disappointing.

Operative Considerations

Mortality from thyroidectomy at present is near zero. Meticulous attention to operative technique, proper preoperative preparation and selection of patient and adequate posoperative care have contributed to the safety of thyroid operations. It is worth remembering that

operation is only one aspect in the management of thyroid disorders and for adequate management services of the cardiologist, endocrinologist, anesthesiologist, and pathologist often are needed.

Position of the Patient

Extension of the neck, necessary for adequate exposure, is obtained by placing a pillow or a sandbag beneath the shoulder blades. Bleeding is minimized by decreasing venous engorgement by placing the patient in a semisitting position.The neck is draped exposing the entire anterior aspect of the neck from the chin to the suprasternal notch.

The Incision

In addition to providing adequate exposure, the incision should be cosmetically pleasing. The ideal incision will be at a level where a necklace might rest and cover the scar. The desired cosmetic results will not be obtained by too high or too low an incision, one that is asymmetric, or one that is not along the natural skin crease in the neck.

Elevation of the Flaps

For elevating the flaps, dissection is carried out in the relatively avascular plane between the platysma and deep fascia. The skin, subcutaneous tissue, and platysma muscle are raised as a single layer. The superior flap is raised to the level of the thyroid cartilage and the inferior one to the level of the sternal notch.

Exposure to the Thyroid Gland

Following elevation of the flaps, the deep cervical fascia is incised in the midline between the strap muscles. The midline is identified in the lower part of the neck by the presence of a small amount of fat between the muscles and by the absence of muscle mass to palpation. Lateral retraction of the strap muscles and incision of the anterior layer of the pretracheal fascia exposes the thyroid gland. Wider exposure, when needed, is obtained by transection of the strap muscles. Routine transection of the strap muscles is not necessary. Transection of the muscles near their insertion is recommended to preserve their innervation.

Mobilization of the Gland

Ligation and division of the middle thyroid vein is a prerequisite in mobilizing the gland medially. Unless handled gently, avulsion of the middle thyroid vein from the internal jugular vein can occur resulting in hemorrhage. Gentle median traction on the gland and lateral traction on the carotid sheath expose the vein for safe ligation.

Isolation of the Recurrent Laryngeal Nerve

To avoid injury, the recurrent laryngeal nerve should be exposed before ligation of the inferior thyroid vessels. The posterolateral edge of the gland is exposed by displacing the gland medially and the carotid sheath laterally. The nerve often can be palpated as a cord in the area between the gland and the carotid sheath. Dissection in the areolar tissue, parallel to

the course of the nerve, exposes the structure. Once exposed, the nerve is traced to its entrance into the larynx. The nerve also may be identified at its site of entrance into the larynx by its location below and anterior to the cricothyroid articulation.

Ligation of the Inferior Thyroid Vessels

Blind ligation of the artery, because of its variable relation to the recurrent laryngeal nerve, is hazardous. Prior identification of the nerve renders ligation of the artery safe. Although time consuming, individual ligation of the inferior thyroid vessels close to the thyroid gland is preferable to mass ligation for preserving blood supply to the parathyroid gland.

Superior Pole Mobilization

Downward traction on the gland along with elevation of the strap muscles exposes vessels to the superior pole. The vessels should be ligated individually under direct vision, close to the gland, to avoid injury to the superior laryngeal nerve or its branches. Furthermore, individual ligation helps in mobilizing the tongue of the thyroid tissue that ascends lateral to the entry of the vessels into the gland.

Identification of the Parathyroid Glands

Unless invaded by malignancy, every attempt should be made to identify and preserve the parathyroid glands. Their usual location and the characteristic brownish color are helpful in their identification. The superior gland usually is located at the level of the junction of upper and middle thirds of the thyroid, along its posterior border in close proximity to the entrance of the recurrent laryngeal nerve into the larynx. The location of the inferior parathyroid is more variable. Usually it is located close to the thyroid gland where the inferior thyroid vessels enter the gland.

Division of the Isthmus

Loose alveolar tissue between the isthmus and the trachea provides an avascular space for separation of the isthmus from the trachea. During separation, injury to trachea from a sharp instrument should be avoided.

With completion of the above steps, the gland will be ready for resection. The extent of glandular resection depends on the pathologic condition and may involve excision of the nodule, removal of the entire lobe, subtotal thyroidectomy (removal of seven-eights of the gland) or total thyroidectomy (removal of all grossly visible thyroid gland).

Closure of the Wound

Prior to closure, the head is flexed and the adequacy of hemostasis ascertained. If previously transected, strap muscles are approximated with mattress sutures; the deep cervical fascia and platysma are approximated, and the skin edges are carefully brought together with fine sutures or clips. Drainage of the wound is not often necessary, and when a drain is left in it is brought out through one angle of the incision.

Thyroidectomy and Neck Dissection

In thin patients, upward extension of the collar incision on both sides provides adequate exposure for neck dissection. In obese patients, and in those with scar from a previous biopsy of the cervical nodes, an incision extending from the mastoid process to the sternal notch and along the clavicle to the trapezius muscle is necessary for adequate exposure. In either event, skin flaps are raised exposing structures from the parotid gland superiorly to the sternum inferiorly, from the trapezius muscle posteriorly to the thyroid gland anteriorly. After detaching the sternomastoid, sternohyoid, and sternothyroid muscles from their attachments to the clavicle and sternum, the internal jugular vein is identified and dissected free from carotid artery and vagus nerve. The vein is transsected low in the neck after ligation. The entire mass of lymphatics, muscle, and the vein are dissected en bloc from the underlying muscle avoiding injury to the brachial plexus, phrenic nerve, spinal accessory nerve, and recurrent laryngeal nerve. The dissection is completed by transsection of the insertion of the strap muscles and sternomastoid muscle and high ligation and division of the internal jugular vein.

Sternal Goiter

Most substernal goiters can be excised by the cervical approach. Furthermore, since the arterial blood supply to the substernal goiter arises in the neck, the cervical approach provides ready access for controlling the arteries. Bleeding, when it occurs, is likely to be venous because of the tourniquet effect of the enlarged gland on the mediastinal vessels. Prompt delivery of the gland into the neck, by relieving the tourniquet effect, allows the veins to collapse and the bleeding to stop. In the majority of instances, the gland can be delivered into the neck by freeing it from the pleura and surrounding mediastinal structures by gentle finger dissection. If difficulty is encountered in delivering a noncancerous goiter into the neck, the contents of the gland are evacuated, after incising the capsule to decrease its size and facilitate its delivery into the neck. A transsternal approach is rarely required.

Transsternal Approach

For removing malignant lymph nodes in the mediastinum and for removing substernal goiters not amenable to the cervical approach, anterosuperior mediastinal exposure is indicated. From the collar incision, a vertical midline incision is made to the level of the fourth costal cartilage. Pectoral muscle attachment to the sternum is freed by subperiosteal elevation. The intercostal muscles in the third space are divided and separated on either side of the sternum. The sternum is transsected at this level and then divided in the midline resulting in an inverted T-shaped incision. Lateral retraction of the sternum exposes the structures in the anterior mediastinum for dissection. The sternum, after completion of the dissection, is approximated with stainless steel wire which is passed through drill holes in the bone.

Postoperative Complications and Their Management

The complications of thyroid surgery can be discussed in relation to the wound, hemorrhage, respiratory difficulty, nerve injury, thyroid storm, recurrent hyperthyroidism, hypothyroidism, and hypoparathyroidism.

Wound Complications

These include edema of the flaps, seroma, hematoma, and infection. Edema is often self-limiting and aspiration relieves seroma. Wound infection is usually the result of a concomitant tracheostomy. Adequate drainage and administration of antibiotics help in clearing the infection.

Hemorrhage

Immediate or delayed hemorrhage can occur. The former, a serious complication, should be recognized promptly. Immediate hemorrhage usually occurs in the early postoperative period especially during extubation. The hemorrhage may be either arterial or venous in origin. During coughing, sneezing, vomiting, or straining, insecure venous ligatures can slip secondary to increased venous pressure and profuse bleeding can occur from even small vessels. Profuse hemorrhage may manifest several hours after the operation as a swelling of the neck or stridor. In either instances, it is important to open the wound to the level of the trachea to relieve compression and to insert an endotracheal tube to provide an adequate airway. The wound is explored, preferably under general anesthesia, to secure hemostasis.

Delayed bleeding, which occurs 2-3 days following operation, is due to slow oozing from small vessels. The neck swells and the patient complains of a feeling of tightness. Respiratory difficulty usually is not present. Blood and serum are evacuated by aspiration through a large bore needle or by opening the wound.

Respiratory Obstruction

Laryngeal spasm, edema, hemorrhage, and vocal cord paralysis produce respiratory obstruction. Hypothyroid patients are particularly vulnerable. In them, the already narrowed airway can be readily compromised as the marging of safety between an adequate and inadequate airway is small. Adequate air exchange is provided by either endotracheal intubation or tracheostomy.

Nerve Injury

Stretching, suturing, severing, and crushing can damage both the superior and the recurrent laryngeal nerves or their branches.

Unless complicated by laryngeal edema and the resulting respiratory difficulty, unilateral vocal cord paralysis in the immediate postoperative period may remain unnoticed. Bilateral vocal cord paralysis results in stridor and poses a threat to the patient's life by asphyxiation. Prompt restoration of air exchange is necessary for survival. Paradoxically, the voice remains normal, since the vocal cords occupy a median or paramedian position. Presence of a normal voice could mislead one into discarding the possibility of bilateral nerve injury. Lesser degrees of paralysis result in a monotone quality to the voice; sentences are hurried and interrupted by inspiratory pauses to fill the lung with sufficient air for continuation of speech. Laughter and cough are suppressed to minimize air loss. Suppression of cough, in the immediate postoperative period, predisposes the patient to the development

of pulmonary complications. In patients developing respiratory difficulty or stridor several years following thyroidectomy, hypothyroidism and myxedematous infiltration of the vocal cord should be suspected.

Primary repair of the injured nerve has been noted to provide the best result in experimental dogs. Therefore, when nerve injury is diagnosed, the neck is explored to repair the damaged nerve. Three options are to be considered if the nerve function fails to return following primary repair. These include: a valved tracheostomy tube, arytenoidectomy, and nerve-muscle pedicle innervation. While the permanent use of a valved tracheostomy assures a near normal voice and obviates the need for additional operative procedures, the success depends upon the patient, who should be willing to care for a tracheostomy tube and tolerate the associated problems. Arytenoidectomy provides an adequate airway but changes the voice. In the nerve-muscle pedicle innervation operation, the posterior cricoarytenoid muscle is innervated to provide abductor function. Innervation is provided by a branch of the ansa hypoglossi nerve supplying the anterior belly of the omohyoid muscle. Good results with this procedure are reported in patients free from ankylosis of the cricoarytenoid articulation.

Unilateral Recurrent Laryngeal Nerve Paralysis

Although not life threatening, unilateral nerve injury produces varying degrees of incapacity. Since the affected cord remains flaccid, adequate closure of the glottis is not achieved during swallowing, phonation, and coughing. Lack of glottic closure results in ineffective cough, rendering eradication of pulmonary complications difficult. The glottic closure can be improved by rendering the paralyzed cord firm by injecting it with glycerin, Gelfoam paste, or Polytef. The effect of glycerin injection lasts for 2-3 days and that of Gelfoam paste 6-10 weeks. The effect of Polytef injection is permanent.

Superior Laryngeal Nerve Injury

The internal branch is rarely injured. The external branch may be injured on one or both sides, along with the recurrent laryngeal nerve and in various combinations. In unilateral nerve injury, the damage is often overlooked and at rest, the larynx appears normal but becomes asymmetric during phonation. Bilateral injury may be missed unless tensing of the vocal cords is looked for during phonation. Excess leakage of air during phonation produces a low-pitched, poorly controlled voice.

Isolated superior laryngeal nerve paralysis need not be treated since it is often adequately compensated. In patients with problems of phonation, Teflon injection has been found helpful.

Thyroid Storm

Once a fairly common complication, thyroid storm is rarely seen since the introduction of antithyroid drugs in the management of thyrotoxic patients. "Thyroid storm" refers to a life-threatening exacerbation of all the metabolic features of thyrotoxicosis. Fever, which is not a feature of uncomplicated thyrotoxicosis, is pathognomonic of thyroid storm. Until proved to the contrary, thyroid storm should be suspected in thyrotoxic patients with a temperature higher than 100°F.

The prognosis depends on how soon the treatment is instituted; the sooner thre treatment, the better the prognosis. Therefore, treatment should be begun at the earliest suggestion without waiting for the overt signs to develop.

Soidium iodide, the first drug used effectively in the management of thyroid storm, is given in combination with other agents. It is no longer relied upon as the sole agent for the management of this complication. Propylthyouracil is administered in large doses. By its administration, synthesis of thyroid hormone as well as peripheral conversion of thyroxine (T4) to the more potent triiodothyroxine (T3) are blocked. The peripheral effects of thyroid hormone are blocked by administering sympatholytic agents such as propranolol. A beta-adrenergic blocking agent, propranolol, following oral administration, exerts its effect in 4-6 hours. Where immediate response is desired, the drug can be given intravenously with closxe cardiac monitoring. Although the mechanism of action is not yet clear, cortisone has been found to be highly effective.

In addition to the above specific measures, supportive measures are instituted including ice packs or cooling blanket to decrease body temperature; administration of fluids and electrolytes, sedatives, oxygen, and multivitamins. Salicylates, because of their ability to facilitate conversion of T4 to the more potent T3, are contraindicated.

Hypothyroidism and Hyperthyroidism

Exogenous thyroid hormone is administered to treat hypothyroidism resulting from excision of excessive amount of the gland. Insufficient excision of the gland results in persistent hyperthyroidism. To avoid the risk of reexploration, radioactive iodine is the preferred method of treating recurrent or persistent hyperthyroidism.

Hypoparathyroidism

Inadvertent removal of the parathyroid glands or damage to their blood supply leads to hypocalcemia, which may be latent, transient, or permanent. Latent hypoparathyroidism, which may persist for years, may not become evident until calcium-lowering drugs, such as furosemide and steroids, are administered or metabolic demand for calcium is increased as in pregnancy.

The symptoms of hypoparathyroidism are due to decreased ionized serum calcium and resulting neuromuscular excitability. The level of calcium, as well as the rate of fall in serum calcium, determine whether a patient does or does not develop symptoms. The symproms include paresthesia of the limbs and perioral tissues. Laryngeal stridor, rarely convulsions, can occur with severe hypocalcemia. Facial muscle irritability and carpopedal spasms may occur spontaneously, or be demonstrated by tapping the branches of the facial nerve (Chvostek's sign) and by occlusion of the blood supply to the upper extremity with a tourniquet (Trousseau's sign). Weakness, fatigue, numbness, tingling, emotional instability, anxiety, depression, and delusions are features of chronic hypocalcemia. The convulsions of hypocalcemia should be differentiated from epilepsy. Other sequelae of chronic hypocalcemia include lenticular opacity and dystrophic changes in the skin and its appendages.

Calcium gluconate, when administered intravenously, promptly restores the serum calcium level and alleviates symptoms of hypocalcemia. The injections are repeated as often as needed to maintain the serum calcium level at 8 mg/dL. For correction of persistent hypocalcemia, oral vitamin D, or its more potent analogues, and calcium are administered. The chance of the occurrence of tetany is decreased by lowering the serum phosphorus level by the exclusion of foods rich in phosphorus such as chocolate and dairy products. Aluminum hydroxide gel, which binds dietary phosphorus and thereby prevents its absorption through the gut, is helpful in further lowering serum phosphorus. The calcium level in serum should be closely monitored for a prolonged period to avoid hypercalcemia and its sequelae - hypercalciuria and renal stone formation - resulting from vitamin D intoxication.

The Parathyroid Glands

Hyperparathyroidism, the most frequent parathyroid disorder requiring surgical treatment, results from both hyperplasia and neoplasia of the thyroid glands. The former may be either sporadic or familial, or may occur as a component of the syndrome of multipe endocrine adenomatosis. Adenoma and carcinoma constitute the neoplastic lesions. The incidence of hyperplasia and adenoma varies widely from series to series because of the difficulty in their histologic differentiation. The reported incidence of carcinoma ranges from 0.6-4%.

Hyperparathyroidism may be primary or secondary. In primary hyperparathyroidism, idiopathic disruption of the normal feedback mechanism regulating parathormone secretion results in inappropriately high parathormone secretion for the serum calcium level. On the contrary, in secondary hyperparathyroidism, an increased amount of parathormone is secreted to compensate for the decreased serum calcium level which occurs in chronic renal disease, hypovitaminosis D, vitamin D-dependent rickets, calcium malabsorption, hyperphosphatemia, and renal tubular acidosis. Hypersecretion of the parathormone usually subsides once the causative factor has been eliminated. However, after being stimulated for a long period, the glands may fail to revert to normal function and continue to secrete parathormone inappropriate to the calcium level. This situation is termed tertiary hyperparathyroidism. Pseudohyperparathyroidism refers to the hyperparathyroid state resulting from the secretion of parathormone or parathormonelike substance by a variety of nonparathyroid tumors.

In recent years, the most frequent presentation of hyperparathyroidism has been the finding of an elevated serum calcium level on a routine examination using the multiphasic channel analysis. Therefore, in the differential diagnosis, other conditions causing hypercalcemia should be considered.

These include:

Sarcoidosis

Hypercalcemia presumably is due to increased absorption of calcium from the gastrointestinal tract secondary to exaggerated sensitivity to vitamin D. The diagnosis often is made by findings on chest x-ray, lymph node biopsy, and a normal serum parathormone level.

Multiple Myeloma

An elevated serum calcium level is present in about 40% of the patients. X-ray examination of bones, bone marrow examination, and serum electrophoresis aid in establishing the diagnosis.

Vitamin D Intoxication

Prolonged excessive ingestion of vitamin D results in an elevated serum calcium from increased bone resorption and enhanced gastrointestinal absorption. A careful history provides the diagnostic clue.

Milk-Alkali Syndrome

This is a complication resulting from ingestion of calcium containing absorbable antacids and milk for the treatment of peptic ulcer. This condition has become less prevalent since nonabsorbable antacids are used more frequently than in the past. The history will provide a diagnostic clue and, when cessation of ingesting milk and absorbable antacids brings down the serum calcium level, the diagnosis is confirmed.

Immobilization

Prolonged immobilization results in loss of calcium from bone and when the rate of bone resorption exceeds the ability of the kidneys to excrete calcium, hypercalcemia results.

Thyrotoxicosis

Marked hypercalcemia is rare and probably is due to increased bone resorption. Thyroid function studies confirm the diagnosis.

Adrenal Insufficiency

The cause of hypercalcemia is not known.

The diagnosis of primary hyperparathyroidism is established by excluding other causes of hypercalcemia, including malignancy, and by finding an elevated serum calcium level in association with an elevated parathormone level. Increased urinary cyclic adenosine monophosphate confirms the presence of parathormone effect, but not necessarily primary hyperparathyroidism.

The presenting features of primary hyperparathyroidism are related to hypercalcemia and the effect of parathormone on bones. Symptoms resulting from hypercalcemia are by no means unique to hyperparathyroidism and include renal stones, nephrocalcinosis, depression, easy fatigability, peptic ulcer, pancreatitis, constipation, and mental changes. Increased calcium in the urine results in polyuria and polydipsia. Band keratitis and calcium deposits in palpebral tissue may be present. Bone pain, bone cysts, and pathologic fractures result from bone resporption.

Surgical Management

In recent years, because of the ready availability of multiphasic serum analysis, primary hyperparathyroidism is diagnosed with increasing frequency in asymptomatic patiens. Such early diagnosis poses questions: what is the natural course of the disease in this group of patients, and should they be operated upon? There are no definite answers. A prospective study of such patients at the Mayo Clinic revealed that 20% required operation within 5 years because of the development of symptoms and another 20% were lost to follow-up. Based on their experience, the Mayo clinic group recommends surgical treatment in asymptomatic patients, unless the risk of operation is excesssive because of the presence of concomitant medical disorders.

The aim of surgical treatment is to remove all abnormal parathyroid tissue and to conserve enough of the tissue to maintain euparathyroid status. While the aim is defined, execution poses problems because of the variable number and location of the glands, their small size, and the lack of accurate histologic criteria to differentiate normal from abnormal glands and hyperplasia from neoplasia.

Number and Position of the Glands

Normally, four glands are present. A decrease or increase in their numbers can result from fusion and fission of the developing anlage. Two glands were present in 0.2%, three glands in 6.1%, four glands in 87%, five glands in 6%, and six glands in 0.5% of autopsy studies conducted by Gilmour.

The superior parathyroid glands develop from the fourth branchial pouches and the inferior parathyroids from the third. Because of their greater descent, the position of the inferior parathyroids is more variable. The gland may be located in close proximity to the thymus, pericardium, or heart. A superior gland, when it fails to descend to its normal position, will be located high in the neck near the hyoid bone. In addition to their variable locations related to embryologic development, an enlarged gland may shift its position because of its weight and the influence of negative intrathoracic pressure. An enlarged parathyroid gland may be located anywhere betweem the hyoid bone and the mediastinum. It may be present within the thyroid gland, behind the esophagus, in the anterior or posterior mediastinum, between the trachea and esophagus, or within the carotid sheath.

Gross and Microscopic Features

The average gland, which weighs approximately 35 mg, may be oval, round, irregular, or flattened, and has a characteristic tan brown color.

In addition to parathyroid tissue, the gland contains adipose tissue, which increases with age. The differentiation between a normal and an abnormal gland and between hyperplasia and neoplasia is not always easy on microscopic examination. The diagnosis of adenoma is favored in the presence of uniglandular enlargement and that of hyperplasia with multiglandular enlargement. The diagnosis is further complicated by the presence of microscopic hyperplasia in normal-sized glands and, conversely, by the abscence of abnormal microscopic features in enlarged glands. Wang and Rieder have described an intraoperative

density test for differentiating a normal from an abnormal gland. They have observed that abnormal parathyroid tissue sinks in mannitol solution within the density range of 1.049-1.069, whereas normal parathyroid tissue floats. The diagnosis of adenoma is made when tissue from one gland sinks, while tissue from another floats, indicating uniglandular involvement. When tissue from both glands sink the diagnosis of hyperplasia is made, on the assumption that glandular involvement is generalized.

Localization Studies

Preoperative knowledge of the location of the glands in any patient undergoing neck exploration is of obvious advantage to the surgeon. Unfortunately, a safe, reliable, noninvasive, and cost-effective test is not available for localizing the glands.

A clue to the location of an abnormal gland may be obtained by a mass seen in the mediastinum in a chest x-ray or by extrinsic compression of the barium column in an esophagogram. Scanning of the gland, using radioactive selenomethionine, has not proved helpful. Sonography and computed tomography have had limited trials and need to be further evaluated. Catheterization of neck veins, and parathormone assay on blood drawn at different sites, is helpful in localizing the abnormal gland. Selective angiography can aid in locating the abnormal gland, but is less dependable than venous catheterization and parathormone assay of venous blood. Both these tests - selective angiography and venous catheterization - are not without complications. Hemiplegia and paraplegia have been reported to occur following angiography. In addition, these tests are not uniformly successful, they require trained personnel for their performance, and are not cost effective. These studies, therefore, are reserved for patients requiring reexploration following a cervical exploration which was unsuccessful in locating the abnormal gland.

Intraoperative location of the gland has been attempted by intravenous injection of methylene blue. The recommended dose is 5 mg/kg of body weight diluted in 250-500 mL of a crystalloid solution. The concomitant staining of thyroid tissue by the dye has hindered its usefulness.

Operative Strategy

Unless the neck exploration is carried out in a systematic, unhurried manner with meticulous attention to avoid staining of tissues with blood, identification of the glands become difficult, if not impossible.

Opinions vary as to the extent of neck exploration and glandular resection that has to be performed. Wang and Rieder recommend removal of an enlarged gland and termination of the operation if another ipsilateral gland is normal. On the other extreme, Paloyan et al have recommended near-total parathyroidectomy. Evidence indicates that the more radical approach of Paloyan, while increasing the incidence of hypoparathyroidism, does not increase the cure rate.

A reasonable approach is to explore both sides of the neck and to visually identify all four parathyroid glands. Biopsy of the gland is resorted to if doubt exists as to its nature. While taking the biopsy, care should be taken to avoid injuring the blood supply of the gland.

In instances of uniglandular enlargement excision of the involved gland, and in instances of multiglandular enlargement excision of three and one-half glands (subtotal parathyroidectomy), have given satisfactory results in controlling hypercalcemia. In patients with familial hyperparathyroidism and multiple endocrine adenomatosis, subtotal parathyroidectomy is the procedure of choice even though only one gland is enlarged, because of the high incidence of recurrence with resection of a lesser extent.

While performing subtotal parathyroidectomy, it is important to transect the gland that is to be retained before removal of the other glands. This precaution provides opportunity to leave a vascularized remnant of another gland if the earlier transected gland becomes devascularized. Unless this precaution is taken, the patient may become permanently hypoparathyroid. In the presence of a hard greyish mass, carcinoma should be suspected, and the gland with its surrounding structures is widely excised to avoid capsular disruption and spillage of cells. Recurrence can occur with spillage of the malignant cells.

Failure of visualization of one or more glands may pose problems. If an abnormal gland is found and the other glands visualized are normal, exploration is terminated after a reasonable search, since the chance of cure is high. Under these circumstances, extensive search is ill-advised because of the risk of devascularizing normal parathyroid tissue and injuring the recurrent laryngeal nerve. If all the four visualized glands are normal, a search should be made for a supernumerary gland. When only three normal glands are visualized, the fourth missing gland should be diligently searched out. The missing gland may be located high in the neck at the level of the hyoid bone, in the mediastinum, inside the thyroid gland, in the carotid sheath, or in the retroesophageal or retrotracheal space.

The relationship of the recurrent laryngeal nerve to the parathyroid gland is of help in choosing the areas to be explored for the missing gland. The superior gland is likely to be in the posterior mediastinum posterior to the nerve and the inferior gland in the anterior mediastinum anterior to the nerve. When the inferior gland is missing, the thymus is removed through the cervical approach, and if still not found within the thymus, an ipsilateral hemithyroidectomy is performed to remove a possible intrathyroid gland. If still not found, the retrotracheal, retroesophageal areas, and the carotid sheaths are explored. Every attempt should be made to locate the missing gland during the first exploration since subsequent exploration is technically more difficult and hazardous.

When the missing gland is not detected following a careful thorough neck exploration, the operation is terminated. Some patients are cured presumably by destruction of the blood supply to the abnormal gland during neck exploration. Those with persistent hypercalcemia are restudied to confirm the diagnosis and to localize the missing gland. Mediastinal exploration will be required in about 55% of the cases. Interestingly, a majority of the missing glands are found in the neck at reexploration.

Secondary Hyperparathyroidism

The number of patients with secondary hyperparathyroidism has increased as a result of the reduction in mortality from chronic renal failure by effective dialysis, improved medical management, and increasing success with renal transplantation.

Maintenance of normal serum calcium and phosphorus levels is aimed for to prevent parathyroid stimulation and development of secondary hyperparathyroidism. Skeletal and extraskeletal complications are minimized by maintaining normal levels of serum calcium and phosphorus. A decrease in the dietary intake of phosphorus is essential to prevent hyperphosphatemia. Further reduction in the serum phosphorus level is achieved by preventing absorption of phosphorus in the gut by binding dietary phosphorus with aluminium hydroxide or carbonate. Administration of calcium supplements, vitamin D, or its more potent analogues, help in elevating the serum calcium level. Despite these measures, renal osteodystrophy may progress in some patients necessitating parathyroidectomy to treat bone pain, pathologic fractures, intractable pruritus, and extraskeletal calcification. The procedure of choice in such patients is subtotal parathyroidectomy or total parathyroidectomy with autotransplantation of parathyroid tissue into a forearm muscle.

Total Parathyroidectomy, Heterotopic Autoimplantation, and Cryopreservation

Parathyroid tissue, both in experimental and clinical studies, has been successfully implanted into muscle. In those instances where the recurrence is high following subtotal parathyroidectomy, to avoid the risks of cervical reexploration, total parathyroidectomy and autoimplantation into a forearm muscle are resorted to. Following autoimplantation into a forearm muscle, if hyperparathyroidism recurs, the problem is easily dealt with by excising portions of the implanted parathyroid tissue under local anesthesia. Indications for this procedure include renal osteodystrophy in patients who are not candidates for renal transplantation, multiple endocrine adenomatosis, and familial parathyroid hyperplasia. There is risk of rendering a patient hypoparathyroid, who had total parathyroidectomy and autoimplantation, if the implant fails to survive. Preservation of the excised parathyroid tissue provides material for subsequent reimplantation, if the need arises. It has been demonstrated that parathyroid tissue frozen in dimethyl sulfoxide and autologous serum remains viable as long as 9 months.

Hypoparathyroidism

Primary hypoparathyroidism is a rare diseae. Hypoparathyroidism is, in almost all instances, secondary to thyroidectomy and is discussed under complications of thyroidectomy.