Chapter 36
THYROID AND PARATHYROID

THYROID

Anatomy

Gross Normal adult thyroid gland weighs 15–20 g. It consists of two lateral lobes that extend along the sides of trachea to the level of the middle thyroid cartilage and is connected centrally by an isthmus. A pyramidal lobe is present in 80 percent; it extends left of the midline upward from the isthmus along the anterior surface of the thyroid cartilage. It is a remnant of embryonic thyroglossal duct. Four parathyroid glands are found on the posterolateral surface of the lobes. Arterial supply is superior from the external carotid and inferior from the thyrocervical trunk of the subclavian arteries.

Microscopic The thyroid is divided into lobes that contain 20–40 follicles, which are spherical and average 30 μm in diameter. Follicles contain a central store of colloid secreted from epithelial cells that are influenced by thyroid-stimulating hormone (TSH). C cells or parafollicular cells contain and secrete the hormone calcitonin; they are part of the amine-containing precursor uptake decarboxylase (APUD) series.

Recurrent Laryngeal Nerves These originate in the vagus nerves; on the right, the recurrent nerve loops under the subclavian artery to ascend obliquely and enter the larynx at the level of the cricoid cartilage. On the left, it loops posteriorly around the ligamentum arteriosus and ascends medially in the tracheoesophageal groove to enter the larynx. The right recurrent nerve is in the tracheoesophageal groove in 64 percent of people and in the left in 77 percent; it is lateral to the trachea on the right in 28 percent and on the left in 17 percent. Rarely, it is anterolateral to the trachea (right 8 percent and left 6 percent). The recurrent nerves run behind the inferior thyroid artery in 53 percent on the right and 69 percent on the left; in others it is anterior to the artery on the right in 37 percent and on the left in 24 percent and between the branches of the

P.784

artery on the right in 7 percent and on the left in 6 percent. In 1 percent is it nonrecurrent almost always on the right because of a vascular anomaly of the right subclavian artery; when on the left, the nerve arises from the vagus to run directly to the larynx close to the superior thyroid vessels and can be at risk when these vessels are transected. Injury to nerves results in vocal cord paralysis.

Superior Laryngeal Nerve Most often the nerve is in close proximity to the superior pole vessels; it can be at significant risk if not identified at operation. To avoid injury, the superior pole vessels should be individually ligated and divided low on the thyroid gland and dissected laterally to the cricothyroid muscle.

Anomalies

The median thyroid anlage can fail to develop, resulting in athyreosis, or it may fail to descend, resulting in lingual thyroid, and this occurs more often in females. It can present as a mass in the region of foramen cecum at the base of the tongue; if it enlarges, it can cause dysphagia, dysphonia, or dyspnea. Treatment should be suppression with thyroxine or ablation with radioactive iodine. Surgery is indicated for hemorrhage, degeneration, and necrosis or threatened airway.

Physiology

Through release of thyroxine (T_4) and triiodothyronine (T_3), the thyroid gland influences the metabolic rate of all tissues. Release of T_4 and T_3 is stimulated by the TSH, which can be suppressed by T_4 and T_3. TSH is also stimulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH). Increased secretion in thyroid hormone increases metabolic rate; the rate decreases when secretion is decreased. Calcitonin is produced by C cells. It has use in the treatment of hypercalcemia and Paget's disease of bone and as a tumor marker for medullary carcinoma.

Iodine Metabolism Formation of thyroid hormones depends on exogenous iodine, which is found in dietary sources. It is rapidly converted to iodides in the gut and distributed into extracellular space; it is then concentrated in the thyroid (90 percent) or excreted in urine.

Hormone Synthesis Steps in the synthesis are

1. Active transport of iodine from plasma into thyroid cells, gradient 50:1 or more. Influenced by TSH inversely with glandular iodine content.

P.785

2. Rapid oxidation of iodides to iodine.

3. Tyrosine radicals iodinated to 3-monoiodotyrosine (MIT) and 3–5-diiodotyrosine (DIT). TSH-sensitive.

4. Coupling to form hormonally active iodothyronines; T_4 from two DIT molecules and T_3 from one DIT and one MIT molecule.

Storage, Secretion, and Metabolism of Thyroid Hormone T_4 and T_3 are bound to thyroglobulin and stored in the colloid of the thyroid follicles. Release of active hormones is by endocytosis; hydrolysis results in production of all component parts. Through deiodination, most iodide is released and reused in the follicle; the iodothyronines are secreted. The steps are TSH-dependent.

Active thyroid hormones circulate in plasma attached to plasma proteins: thyroid hormone–binding globulin (TBG), thyroid hormone–binding prealbumin (TBPA), and albumin. T_4:T_3 ratio is 10–20:1. T_3 is three to four times more active than T_4 and has a half-life of 3 days. T_4 has a half-life of 7–8 days.

Regulation of Thyroid Activity TRH is produced by the hypothalamus and stimulates anterior pituitary cells to secrete TSH, which in turn stimulates all processes leading to synthesis of thyroid hormone. TSH regulation is the direct feedback exerted on the pituitary

by the level of thyroid hormone in the blood.

Assessment of Patients with Thyroid Disease

History There are two types of thyroid disease: problems relating to function (hyperthyroidism/hypothyroidism) and thyroid masses. Symptoms such as dysphagia, dysphonia, dyspnea, or a choking sensation are frequent. Pain is uncommon, but localized pain may suggest malignancy; pain radiating to the arm is suggestive of thyroiditis or hemorrhage within the thyroid gland. Change in the character of the voice may suggest involvement of the recurrent laryngeal nerves. Past exposure to radiation, family history of thyroid disease, and iodine deficiency or ingestion of goitrogenic drugs are significant.

Examination Most masses are visible. Look for retrosternal goiter arising from beneath the sternum and clavicles. Palpation of a seated patient is usually from the back with the neck slightly extended; palpate for size and consistency and regional lymph nodes. Listen for a bruit.

Fine-Needle Aspiration Cytology (FNAC) Slides are made from cellular material aspirated from a nodule with a 23-gauge needle.

P.786

Skilled cytopathologists can accurately diagnose most thyroid diseases. This is less accurate for patients with thyroid nodules, familial nonmedullary thyroid cancer, or exposure to low-dose therapeutic radiation.

Thyroid Function Tests Normal values are

	Serum TSH	0.15–4.2 mIU/L
	Total T_4	55–150 nmol/L
	Free T_4	12–28 pmol/L
	Total T_3	1.5–3.5 nmol/L
	Free T_3	3–9 pmol/L

Thyrotoxicosis

Thyrotoxicosis results when excessive levels of active thyroid hormone are secreted. There are two predominate causes: Graves' disease (diffuse toxic goiter) and toxic solitary or multinodular goiter (Plummer's disease).

GRAVES' DISEASE

This is an autoimmune disease; thyroid-stimulating antibodies are directed at TSH receptors on follicular cells. This stimulates the receptors and results in excess thyroid hormone production.

Macroscopically, the thyroid gland is diffuse and smoothly enlarged with increased vascularity. Microscopically, it is hyperplastic with columnar epithelium and minimal colloid.

Clinical Features Common to All Forms of Thyrotoxicosis *Symptoms* There are manifestations of increased caloric turnover, heat intolerance, thirst, sweating, weight loss despite adequate intake, amenorrhea, tachycardia or atrial fibrillation, and congestive heart failure (CHF). Adrenergic stimuli may include fatigue, agitation and excitability, disturbed sleep pattern, emotional lability, hyperkinesis, tremor, and diarrhea. Patients with extreme involvement may exhibit psychosis.

Physical Examination The examination may disclose weight loss, flushing, warm and moist skin, inappropriate sweating, tachycardia, widening of pulse pressure, fine tremor, muscle wasting, and hyperactive tendon reflexes.

The Graves' disease triad is goiter including the pyramidal lobe, thyrotoxicosis, and exophthalmos. Patients may have pretibial myxedema, gynecomastia, or an audible bruit over the gland. Eye signs include (1) spasm of the upper lid with retraction and lid lag,

P.787

(2) external ophthalmoplegia, (3) exophthalmos with proptosis, (4) supraorbital and infraorbital swelling, and (5) congestion and edema.

Autonomous thyroid function is characterized by decreased or undetectable levels of TSH, elevated circulating T_3/T_4 levels, or raised levels of circulating thyroid autoantibodies. Radioactive iodine (RAI) scan shows diffuse uptake through the gland of 45–90 percent.

Treatment of Graves' Disease *Antithyroid Drugs* Beta blockers (propranolol) are used to alleviate peripheral adrenergic effects. Main antithyroid drugs are propylthiouracil (PTU) and methimazole (Tapazole), which inhibit organic binding of iodine and the coupling of iodotyrosines. They have no effect on the underlying cause of the disease. T_4/T_3 levels help in assessing response to treatment. It is hoped that natural remission will occur after the patient is rendered euthyroid. The relapse rate is 50 percent after 12–18 months; recurrent hyperthyroidism requires definitive treatment with RAI or surgery.

Radioactive Iodine Therapy (^{131}I) Most patients in the United States undergo radioiodine treatment. Patients should be euthyroid and have stopped all antithyroid drugs 2–3 weeks before treatment. The initial dose of ^{131}I is about 8500 cGy; 20 percent require a second dose. Patients under age 35 usually are treated with thyroidectomy and older patients with ^{131}I. It is contraindicated in pregnant or nursing females. Complications of ^{131}I therapy include exacerbation of thyrotoxicosis with arrhythmias, overt thyroid storm, hypothyroidism, increased ophthalmopathy, and hyperparathyroidism.

Surgery Surgery is advised when RAI is contraindicated. It is preferred for young patients with severe thyrotoxicosis and large goiters. Toxic adenoma should be excised. Patients should be euthyroid with antithyroid drugs continued to the day of surgery or Lugol's iodine

solution 3 drops bid for 10 days preoperatively. Some prefer 5–7-day preparation with propranolol. Iodine reduces the vascularity of the gland.

Advantages of thyroidectomy are immediate cure, decreased long-term incidence of hypothyroidism, simultaneous removal of coexisting carcinomas, and possible relief of ophthalmopathy. The disadvantages are recurrent laryngeal nerve injury (1 percent) and hypoparathyroidism (transient 13 percent, permanent 1 percent).

TOXIC MULTINODULAR GOITER

Also known as *Plummer's disease,* this is the result of one or more thyroid nodules trapping and organifying more iodine and secreting

more thyroid hormone independent of TSH control. Hyperthyroidism is milder than Graves' disease and without extrathyroidal manifestations of ophthalmopathy. Antithyroid antibodies usually are absent. ^{131}I uptake is localized to autonomous toxic nodules, and the remaining thyroid tissue is suppressed. Surgical excision is the preferred treatment.

THYROID STORM

This is life-threatening, but it is rare during surgery. It usually is precipitated by infection, labor, administration of iodine, or after ^{131}I treatment. Symptoms are similar to those of severe thyrotoxicosis with profound tachycardia, fever, confusion, dehydration from nausea, vomiting, and fever, and eventual coma. The best management is prevention. Patients should be euthyroid before operation. The acute phase is managed with fluid replacement, antithyroid drugs, beta blockers, sodium iodate solution, steroids, and a cooling blanket.

Hypothyroidism

This occurs because of a deficiency in the circulating levels of thyroid hormone. It is cretinism in neonates and is characterized by neurologic impairment and mental retardation. Early treatment lessens the neurologic deficits. It may be associated Pendred's syndrome and Turner's syndrome. Juvenile hypothyroidism appears at a younger age and can result in abdominal distention, umbilical hernia, and rectal prolapse. In adults, symptoms are insidious, and patients may be unaware. Principal causes in the United States are autoimmune thyroiditis and iatrogenic (e.g., thyroidectomy, RAI treatment, or medications).

Clinical Manifestations Hypothyroidism secondary to autoimmune thyroiditis is more common in females (80 percent). In adults, symptoms are nonspecific: tiredness, weight gain, cold intolerance, constipation, and menorrhagia. Severe hypothyroidism (*myxedema*) is characterized by facial and periorbital puffiness, rough, dry, yellow-tinged skin, hair loss with the remainder dry and brittle, and slowed speech. Other indications include an enlarged tongue, dementia, bradycardia, cardiomegaly, and pericardial or pleural effusions.

Laboratory Findings Low circulating T_4 and T_3 levels with raised TSH levels are evidenced in primary failure, in secondary (pituitary) failure, TSH levels are low. Thyroid

autoantibodies may be present. Other findings are anemia and flattened T waves.

P.789

Treatment Thyroxine is given in doses of 50–200 µg/day. The dosage is titrated against TSH levels. For severe disease in the elderly, the dose is started lower and increased slowly. Myxedema coma requires emergency treatment with large doses of intravenous thyroxine.

Thyroiditis

HASHIMOTO'S DISEASE

This is an autoimmune disease; it is more common at ages 30–60 years; the female-to-male ratio is 10:1. It can be familial and is autosomal dominant.

Pathology The gland is firm, granular, and mildly enlarged, and the enlargement is symmetric. There is follicular and Hürthle cell hyperplasia with lymphocyte and plasma cell infiltration and formation of lymphoid follicles. Epithelial cell degeneration and fragmentation of the basement membrane occur. It can lead to fibrosis.

Clinical Manifestations Twenty percent present with hypothyroidism, and a few present with hyperthyroidism. Most are euthyroid. Common symptom is tightness in the throat with painless, nontender enlargement of the thyroid gland.

Diagnostic Findings Tests are biphasic with early signs of hyperfunction, later hypofunction, and then normalization. Diagnosis is confirmed by circulating antithyroid antibodies. FNAC may confirm the diagnosis or document cancer.

Treatment This disorder is best treated with thyroid hormone for goiter and long-term monitoring of TSH. Surgery is indicated for obstructive symptoms or cosmesis for a markedly enlarged gland.

SUBACUTE THYROIDITIS (DEQUERVAIN'S THYROIDITIS)

This is granulomatous or giant cell thyroiditis, an uncommon acute inflammatory disease that might be precipitated by viral infection. Patients present with fever, malaise, and unilateral or bilateral thyroid pain; they may have a recent history of upper respiratory tract infection. The gland is tender and firm, with one or both lobes enlarged.

Acute inflammation and degenerative follicles with giant cell granulomas may show on FNAC. Laboratory findings indicate an elevated erythrocyte sedimentation rate (ESR) with neutrophilia; also, there usually are elevated thyroid function tests. RAI uptake is low.

P.790

Treatment Nonsteroidal anti-inflammatory drugs (NSAIDS) are used for pain relief, and beta blockers are used for thyrotoxicosis. In more severe cases it may be necessary to prescribe steroids for short periods. The disease usually lasts 1–6 weeks and resolves spontaneously. Some patients can alternate between bouts of exacerbation and remission.

REIDEL'S THYROIDITIS

This is a rare disease characterized by dense, invasive fibrosis that may extend beyond the thyroid capsule and involve surrounding structures. It can lead to hypothyroidism. Symptoms include hoarseness, stridor, and dyspnea. The gland feels woody and is nontender.

Treatment Treatment is with tamoxifen or steroids. Isthmectomy to relieve compressive symptoms or establish diagnosis may be necessary.

ACUTE SUPPURATIVE THYROIDITIS

This is a rare disease of childhood or adolescence and is associated with upper respiratory tract infection. Symptoms are manifest as acute thyroid pain and dysphagia, fever, and occasionally, rigors. Most common bacterial agents are streptococci, staphylococci, and pneumococci. Treatment is with intravenous antibiotics and drainage.

Goiter

Goiter is an enlargement of the thyroid gland in a euthyroid patient.

Familial Goiter Familial goiter is caused by an inherited enzyme defect; it is usually autosomal recessive.

Endemic Goiter This is defined as thyroid enlargement affecting a significant number of people of a particular locale. The most important factor is iodine deficiency and ingestion of goitrogens. Prophylactic iodination in the form of table salt is successful in reducing the incidence.

Sporadic Goiter This is goiter for which no definitive causes can be established.

Pathology The thyroid gland may be diffusely enlarged and smooth or grossly nodular. Early hyperplasia is reversible. Nodules are filled with gelatinous, colloid-rich substance interspersed with normal tissue.

P.791

Clinical Manifestations Most patients are asymptomatic, but patients may present with pressure in the neck and a mass. Dysphagia or tracheal compression occurs with respiratory distress, particularly with substernal extension. Sudden pain with rapid expansion is caused by hemorrhage. The gland may feel soft and diffusely enlarged or may evidence multiple nodules of varying size and firmness. FNAC accurately defines a colloid nodule.

Treatment Diffuse goiter and familial goiter respond to thyroxine. Surgical indications include cosmesis, compressive symptoms, substernal goiter, or malignancy on FNAC.

Solitary or Dominant Thyroid Nodule

Four percent of population have palpable thyroid nodules; 40 per million will be malignant. There are two high-risk groups for cancer. The first group consists of those with a family history of thyroid cancer. Medullary cancer is autosomal dominant (RET point mutation); 6 percent of papillary cancers have family history. The second group consists of those with a

history of low-dose irradiation to the head and neck, which was used to treat "enlarged thymus," tonsils, and acne vulgaris. There is a linear increase in risk from 6.5–2000 cGy. The cancer tends to be papillary and multifocal.

Clinical Manifestations *History* Forty percent of nodules with a history of irradiation are malignant. Important criteria are the time of onset (recent or growing), age and gender (nodule in a child or adolescent or new nodule in male over 40 or a female over 50 is likely to be malignant), rapid enlargement, husky voice (recurrent nerve involvement), and dyspnea or dysphagia (indicating compression).

Physical Examination Most nodules are benign (colloid nodules or adenomas). Fifteen percent of solitary nodules are malignant; those which are firm or hard and fixed are two to three times more likely to be malignant. Lymph node enlargement suggests malignancy.

Diagnostic Studies *Fine-Needle Aspiration for Cytology* This is the procedure of choice for evaluating thyroid nodules. Nodules can be categorized as benign (65 percent), suspicious (15 percent), malignant (5 percent), and nondiagnostic (15 percent). Incidence of false-positive results is 1 percent and false-negative is 5 percent. Ultrasound differentiates solid from cystic and monitors size. Computed tomography (CT) and magnetic resonance imaging (MRI)

P.792

are unnecessary except for very large or substernal lesions. Thyroid isotope scanning indicates functional activity. It is useful only in follicular lesions.

Thyroid function tests usually are not useful. Thyroglobulin levels are used to follow post-total thyroidectomy patients for cancer. Serum calcitonin levels are measured in anyone with a family history of medullary cancer or multiple endocrine neoplasia type II (MEN II). Those who are RET oncogene positive need a 24-h urine collection for determination of vanillylmandelic acid (VMA), metanephrine, and catecholamine levels.

Treatment Colloid nodule is operated on for cosmesis or symptoms. Lesions are measured with ultrasound. A baseline thyroglobulin level is determined, and a repeat FNAC is performed in 6 months if the lesion enlarges. Thyroid lobectomy is indicated for nodules enlarging on suppressive doses of thyroxine, cysts recurrent after three aspirations or complex on ultrasound, or symptoms. Patients who have had previous irradiation should be considered for thyroidectomy.

Malignant Tumors

Tyroid cancer occurs in about 40 per million persons per year; 90–95 percent are differentiated (papillary, follicular, or Hürthle cell), 6 percent are medullary, and of those, 30 percent are familial.

Molecular Basis of Thyroid Tumors Oncogenes contribute directly to tumor genesis. Several oncogenes are involved in thyroid tumor genesis.

PAPILLARY CARCINOMA

Papillary carcinoma is the most common of thyroid cancers (80 percent). There is a 2:1

female-to-male ratio, and the mean age at presentation is 35 years.

Pathology Tumors are hard and whitish. Macroscopic calcification, necrosis, or cystic change may be apparent. Histologically, papillary carcinomas may be pure follicular with intranuclear inclusions or a mixed pattern. Cells are cuboidal with abundant cytoplasm, crowded nuclei and intranuclear cytoplasmic inclusions (Orphan Annie cells), and calcium deposits (psammoma bodies). Bewteen 30 and 87.5 percent are multifocal. Commonly, there is lymphatic spread within the gland and to local nodes, but the tumor may invade adjacent structures (e.g., trachea, esophagus, and recurrent laryngeal nerves).

P.793

Tumors are classified as *minimal or occult* (less than 1 cm and without local invasion or nodal spread), *intrathyroidal* (more than than 1 cm and confined to the thyroid gland), and *extrathyroidal* (locally advanced with invasion into adjacent structures). Other types are tall cell, columnar, Hürthle cell, and poorly differentiated variants that are more aggressive.

Clinical Manifestations Most patients are euthyroid and present with a slowly growing, painless mass in neck. Ipsilateral lymphadenopathy may be present and is most common in children, as are lung metastases.

Prognostic Indicators Prognosis is determined by use of the AGES scale (*a*ge, *g*rade, *e*xtent, and *s*ize), the MACIS scale [*m*etastases, *a*ge at presentation (40 or less), *c*ompleteness of resection, extrathyroidal *i*nvasion, and *s*ize], and DNA ploidy. Distant metastases are most grave. Local invasion increases mortality tenfold.

Surgical Treatment For patients with minimal disease, lobectomy with isthmectomy usually is sufficient. In all others, total or near-total thyroidectomy is preferred, which will manage multifocal disease (4.2–26 percent), decrease the incidence of local recurrence (disease related mortality 30–50 percent), reduce the risk of anaplastic transformation (1 percent in residual disease), and facilitate the diagnosis of unsuspected metastases by radioiodine scanning (metastases identified and ablation with RAI). Lymph node metastases are treated with modified radical neck dissection.

FOLLICULAR CARCINOMA

This represents 10 percent of thyroid cancers; it occurs more often in females at a ratio of 3:1, and the mean age at presentation is 50 years.

Pathology It is usually solitary, and 90 percent are encapsulated. Vascular invasion and hematogenous spread to bone, lung, and liver are more common than lymphatic spread. Histologically, follicles are present; colloid may be absent. Categories include *minimally invasive* and *frankly invasive.*

Clinical Manifestations Usually presents as a solitary nodule and a recent change in long-standing goiter. One percent are hyperfunctioning. Diagnosis is by FNAC.

Surgical Treatment and Prognosis Follicular neoplasm diagnosed on FNAC should undergo lobectomy, including the isthmus

P.794

and pyramidal lobe. Intraoperative frozen sections should be performed when there is

evidence of capsular or vascular invasion. Total thyroidectomy is indicated for carcinoma, except in patients with minimally invasive follicular cancers. Total thyroidectomy enables ^{131}I detection and ablation of metastatic disease. Mortality is 15 percent at 10 years and 30 percent at 20 years, but the long-term prognosis is worse when the age of presentation is over age 50.

HÜRTHLE CELL CARCINOMA

These represent 3 percent of thyroid cancers and are considered by the World Health Organization (WHO) to be a variant of follicular neoplasm. Tumors contain sheets of eosinophilic cells. Tumors possess TSH receptors and produce thyroglobulin. Only 10 percent trap RAI. They often are multifocal and bilateral and are more likely to metastasize to local nodes (25 percent). Hürthle cell neoplasm is diagnosed by FNAC; 20 percent are malignant. Treatment is similar to that of follicular cancer. When malignancy is confirmed on frozen or permanent section, total thyroidectomy with central node dissection is appropriate. With palpable nodes, modified radical neck dissection should be performed and the patient treated with T_4 postoperatively.

MEDULLARY CARCINOMA

These represent 5 percent of thyroid malignancies and arise from C cells or parafollicular cells, which secrete calcitonin. These cells are neuroectodermal and originate from the ultimobranchial bodies and then join the thyroid gland proper and are concentrated mainly in the superior poles laterally. They are part of the APUD complex.

Pathology Tumors are located in the middle to upper poles of the thyroid and are 75 percent unilateral. Familial cases are more likely multicentric with premalignant C-cell hyperplasia; 90 percent are bilateral. Microscopically, sheets of cells are separated by areas of collagen and amyloid; cells may be polyhedral and resemble carcinoid or spindle cells. The tumor spreads to regional nodes in the neck and superior mediastinum and then distally. These tumors stain positively for calcitonin peptide (CGRP), carcinoembryonic antigen (CEA), and histaminase.

Clinical Manifestations Patients usually present with a neck mass; 15–20 percent have palpable nodes. Local pain is more common, and local invasion may produce symptoms of dysphagia, dyspnea, or dysphonia. The female-to-male ratio is 1.5:1. Age at presentation is 50–60 years, except in familial cases, which present at a younger age. Tumors may secrete a variety of peptides. Debilitating diarrhea is a late symptom.

P.795

Diagnosis Diagnosis is established by history, mass on examination, raised serum calcitonin or CEA level, and FNAC. New patients should be screened for RET point mutations and pheochromocytoma.

Medullary thyroid carcinoma (MTC) is sporadic (70 percent) or familial (30 percent), which occurs as MEN IIA and MEN IIB syndrome. *MEN IIA* consists of MTC, pheochromocytoma or medullary hyperplasia, and hyperparathyroidism. C-cell hyperplasia is present in all. Bilateral pheochromocytomas are detectable in 50 percent. Patients may have Hirshsprung's disease and cutaneous amyloidosis.

MEN IIB patients are found with MTC, bilateral pheochromocytomas, and mucosal ganglioneuromas. Patients display a thickened tongue and lips. Marfanoid features, slipped epiphyses, and pectus excavatum also may occur.

Treatment Total thyroidectomy is the treatment of choice because of the high incidence of multicentricity and more aggressive course. More than 60 percent have positive nodes. Neck dissection is necessary if nodes are involved or for tumors larger than 2 cm. Debulking ameliorates APUD effects. Pheochromocytomas should be operated on before thyroidectomy; laparoscopic removal is favored. Abnormal parathyroids are removed; normal parathyroid should be preserved. When a normal parathyroid cannot be maintained on a vascular pedicle, it should be removed and then autotransplanted to the nondominant forearm.

Postoperative Follow-Up and Prognosis Patients should have periodic examinations with levels of serum calcitonin and CEA monitored. For suspected recurrence, CT, MRI of the neck and mediastinum, ultrasound, and selective venous catheterization can be used, as well as hepatic vein and jugular sampling after pentagastrin stimulation. Survival is 80 percent at 10 years and 45 percent with nodal metastases. With positive genetic screening, prophylactic thyroidectomy for C-cell hyperplasia is performed before age 5 years to prevent MTC.

ANAPLASTIC CARCINOMA

This is the most aggressive of thyroid cancers. Few survive 6 months after diagnosis. Most anaplastic carcinomas arise from differentiated cancers during the seventh and eighth decades.

Pathology Growth is extremely rapid. Tumors are unencapsulated with invasion of surrounding tissues. Sheets of cells are seen with marked heterogeneity. Cells may be spindle-shaped, polygonal, or multinucleated giant cells.

P.796

Clinical Manifestations Long-term masses enlarge rapidly and become painful. Dysphonia, dysphagia, and dyspnea are common. The mass is hard and fixed. Diagnosis is by FNAC.

Treatment All forms of treatment are disappointing. A combination of radiation therapy with doxorubicin and debulking may have some effect.

LYMPHOMA

One percent of thyroid malignancies are lymphomas. Diagnosis is by FNAC with biopsy for definitive diagnosis, if necessary. Patients usually respond rapidly to chemotherapy; a combined treatment with radiation therapy and chemotherapy often is recommended. Thyroidectomy and nodal resection are used to alleviate symptoms of airway obstruction in those who do not respond quickly to initial treatment.

METASTATIC CARCINOMA

Between 2 and 4 percent of patients dying of malignant disease have metastases in the

thyroid. Kidney, lung, breast, and melanoma are the most likely sources.

Surgery of the Thyroid

Operative Technique Endotracheal anesthesia is used. The neck is extended. An equilateral low collar incision is made in a skin crease. The upper flap is raised to the upper border of the thyroid cartilage. The lower flap is mobilized to the suprasternal notch. The cervical fascia is incised in the midline. The sternothyroid and sternohyoid muscles are retracted or, if the gland is large, divided. This lobe is rotated medially, and the middle thyroid veins are divided. The cricothyroid space is opened. The external branch of the superior laryngeal nerve to the inferior pharyngeal constrictor and cricothyroid muscles is identified and preserved. Upper pole vessels are ligated separately, close to the lobe. The lobe is retracted medially, and branches of the inferior thyroid artery are ligated and divided near the capsule to preserve blood supply to the parathyroids. The recurrent laryngeal nerve is unroofed gently. In the operation for Graves' disease, 2–4 g of posterior thyroid tissue is left and secured to the lateral tracheal fascia, or the lobe may be removed totally. Parathyroids should be identified and preserved with their blood supply or autotransplanted. The isthmus is separated from the anterior trachea leaving no remnant. The wound is closed in layers.

Intrathoracic goiter usually represents an extension of cervical thyroid tissue into the chest, which usually can be removed through a cervical incision. Occasionally, transsternal resection is necessary.

P.797

Complications Mortality is very low; serious morbidity occurs in less than 2 percent.

Recurrent Laryngeal Nerve Injury This is relatively uncommon (1 percent of thyroid operations). It is more likely with large, invasive, or recurrent tumors. It may be temporary (6–12 months) or permanent. With abductor laryngeal palsy, the vocal cord assumes a medial position. The voice is husky and hoarse. Bilateral vocal cord paralysis can compromise the airway. It is wise to evaluate vocal cord function preoperatively.

Hypoparathyroidism This occurs 0.5–2 percent of patients. The incidence varies with size and invasion of the tumor, pathology, extent of the procedure, and experience of the surgeon. It rarely results from removal of all glands. Hypoparathyroidism results from parathyroid ischemia as a consequence of disruption of the blood supply. Risk can be minimized by dissection along the thyroid capsule and gently teasing the parathyroid gland on a broad plane of tissue away from the thyroid gland in a posterolateral direction. Devascularized gland may be minced and implanted in pockets in the sternomastoid or the arm.

Hypoparathyroidism is manifest within days of operation with signs of circumoral numbness, tingling of fingertips, and anxiety. Chvostek sign occurs early, followed by Trousseau's sign and carpopedal spasm. This may lead to tetany. The serum calcium level is reduced, and the phosphorus level is increased. Symptoms may be transient and resolve in a few days or be permanent.

Treatment is with 1 g calcium by mouth every 4 h. If calcium remains low, intravenous

calcium (1–10 ampules of calcium gluconate) is given over several hours. For permanent hypoparathyroidism, vitamin D (Rocaltrol 0.25–1.0 µg/d) is given in addition to calcium.

Postoperative Management of Differentiated Thyroid Cancer Postoperatively, patients should be placed on thyroxine as replacement hormone and to suppress TSH. Thyroglobulin levels in patients who have undergone total thyroidectomy should be below 2 ng/dL when the patient is taking thyroxine and below 3 ng/mL when the patients is not taking thyroxine. A thyroglobulin level above 3 ng/mL is highly suggestive of metastatic disease.

Radioiodine Therapy Metastatic differentiated thyroid cancer can be detected and treated by RAI in 75 percent of patients. Treatment is facilitated by removal of all normal thyroid tissue, which effectively competes for uptake of iodine. Thyroxine replacement should be withheld long enough for TSH to rise. A

P.798

screening dose of 2 mCi ^{131}I is administered, and the uptake is measured at 24 h. Hot spots are treated with a larger dose; then thyroxine is restarted. The maximum lifetime dose is 1000 mCi.

External-beam radiotherapy occasionally is required to control unresectable disease. Taxol has been reported recently to have some value.

PARATHYROID

Anatomy

The superior parathyroid glands arise from the fourth branchial pouch with ultimobranchial bodies so as to remain close to the posterior portion of the upper thyroid lobes near the cricothyroid membrane entrance of the recurrent laryngeal nerve. When enlarged, they descend into or along the tracheoesophageal groove and stay in a posterior plane; they may be found in the posterior or middle mediastinum. The inferior parathyroids arise from the third branchial pouch with the thymus. Ectopic sites are more common and more widely distributed; these sites range from an intrathymic gland in the anterosuperior mediastinum to an undescended interior parathyroid gland located superior to the superior parathyroid gland. Inferior parathyroids are found most commonly within 2 cm of the lower pole of the thyroid (60 percent). Most of the remainder are found in the thymic tongue. A normal parathyroid usually weighs less than 50 mg and measures 3 × 3 × 3 mm. They are browner than fat and opalescent.

Pathology

Primary hyperparathyroidism is due to parathyroid adenomas (90 percent), hyperplasia, or rarely, carcinoma. Double adenomas occur in 2 percent. Hyperplasia occurs in 8 percent with sporadic disease and is almost universal in familial disease. Hyperplasia is seldom symmetric. Normal glands primarily contain chief cells with occasional oxyphil cells. Adenoma is composed of sheets of either or both. Macroscopic appearance is the most accurate means of identifying parathyroid pathology.

Physiology of Calcium Homeostasis

Parathyroid Hormone (PTH) PTH is a single-chain polypeptide. The *N*-terminal portion is biologically active with a half-life 2 min. The hormone increases osteoclast and osteoblast activity. It increases the rate of production of the active form of vitamin D,

which increases absorption of calcium from the gut. There is increased excretion of bicarbonate and of phosphate by the kidney, lowering the serum phosphate level.

Calcium Calcium is the principal regulator of PTH release through receptors on parathyroid cells. Calcium is essential for most physiologic functions. The body contains about 1000 g calcium. Total calcium level must be considered in its relationship to plasma protein levels.

Vitamin D Vitamin D is vital to calcium hemostasis. Vitamin D is absorbed from the GI tract and synthesized in the skin. It is converted by the liver to 25-hydroxycholecalciferol, which is converted to its active form (1,25-dihydroxycholecalciferol) in the kidneys. Vitamin D_3 increases absorption of calcium and promotes phosphate retention; it elevates serum calcium and phosphate levels and enhances the mineralization of bone. In the presence of PTH, when serum calcium and phosphorus levels are low, synthesis of $1,25\text{-}(OH)_2\,D_3$ is increased. This mechanism is feedback controlled.

Primary Hyperparathyroidism (PTH)

Hypercalcemia is a result of overproduction of PTH by one or more parathyroid glands. It occurs in 1 in 700 persons (the female-to-male ratio is 3:1) and 1 in 200 postmenopausal women.

Etiology The exact cause is unknown. Typically, it is caused by benign enlargement of one (90 percent) or two (2 percent) parathyroid glands; the condition is referred to as *benign adenoma(s)*. Multigland enlargement accounts for 8 percent. Parathyroid carcinoma is a rare cause (<1 percent).

Clinical Manifestations Before serum calcium levels were measured routinely, patients typically presented with renal stones (64 percent), bone disease (20 percent), peptic ulcer (12 percent), and hypertension (4 percent). After successful surgical management, nearly all patients realize that they had been symptomatic.

Evaluation Diagnosis is commonly one of exclusion. Differential diagnosis includes a history of the use of thiazide diuretics, lithium, excessive vitamin A or D, extraordinary amounts of milk or antacids (milk-alkali syndrome), granulomatous disease (sarcoidosis, tuberculosis, histoplasmosis, etc.), malignancy (renal cell carcinoma, multiple myeloma, squamous or small cell lung cancer that can

produce a parathyroid hormone-like polypeptide), and metastatic malignancy (commonly prostate or breast). A family history of MEN or benign familial hypocalciuric hypercalcemia (low urinary calcium excretion) may be an indication. Physical examination rarely is helpful (neck mass, voice abnormality, or hoarseness could indicate parathyroid cancer). Adenomas, regardless of size, rarely are palpable. A single serum calcium determination is cost-effective and sufficient. Diagnosis is virtually certain if PTH is inappropriately high; it

should be near zero. Serum phosphorous level should be low.

Imaging Radiologic studies are unnecessary unless previous neck operations have been undertaken. With reoperation, in those in whom dissection is more hazardous, ultrasound of the neck with FNAC of any suspicious cervical mass is useful. If equivocal, technetium-99m sestamibi scanning has great sensitivity in identifying missed parathyroid tissue. CT, MRI, and venous sampling are expensive and less accurate.

Treatment The indication for surgical intervention is the diagnosis of primary hyperparathyroidism. Expected success rate is 98 percent, and there is negligible mortality and minimal morbidity. For recurrent or persistent hyperparathyroidism, repeat exploration is indicated if the offending gland is localized in imaging studies. Expected success rate is 90 percent. For a solitary adenoma, excision without biopsy of the other glands is sufficient. Double adenomas should both be removed. For multigland hyperplasia, three and one-half gland parathyroidectomy or total parathyroidectomy with reimplantation of 50 mg in the neck or forearm is an option. Normocalcemia within 24–72 h can be expected. Transient hypocalcemia is common; the cause is bone hunger (low serum phosphate and normal PTH levels) or hypoparathyroidism (elevated phosphate and abnormally low PTH levels). Hospitalization is overnight while calcium levels are checked and stabilized before discharge. Calcium is checked at 1–2 months and then yearly.

Technique A 10-cm collar incision 2 fingerbreadths above the sternal notch is made. The operative technique should be gentle and unhurried with a bloodless field. The strap muscles are retracted or divided, and the thyroid is elevated anteriorly, superiorly, and then medially. Superior parathyroids usually are found close to the posterolateral aspect of the upper pole. Takedown of the upper pole seldom is necessary. Inferior glands are intimately involved with the lower pole and the thyrothymic tongue of fat that extends inferiorly toward the mediastinum. They are often subscapular. Glands

P.801

may be found as high as the angle of the mandible or as low as in thymus, in the anterior mediastinum, or in the aortopulmonary window in the posterior mediastinum. If the superior gland is not found, the tracheoesophageal groove below the inferior artery and lower gland should be investigated. Other possible sites are in the thymus, buried within the thyroid, in the carotid sheath, or lateral to the carotid sheath. Bilateral exploration is recommended.

PERSISTENT AND RECURRENT HYPERPARATHYROIDISM (Fig. 36-1)

FIGURE 36-1 Algorithm of the approach to the patient with persistent/recurrent hyperparathyroidism.

An improperly performed primary operation is the cause for the majority of patients with persistent (elevated serum calcium levels that do not return to normal after surgery) or recurrent hyperparathyroidism. The possibility of benign familial hypocalciuric hypercalcemia in which 24-h urine calcium excretion is less than 100 mg must be excluded. Reoperative cure rates of 80–90 percent are reported. Postoperative recurrent laryngeal

nerve palsy or permanent hypoparathyroidism occurs in 3–5 percent. Nonoperative alternatives (angiographic embolization or, preferably, ultrasound-guided alcohol ablation) should be considered. The surgeon should review the prior operative report, and the pathologist should review previously excised tissue. The radiologist should be consulted about localizing with technetium-99m sestamibi and ultrasound (with FNAC). Localization allows focused exploration (unilateral or lateral cervical approach, thoracoscopy, or mediastinal exploration). If all localizing modalities are negative, blind exploration should not be performed.

Secondary Hyperparathyroidism

This is uncommon. There is appropriate parathyroid hyperplasia with elevation of PTH secretion in patients with chronic renal failure causing hyperphosphatemia and decreased vitamin D production with calcium maintained in normal range or intestinal malabsorption (calcium and vitamin D absorption diminished to the point of hypocalcemia).

Clinical Manifestations Symptoms include bone pain or fractures, renal osteodystrophy or soft-tissue calcifications (calciphylaxis), and pruritus.

Treatment Treatment is nonsurgical dietary restriction of phosphate and oral phosphate binders, oral calcium, and vitamin D. Surgery is performed for hyperplasia involving all glands and uncontrollable symptoms.

P.802

P.803

Tertiary Hyperparathyroidism

This is the continuation of secondary hyperparathyroidism. PTH secretion becomes autonomous, and the serum calcium level becomes elevated. It is observed most commonly in patients with long-standing renal dysfunction who undergo renal transplantation. With restored renal function, PTH levels usually return to normal. Surgery is indicated for persistent disease.

Multiple Endochrine Neoplasia and Hyperparathyroidism

Multiple endocrine neoplasia (MEN) has an autosomal dominant pattern of inheritance. The hallmark is multicentricity and bilaterality.

MEN type I includes pituitary (15–50 percent), parathyroid (100 percent), or pancreatic (30–80 percent) neoplasms. MEN type IIA (Sipple's syndrome) includes C-cell hyperplasia and, subsequently, medullary thyroid carcinoma if total thyroidectomy is not done prophylactically, adrenal medullary hyperplasia/pheochromocytoma (50 percent), and parathyroid abnormality (10–25 percent). MEN type IIB patients can develop medullary thyroid cancer and adrenal neoplasms with marfanoid habitus and mucosal neuromas. Parathyroid chief cell hyperplasia is uncommon. Malignancy shortens life if prophylaxis is not undertaken.

Clinical Manifestations Seventy-five percent of patients have a family history of endocrine abnormalities. With time patients present with visual changes, kidney stones, ulcer pain or

diabetes (MEN I), neck masses and hypertension (MEN IIA), or buccal and lingual nodules, hypertension, neck masses, and marfanoid habitus (MEN IIB). Patients should have serologic surveillance of appropriate markers.

Testing for the RET proto-oncogene is indicated for those with a family history of medullary cancer, and prophylactic thyroidectomy is performed if the history is positive. Parathyroid surgery is performed to prevent the ravages of primary hyperparathyroidism. It is not uncommon for these patients to have 5–6 parathyroid glands. Exploration should be thorough and should include transcervical thymectomy. Treatment includes removal of all but 50 mg parathyroid tissue or total parathyroidectomy with autotransplant of heterotopic tissue.

Hypercalcemic Crisis

This life-threatening systemic condition is accompanied by an elevation of serum calcium to 13 mg/dL or higher. Symptoms vary from neuromuscular changes with mild fatigue and irritability to

P.804

coma. Dehydration is common. GI manifestations include anorexia, nausea, vomiting, and weight loss. Cardiac dysrhythmias may be lethal. Cancer cachexia may be evident with skeletal metastases. A palpable neck mass with hypercalcemic crisis is parathyroid carcinoma until proved otherwise. Differential diagnosis includes all causes of hypercalcemia. Ninety percent of patients will either have advanced malignancy or hyperparathyroidism.

Treatment Intravenous saline is advanced to achieve a diuresis of 100 mL/h or higher. About 4–5 L is required to overcome dehydration. Once hydrated, the patient should receive loop diuretics to stimulate natruresis and subsequent calciuresis. Cardiac dysrhythmias are treated with standard agents. When hypercalcemia persists, treatment with mithramycin, phosphate binders, vitamin D, estrogen, calcitonin, or steroids may help. Vocal cord function should be checked. Ultrasound may identify a large adenoma and allow focused exploration. Even with coma or hemodynamic instability, operation should not be delayed.

Parathyroid Carcinoma

This occurs in less than 1 percent of cases of hyperparathyroidism.

Preoperative Findings Findings are (1) palpable neck mass, (2) markedly abnormal biochemistry, calcium usually higher than 13 mg/dL, PTH elevated tenfold, and alkaline phosphatase elevated threefold, and (3) complications of hyperparathyroidism.

Intraoperative Findings There is evidence of a parathyroid mass, which is firmer than the usual. The gland is not the normal bean-shaped kidney color but irregular, pale white, and adherent to surrounding structures.

Pathology Most masses weigh more than 2 g and are composed of a thick fibrous capsule, with fibrous septa interdigitating throughout the tumor, and enlargement, hyperchromasia, and variation in nuclear size are seen. Capsular and local tissue invasion usually is found.

Treatment En bloc resection of the tumor and involved surrounding structures is performed, usually by thyroid lobectomy. If lymph nodes are involved, appropriate resection is needed. Radiation and chemotherapy are of limited usefulness. Symptomatic hypercalcemia is treated with mithramycin and biophosphonates. Recurrence is at least 66 percent. Surgical debulking may be needed

P.805

to control hypercalcemia. Five-year survival is 69 percent. Death often is related to the consequences of hypercalcemia.

For a more detailed discussion, see Sadler GP, Clark OH, van Heerden JA, and Farley DR: Thyroid and Parathyroid, chap. 36 in *Principles of Surgery,* 7th ed.