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CHAPTER 19

Endocrine System

CHAPTER CONTENTS

The endocrine system is a highly integrated and widely distributed group of organs that orchestrate a state of metabolic equilibrium, or homeostasis, among the various tissues of the body. Signaling by extracellular secreted molecules can be classified as one of three types—autocrine, paracrine, or endocrine—according to the distance over which the signal acts (Chapter 2). In *endocrine* signaling, the secreted molecules, which frequently are called *hormones,* act on target cells distant from their site of synthesis. An endocrine hormone typically is carried by the blood from its site of release to its target. Increased activity of the target tissue often downregulates the activity of the gland that secretes the stimulating hormone, a process known as *feedback inhibition.*

Hormones can be classified into several broad categories, based on the nature of their receptors:

- *Hormones that trigger biochemical signals upon interacting with cell surface receptors*: This large class of compounds is composed of two groups: (1) peptide hormones, such as *growth hormone* and *insulin,* and (2) small molecules, such as *epinephrine.* Binding of these hormones to cell surface receptors leads to an increase in intracellular molecules, termed *second messengers,* such as cyclic adenosine monophosphate (cAMP); production of mediators from membrane phospholipids (e.g., inositol 1,4,5-trisphosphate); and shifts in intracellular levels of ionized calcium. Elevated levels of one or more of these compounds can change proliferation, differentiation, survival, and functional activity of cells, mainly by regulating the expression of specific genes.
- *Hormones that diffuse across the plasma membrane and interact with intracellular receptors*: Many lipid-soluble hormones pass through the plasma membrane by diffusion to interact with receptors in the cytosol or the nucleus. The resulting hormone-receptor complexes bind specifically to promoter and enhancer elements in DNA,

thereby affecting the expression of specific target genes. Hormones of this type include the *steroids* (e.g., estrogen, progesterone, glucocorticoids), the *retinoids* (vitamin A), and *thyroxine.*

Several processes may disturb the normal activity of the endocrine system, including impaired synthesis or release of hormones, abnormal interactions between hormones and their target tissues, and abnormal responses of target organs to their hormones. Endocrine diseases can be generally classified as (1) diseases of *underproduction or overproduction* of hormones, with associated biochemical and clinical consequences, or (2) diseases associated with the development of *mass lesions,* which may be nonfunctional or may be associated with overproduction or underproduction of hormones.

With the exception of mass lesions, study of endocrine diseases relies heavily on biochemical measurements of the levels of hormones, their regulators, and other metabolites.

PITUITARY

The pituitary gland is a small, bean-shaped structure that lies at the base of the brain within the confines of the sella turcica. It is intimately related to the hypothalamus, with which it is connected by both a *stalk,* composed of axons extending from the hypothalamus, and a rich venous plexus constituting a portal circulation. Along with the hypothalamus, the pituitary has a central role in the regulation of most of the other endocrine glands. The pituitary is composed of two morphologically and functionally distinct components: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). Diseases of the pituitary, accordingly, can be divided into those that primarily affect the anterior lobe and those that primarily affect the posterior lobe.

The *anterior pituitary,* or *adenohypophysis,* is composed of epithelial cells derived embryologically from the developing oral cavity. In routine histologic sections, a colorful array of cells containing basophilic cytoplasm, eosinophilic cytoplasm, or poorly staining (*chromophobic*) cytoplasm is present (Fig. 19–1). Detailed studies using electron microscopy and immunocytochemical techniques have demonstrated that the staining properties of these cells are related to the presence of various trophic polypeptide hormones within their cytoplasm. The release of trophic hormones is in turn under the control of factors produced in the hypothalamus; while most hypothalamic factors are stimulatory and promote pituitary hormone release, others (e.g., somatostatin and dopamine) are inhibitory in their effects (Fig. 19–2). Rarely, signs and symptoms of pituitary disease may be caused by excess or lack of the hypothalamic factors, rather than by a primary pituitary abnormality.

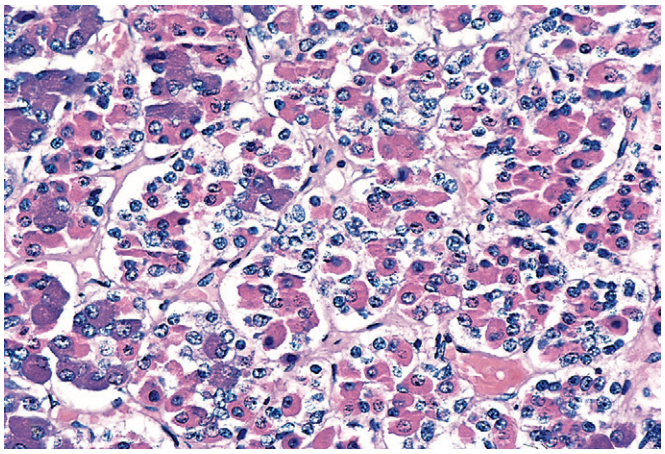


Figure 19–1 Normal architecture of the anterior pituitary. The gland is populated by several distinct cell types containing a variety of stimulating (trophic) hormones. Each of the hormones has different staining characteristics, resulting in a mixture of cell types in routine histologic preparations. Note also the presence of a fine reticulin network.

Symptoms and signs of pituitary disease can be grouped as follows:

- *Hyperpituitarism*-related effects: Hyperpituitarism arises from excessive secretion of trophic hormones. It most often results from an *anterior pituitary adenoma* but also may be caused by other pituitary and extrapituitary lesions, as described subsequently. The symptoms and signs of hyperpituitarism are discussed in the context of individual tumors, later in the chapter.
- *Hypopituitarism*-related effects: Hypopituitarism is caused by deficiency of trophic hormones and results from a variety of destructive processes, including *ischemic injury, surgery or radiation,* and *inflammatory reactions.* In addition, *nonfunctional pituitary adenomas* may encroach upon and destroy adjacent normal anterior pituitary parenchyma, causing hypopituitarism.
- *Local mass effects*: Among the earliest changes referable to mass effect are *radiographic abnormalities of the sella turcica,* including sellar expansion, bony erosion, and disruption of the diaphragma sellae. Because of the close proximity of the optic nerves and chiasm to the sella, expanding pituitary lesions often compress decussating fibers in the optic chiasm. This altered neuroanatomy gives rise to *visual field abnormalities,* classically in the form of defects in the lateral (temporal) visual fields—a so-called *bitemporal hemianopsia.* As in the case of any expanding intracranial mass, pituitary adenomas may produce signs and symptoms of *elevated intracranial pressure,* including headache, nausea, and vomiting. Pituitary adenomas that extend beyond the sella turcica into the base of the brain (invasive pituitary adenoma) produce *seizures* or *obstructive hydrocephalus*; involvement of cranial nerves can result in *cranial nerve palsy.* On occasion, acute hemorrhage into an adenoma is associated with clinical evidence of rapid enlargement of the lesion and depression of consciousness, a situation appropriately termed *pituitary apoplexy.* Acute pituitary apoplexy constitutes a neurosurgical emergency, because it may be rapidly fatal.

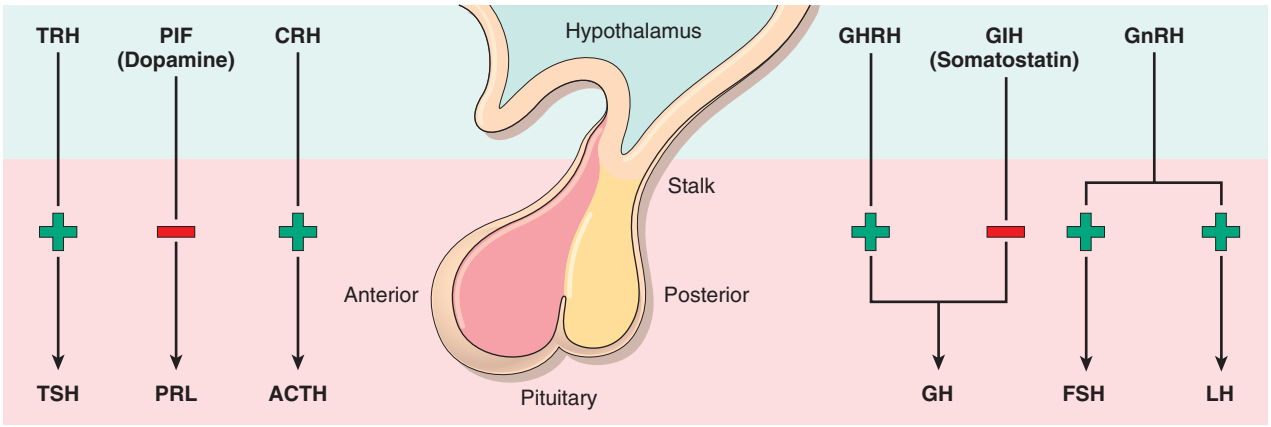


Figure 19–2 The adenohypophysis (anterior pituitary) releases six hormones: adrenocorticotropic hormone (ACTH), or corticotropin; follicle-stimulating hormone (FSH); growth hormone (GH), or somatotropin; luteinizing hormone (LH); prolactin (PRL); and thyroid-stimulating hormone (TSH), or thyrotropin. These hormones are in turn under the control of various stimulatory and inhibitory hypothalamic releasing factors. The *stimulatory* releasing factors are corticotropin-releasing hormone (CRH), growth hormone–releasing hormone (GHRH), gonadotropin-releasing hormone (GnRH), and thyrotropin-releasing hormone (TRH). The *inhibitory* hypothalamic factors are growth hormone inhibitory hormone (GIH), or somatostatin, and prolactin inhibitory factor (PIF), which is the same as dopamine.

HYPERPITUITARISM AND PITUITARY ADENOMAS

The most common cause of hyperpituitarism is an adenoma arising in the anterior lobe. Other, less common, causes include hyperplasia and carcinomas of the anterior pituitary, secretion of hormones by some extrapituitary tumors, and certain hypothalamic disorders. Some salient features of pituitary adenomas are as follows:

- *Pituitary adenomas are classified on the basis of hormone(s) produced by the neoplastic cells, which are detected by immunohistochemical stains performed on tissue sections* (Table 19–1).
- Pituitary adenomas can be *functional* (i.e., associated with hormone excess and clinical manifestations thereof) or *nonfunctioning* (i.e., demonstration of hormone production at the tissue level only, without clinical manifestations of hormone excess). Both functional and nonfunctioning pituitary adenomas usually are composed of a single cell type and produce a single predominant hormone, but there are some exceptions. Some pituitary adenomas can secrete two different hormones (growth hormone and prolactin being the most common combination); rarely, pituitary adenomas are plurihormonal. At the other end of the spectrum, pituitary adenomas also may be truly "*hormone negative,*" as indicated by absence of immunohistochemical reactivity or ultrastructural evidence of hormone production.
- Most pituitary adenomas occur as sporadic (i.e., nonfamilial) lesions. In about 5% of cases, however, adenomas occur as a result of an inherited predisposition (see later).
- Pituitary adenomas are designated, somewhat arbitrarily, as *microadenomas* if they are less than 1 cm in diameter and *macroadenomas* if they exceed 1 cm in diameter.
- Nonfunctioning and hormone-negative adenomas are likely to come to clinical attention at a later stage and are, therefore, more likely to be macroadenomas than

Table 19–1 Classification of Pituitary Adenomas

Pituitary Cell Type	Hormone	Tumor Type	Associated Syndrome*
Corticotroph	ACTH and other POMC-derived peptides	Densely granulated Sparsely granulated	Cushing syndrome Nelson syndrome
Somatotroph	GH	Densely granulated Sparsely granulated	Gigantism (children) Acromegaly (adults)
Lactotroph	Prolactin	Densely granulated Sparsely granulated	Galactorrhea and amenorrhea (in females) Sexual dysfunction, infertility
Mammosomatotroph	Prolactin, GH	Mammosomatotroph	Combined features of GH and prolactin excess
Thyrotroph	TSH	Thyrotroph	Hyperthyroidism
Gonadotroph	FSH, LH	Gonadotroph, "null cell," oncocytic adenomas	Hypogonadism, mass effects and hypopituitarism

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; POMC, pro-opiomelanocortin; TSH, thyroid-stimulating hormone.
*Nonfunctioning adenomas in each category typically manifest with *mass effects* and often with *hypopituitarism*.
Data from Ezzat S, Asa SL: Mechanisms of disease: the pathogenesis of pituitary tumors. Nat Clin Pract Endocrinol Metab 2:220–230, 2006.

are lesions associated with endocrine abnormalities. In addition, nonfunctioning adenomas may cause *hypo*pituitarism as they encroach on and destroy adjacent anterior pituitary parenchyma.

PATHOGENESIS

With recent advances in molecular techniques, substantial insight has been gained into the **genetic abnormalities associated with pituitary adenomas:**

- Guanine nucleotide–binding protein (G protein) mutations are the best-characterized molecular abnormalities in these neoplasms. G proteins have a critical role in signal transduction, transmitting signals from **cell surface receptors** (e.g., growth hormone–releasing hormone receptor) to **intracellular effectors** (e.g., adenyl cyclase), which then generate **second messengers** (e.g., cAMP). G_s is a stimulatory G protein that has a pivotal role in signal transduction in several endocrine organs, including the pituitary. G_s exists as an inactive protein, with guanosine diphosphate (GDP) bound to the guanine nucleotide–binding site of the alpha subunit of G_s, encoded by the *GNAS1* gene. On triggering of the hormone receptor, GDP dissociates, and guanosine triphosphate (GTP) binds to $G_s\alpha$, activating the G protein. GTP-bound $G_s\alpha$ directly interacts with and activates its effectors (such as adenyl cyclase), with a resultant increase in intracellular cAMP. The cAMP acts as a potent mitogenic stimulus for a variety of endocrine cell types, promoting cellular proliferation and hormone synthesis and secretion. The activation of $G_s\alpha$ and the resultant generation of cAMP are **transient** because of an intrinsic GTPase activity in the α-subunit, which hydrolyzes GTP into GDP. **A mutation in the α-subunit that interferes with its intrinsic GTPase activity therefore results in constitutive activation of $G_s\alpha$, persistent generation of cAMP, and unchecked cellular proliferation.** Approximately 40% of growth hormone–secreting somatotroph cell adenomas and a minority of adrenocorticotropic hormone (ACTH)–secreting corticotroph cell adenomas bear *GNAS1* mutations.
- As stated previously, approximately 5% of pituitary adenomas arise as a consequence of an inherited predisposition. **Four genes have been identified thus far as a cause of familial pituitary adenomas: *MEN1*, *CDKN1B*, *PRKAR1A*, and *AIP*.** Germline inactivating mutations of the *MEN1* gene are responsible for multiple endocrine neoplasia syndrome type 1 (MEN-1) (discussed in detail later on). The product of the *CDKN1B* gene is the cell cycle checkpoint regulator p27 or KIP1; germline mutations of *CDKN1B* are responsible for a subset of patients with a "MEN-1 like" syndrome who lack *MEN1* abnormalities. The gene encoding the **aryl hydrocarbon receptor–interacting protein (AIP)** is a recently described pituitary adenoma predisposition gene, and patients with *AIP* germline mutations often develop GH-secreting adenomas at a younger age (before 35 years) than that typical for sporadic GH adenoma patients.
- Mutations of *TP53* in pituitary adenomas are associated with a propensity for aggressive behavior, such as invasion and recurrence.

MORPHOLOGY

The usual pituitary adenoma is a well-circumscribed, soft lesion that may, in the case of smaller tumors, be confined by the sella turcica. Larger lesions may compress the optic chiasm and adjacent structures (Fig. 19–3), erode the sella turcica and anterior clinoid processes, and extend locally into the cavernous and sphenoidal sinuses. In as many as 30% of cases, the adenomas are nonencapsulated and infiltrate adjacent bone, dura, and (uncommonly) brain. Foci of hemorrhage and/or necrosis are common in larger adenomas.

Pituitary adenomas are composed of relatively uniform, polygonal cells arrayed in sheets, cords, or papillae. Supporting connective tissue, or reticulin, is sparse, accounting for the soft, gelatinous consistency of many of these tumors. The nuclei of the neoplastic cells may be uniform or pleomorphic. Mitotic activity usually is scanty. The cytoplasm of the constituent cells may be acidophilic, basophilic, or chromophobic, depending on the type and amount of secretory product within the cell, but it is fairly uniform throughout the neoplasm. **This cellular monomorphism and the absence of a significant reticulin network distinguish pituitary adenomas from non-neoplastic anterior pituitary parenchyma** (Fig. 19–4). The functional status of the adenoma cannot be reliably predicted from its histologic appearance. Adenomas that harbor *TP53* mutations often demonstrate brisk mitotic activity and higher proliferation rates and are designated **atypical adenomas** to reinforce their potential for aggressive behavior.

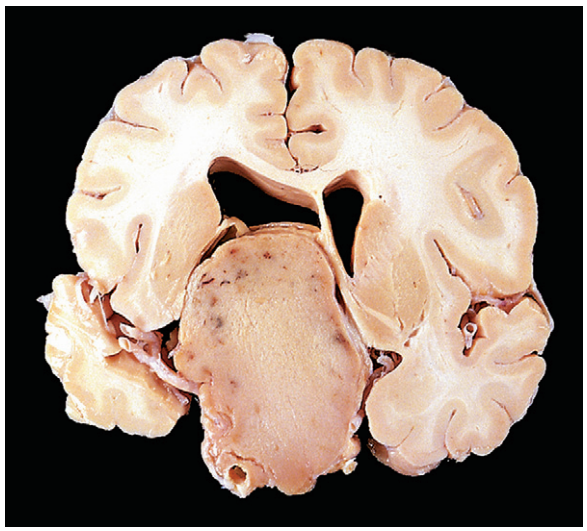


Figure 19–3 Pituitary adenoma. This massive, nonfunctioning adenoma has grown far beyond the confines of the sella turcica and has distorted the overlying brain. Nonfunctioning adenomas tend to be larger at the time of diagnosis than those that secrete a hormone.

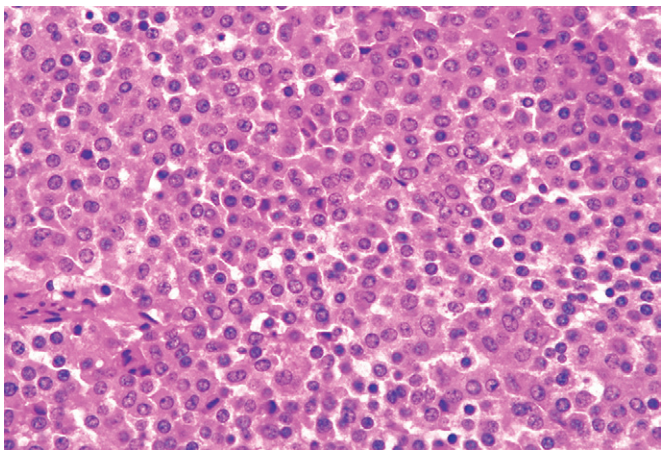


Figure 19–4 Pituitary adenoma. The monomorphism of these cells contrasts markedly with the admixture of cells seen in the normal anterior pituitary in Figure 19–1. Note also the absence of reticulin network.

SUMMARY

Hyperpituitarism

- The most common cause of hyperpituitarism is an anterior lobe pituitary adenoma.
- Pituitary adenomas can be macroadenomas (greater than 1 cm in diameter) or microadenomas (less than 1 cm across), and on clinical evaluation, they can be functional or nonfunctioning.
- Macroadenomas may potentially lead to mass effects, including visual disturbances.
- Functioning adenomas are associated with distinct endocrine signs and symptoms.
- Mutation of the *GNAS1* gene, which results in constitutive activation of a stimulatory G protein, is one of the more common genetic alterations.
- The two distinctive morphologic features of most adenomas are their cellular monomorphism and absence of a reticulin network.

Prolactinomas

Prolactinomas are the most common type of hyperfunctioning pituitary adenoma. They range in size from small microadenomas to large, expansile tumors associated with considerable mass effect. Prolactin is demonstrable within the cytoplasm of the neoplastic cells by immunohistochemical techniques.

Hyperprolactinemia causes amenorrhea, galactorrhea, loss of libido, and infertility. Because many of the manifestations of hyperprolactinemia (e.g., amenorrhea) are more obvious in premenopausal women than in men or postmenopausal women, prolactinomas usually are diagnosed at an earlier stage in women of reproductive age than in other persons so affected. By contrast, hormonal manifestations may be quite subtle in men and older women, in whom the tumor may reach considerable size before coming to clinical attention. Hyperprolactinemia may be caused by conditions or factors other than prolactin-secreting pituitary adenomas, including pregnancy, high-dose estrogen therapy, renal failure, hypothyroidism, hypothalamic lesions, and dopamine-inhibiting drugs (e.g., reserpine). In addition, any mass in the suprasellar compartment may disturb the normal inhibitory influence of hypothalamus on prolactin secretion, resulting in hyperprolactinemia—a mechanism known as the *stalk effect.* Thus, *mild* elevations of serum prolactin (less than 200 μg/L) in a patient with a pituitary adenoma do not necessarily indicate a prolactin-secreting neoplasm.

Growth Hormone–Producing (Somatotroph Cell) Adenomas

Growth hormone–producing neoplasms (somatotroph cell adenomas), including those that produce a mixture of growth hormone and other hormones (e.g., prolactin), constitute the second most common type of functional pituitary adenoma. Because the clinical manifestations of excessive growth hormone may be subtle, somatotroph cell adenomas may be quite large by the time they come to clinical attention. On microscopic examination, growth hormone–producing adenomas are composed of densely or sparsely granulated cells, and immunohistochemical staining demonstrates growth hormone within the cytoplasm of the neoplastic cells. Small amounts of immunoreactive prolactin often are present as well.

Persistent hypersecretion of growth hormone stimulates the hepatic secretion of insulin-like growth factor I (somatomedin C), which causes many of the clinical manifestations. If a growth hormone–secreting adenoma occurs before the epiphyses close, as is the case in prepubertal children, excessive levels of growth hormone result in *gigantism.* This condition is characterized by a generalized increase in body size, with disproportionately long arms and legs. If elevated levels of growth hormone persist, or develop after closure of the epiphyses, affected persons develop *acromegaly,* in which growth is most conspicuous in soft tissues, skin, and viscera and in the bones of the face, hands, and feet. Enlargement of the jaw results in its protrusion (prognathism), with broadening of the lower face and separation of the teeth. The hands and feet are enlarged, with broad, sausage-like fingers. In clinical practice, the gigantism typically is accompanied by evidence of acromegaly.

Growth hormone excess also is associated with a number of other disturbances, including abnormal glucose tolerance and diabetes mellitus, generalized muscle weakness, hypertension, arthritis, osteoporosis, and congestive heart failure. Prolactin is demonstrable in a number of growth hormone–producing adenomas and in some cases may be released in sufficient quantities to produce signs and symptoms of hyperprolactinemia.

Adrenocorticotropic Hormone–Producing (Corticotroph Cell) Adenomas

Most corticotroph cell adenomas are small (microadenomas) at the time of diagnosis. These adenomas stain positively with periodic acid–Schiff (PAS) stains, as a result of

the accumulation of glycosylated ACTH protein. As in the case of other pituitary hormones, the secretory granules can be detected by immunohistochemical methods. By electron microscopy they appear as membrane-bound, electron-dense granules averaging 300 nm in diameter.

Corticotroph cell adenomas may be clinically silent or may cause *hypercortisolism,* manifested clinically as *Cushing syndrome,* because of the stimulatory effect of ACTH on the adrenal cortex. Cushing syndrome, discussed in more detail later with diseases of the adrenal gland, may be caused by a wide variety of conditions in addition to ACTH-producing pituitary neoplasms. When the hypercortisolism is caused by excessive production of ACTH by the pituitary, the process is designated *Cushing disease,* because it is the pattern of hypercortisolism originally described by Dr. Harvey Cushing. Large, clinically aggressive corticotroph cell adenomas may develop after surgical removal of the adrenal glands for treatment of Cushing syndrome. In most instances, this condition, known as *Nelson syndrome,* results from loss of the inhibitory effect of adrenal corticosteroids on a preexisting corticotroph microadenoma. Because the adrenals are absent in persons with Nelson syndrome, hypercortisolism does not develop. Instead, patients present with the mass effects of the pituitary tumor. In addition, because ACTH is synthesized as part of a larger prohormone substance that includes melanocyte-stimulating hormone (MSH), hyperpigmentation also may be a feature.

Other Anterior Pituitary Neoplasms

- *Gonadotroph (luteinizing hormone [LH]–producing and follicle-stimulating hormone [FSH]–producing)* adenomas can be difficult to recognize, because they secrete hormones inefficiently and variably, and the secretory products usually do not cause a recognizable clinical syndrome. They are typically detected when the tumors have become large enough to cause neurologic signs and symptoms, such as impaired vision, headaches, diplopia, or pituitary apoplexy. The neoplastic cells usually demonstrate immunoreactivity for the common gonadotropin α-subunit and the specific β-FSH and β-LH subunits; FSH usually is the predominant secreted hormone.
- *Thyrotroph (thyroid-stimulating hormone [TSH]–producing) adenomas* account for about 1% of all pituitary adenomas and constitute a rare cause of hyperthyroidism.
- *Nonfunctioning pituitary adenomas* comprise both clinically silent counterparts of the functioning adenomas just described (for example, a *silent gonadotroph adenoma*) and true *hormone-negative* (null cell) adenomas; the latter are quite infrequent, and as noted, many have been reclassified using improved diagnostic techniques. Nonfunctioning adenomas constitute approximately 25% of all pituitary tumors. Not surprisingly, the typical presentation with nonfunctioning adenomas is one characterized by mass effects. These lesions also may compromise the residual anterior pituitary sufficiently to produce hypopituitarism.
- *Pituitary carcinomas are exceedingly rare.* In addition to local extension beyond the sella turcica, these tumors virtually always demonstrate distant metastases.

SUMMARY

Clinical Manifestations of Pituitary Adenomas

- *Prolactinomas*: amenorrhea, galactorrhea, loss of libido, and infertility
- *Growth hormone (somatotroph cell) adenomas*: gigantism (children), acromegaly (adults), and impaired glucose tolerance and diabetes mellitus
- *Corticotroph cell adenomas*: Cushing syndrome, hyperpigmentation
- All pituitary adenomas, particularly nonfunctioning adenomas, may be associated with mass effects and hypopituitarism.

HYPOPITUITARISM

Hypofunction of the anterior pituitary may occur with loss or absence of 75% or more of the anterior pituitary parenchyma. This may be *congenital* (exceedingly rare) or may result from a wide range of *acquired* abnormalities that are intrinsic to the pituitary. Less frequently, disorders that interfere with the delivery of pituitary hormone–releasing factors from the hypothalamus, such as hypothalamic tumors, also may cause hypofunction of the anterior pituitary. *Hypopituitarism accompanied by evidence of posterior pituitary dysfunction in the form of diabetes insipidus* (see later) *is almost always of hypothalamic origin.* Most cases of anterior pituitary hypofunction are caused by

- Nonfunctioning pituitary adenomas (discussed earlier)
- Ischemic necrosis of the anterior pituitary, an important cause of pituitary insufficiency. The anterior pituitary has substantial reserve capacity; as a result, destruction of large amounts of the anterior pituitary (75% or greater) must occur before signs and symptoms of hypopituitarism develop. *Sheehan syndrome,* or postpartum necrosis of the anterior pituitary, is the most common form of clinically significant ischemic necrosis of the anterior pituitary. During pregnancy, the anterior pituitary enlarges considerably, largely because of an increase in the size and number of prolactin-secreting cells. This physiologic enlargement of the gland, however, is not accompanied by an increase in blood supply from the low-pressure portal venous system. The enlarged gland is thus vulnerable to ischemic injury, especially in women who experience significant hemorrhage and hypotension during the peripartal period. The posterior pituitary, because it receives its blood directly from arterial branches, is much less susceptible to ischemic injury and therefore usually is not affected. Clinically significant pituitary necrosis also may be encountered in other conditions, including disseminated intravascular coagulation, sickle cell anemia, elevated intracranial pressure, traumatic injury, and shock of any origin. The residual gland is shrunken and scarred.
- Ablation of the pituitary by surgery or irradiation
- Other, less common causes of anterior pituitary hypofunction, including inflammatory lesions such as

sarcoidosis or tuberculosis, trauma, and metastatic neoplasms involving the pituitary.

The clinical manifestations of anterior pituitary hypofunction depend on the specific hormones that are lacking. In children, growth failure (*pituitary dwarfism*) may occur as a result of growth hormone deficiency. Gonadotropin or gonadotropin-releasing hormone (GnRH) deficiency leads to amenorrhea and infertility in women and to decreased libido, impotence, and loss of pubic and axillary hair in men. TSH and ACTH deficiencies result in symptoms of hypothyroidism and hypoadrenalism, respectively, and are discussed later in the chapter. Prolactin deficiency results in failure of postpartum lactation. The anterior pituitary also is a rich source of MSH, synthesized from the same precursor molecule that produces ACTH; therefore, one of the manifestations of hypopituitarism is pallor from loss of stimulatory effects of MSH on melanocytes.

POSTERIOR PITUITARY SYNDROMES

The posterior pituitary, or neurohypophysis, is composed of modified glial cells (termed *pituicytes*) and axonal processes extending from nerve cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. The hypothalamic neurons produce two peptides: antidiuretic hormone (ADH) and oxytocin. They are stored in axon terminals in the neurohypophysis and released into the circulation in response to appropriate stimuli. Oxytocin stimulates the contraction of smooth muscle in the pregnant uterus and of muscle surrounding the lactiferous ducts of the mammary glands. Impairment of oxytocin synthesis and release has not been associated with significant clinical abnormalities. The clinically important posterior pituitary syndromes involve ADH production. They include *diabetes insipidus* and *secretion of inappropriately high levels of ADH.*

ADH is a nonapeptide hormone synthesized predominantly in the supraoptic nucleus. In response to several different stimuli, including increased plasma oncotic pressure, left atrial distention, exercise, and certain emotional states, ADH is released from axon terminals in the neurohypophysis into the general circulation. The hormone acts on the collecting tubules of the kidney to promote the resorption of free water. ADH deficiency causes *diabetes insipidus,* a condition characterized by excessive urination (polyuria) caused by an inability of the kidney to properly resorb water from the urine. Diabetes insipidus can result from several causes, including head trauma, neoplasms, and inflammatory disorders of the hypothalamus and pituitary, and from surgical procedures involving the hypothalamus or pituitary. The condition sometimes arises spontaneously (*idiopathic*) in the absence of an underlying disorder. Diabetes insipidus from ADH deficiency is designated as *central,* to differentiate it from *nephrogenic* diabetes insipidus as a result of renal tubular unresponsiveness to circulating ADH. The clinical manifestations of both diseases are similar and include the excretion of large volumes of dilute urine with an inappropriately low specific gravity. Serum sodium and osmolality are increased as a result of excessive renal loss of free water, resulting in thirst and polydipsia. Patients who can drink water generally can compensate for urinary losses; patients who are obtunded, bedridden, or otherwise limited in their ability to obtain water may develop life-threatening dehydration.

In the *syndrome of inappropriate ADH (SIADH)* secretion, ADH excess is caused by several extracranial and intracranial disorders. This condition leads to resorption of excessive amounts of free water, with resultant hyponatremia. The most common causes of SIADH include the secretion of ectopic ADH by malignant neoplasms (particularly small cell carcinomas of the lung), non-neoplastic diseases of the lung, and local injury to the hypothalamus or neurohypophysis. The clinical manifestations of SIADH are dominated by hyponatremia, cerebral edema, and resultant neurologic dysfunction. Although total body water is increased, blood volume remains normal, and peripheral edema does not develop.

THYROID

The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx. The thyroid gland develops embryologically from an evagination of the developing pharyngeal epithelium that descends from the foramen cecum at the base of the tongue to its normal position in the anterior neck. This pattern of descent explains the occasional presence of *ectopic thyroid tissue,* most commonly located at the base of the tongue (*lingual thyroid*) or at other sites abnormally high in the neck.

The thyroid is divided into lobules, each composed of about 20 to 40 evenly dispersed follicles. The follicles range from uniform to variable in size and are lined by cuboidal to low columnar epithelium, which is filled with thyroglobulin, the iodinated precursor protein of active thyroid hormone. In response to trophic factors from the hypothalamus, TSH (also called *thyrotropin*) is released by thyrotrophs in the anterior pituitary into the circulation. The binding of TSH to its receptor on the thyroid follicular epithelium results in activation and conformational change in the receptor, allowing it to associate with a stimulatory G protein (Fig. 19–5). Activation of the G protein eventually results in an increase in intracellular cAMP levels, which stimulates thyroid hormone synthesis and release mediated by cAMP-dependent protein kinases. Thyroid follicular epithelial cells convert thyroglobulin into *thyroxine* (T_4) and lesser amounts of *triiodothyronine* (T_3). T_4 and T_3 are released into the systemic circulation, where most of these

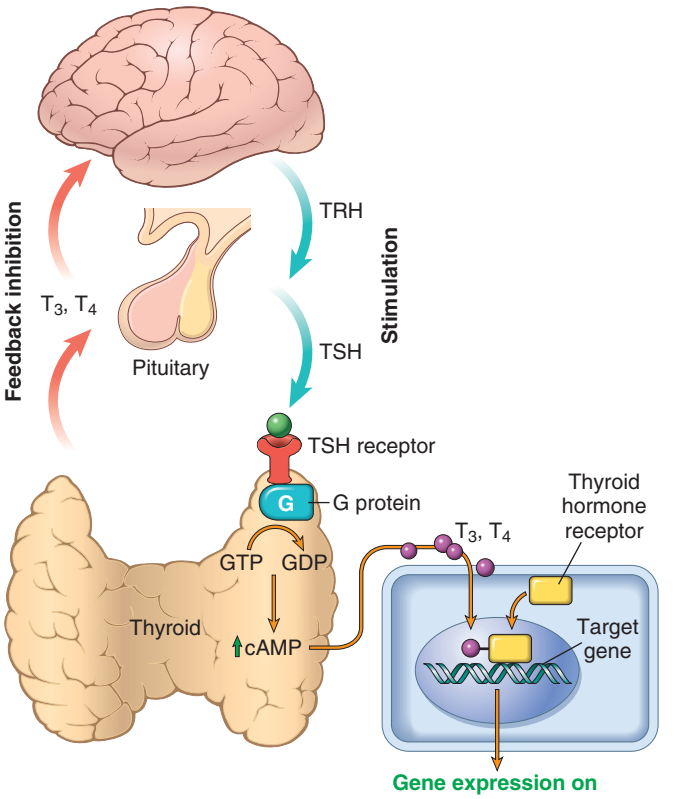


Figure 19–5 Homeostasis in the hypothalamus-pituitary-thyroid axis and mechanism of action of thyroid hormones. Secretion of thyroid hormones (T_3 and T_4) is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary. Decreased levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary, causing T_3 and T_4 levels to rise. Elevated T_3 and T_4 levels, in turn, suppress the secretion of both TRH and TSH. This relationship is termed a negative-feedback loop. TSH binds to the TSH receptor on the thyroid follicular epithelium, which causes activation of G proteins, release of cyclic AMP (cAMP), and cAMP-mediated synthesis and release of thyroid hormones (i.e., T_3 and T_4). In the periphery, T_3 and T_4 interact with the thyroid hormone receptor (TR) and form a complex that translocates to the nucleus and binds to so-called thyroid response elements (TREs) on target genes, thereby initiating transcription.

peptides are reversibly bound to circulating plasma proteins, such as T_4-binding globulin, for transport to peripheral tissues. The binding proteins serve to maintain the serum unbound (*free*) T_3 and T_4 concentrations within narrow limits while ensuring that the hormones are readily available to the tissues. In the periphery the majority of free T_4 is deiodinated to T_3; the latter binds to thyroid hormone nuclear receptors in target cells with 10-fold greater affinity than that observed for T_4 and has proportionately greater activity. *The interaction of thyroid hormone with its nuclear thyroid hormone receptor (TR) results in the formation of a hormone-receptor complex that binds to thyroid hormone response elements (TREs) in target genes, regulating their transcription.* Thyroid hormone has diverse cellular effects, including upregulation of carbohydrate and lipid catabolism and stimulation of protein synthesis in a wide range of cells. The net result of these processes is an increase in the basal metabolic rate.

Clinical recognition of diseases of the thyroid is important, because most are amenable to medical or surgical management. Such diseases include conditions associated with excessive release of thyroid hormones (hyperthyroidism), those associated with thyroid hormone deficiency (hypothyroidism), and mass lesions of the thyroid. Considered next are the clinical consequences of disturbed thyroid function, followed by an overview of the disorders that generate these problems.

HYPERTHYROIDISM

Thyrotoxicosis is a hypermetabolic state due to elevated circulating levels of free T_3 and T_4. Because it is caused most commonly by hyperfunction of the thyroid gland, thyrotoxicosis often is referred to as hyperthyroidism. In certain conditions, however, the oversupply either is related to excessive release of pre-formed thyroid hormone (e.g., in thyroiditis) or comes from an extrathyroidal source, rather than a hyperfunctioning gland (Table 19–2). *Thus, strictly speaking, hyperthyroidism is only one (albeit the most common) category of thyrotoxicosis.* Despite this clear distinction, the following discussion adheres to the common practice of using the terms *thyrotoxicosis* and *hyperthyroidism* interchangeably.

The clinical manifestations of thyrotoxicosis are truly protean and include changes referable to the *hypermetabolic state* induced by excessive amounts of thyroid hormone as well as those related to *overactivity of the sympathetic nervous system*:

- *Constitutional symptoms*: The skin of thyrotoxic persons tends to be soft, warm, and flushed; *heat intolerance* and excessive sweating are common. Increased sympathetic activity and hypermetabolism result in *weight loss despite increased appetite.*
- *Gastrointestinal*: Stimulation of the gut results in hypermotility, malabsorption, and diarrhea.
- *Cardiac*: Palpitations and tachycardia are common; elderly patients may develop congestive heart failure

Table 19–2 Causes of Thyrotoxicosis

Associated with Hyperthyroidism
Primary
Diffuse toxic hyperplasia (Graves disease)
Hyperfunctioning ("toxic") multinodular goiter
Hyperfunctioning ("toxic") adenoma
Iodine-induced hyperthyroidism
Secondary
TSH-secreting pituitary adenoma (rare)*
Not Associated with Hyperthyroidism
Granulomatous (de Quervain) thyroiditis (*painful*)
Subacute lymphocytic thyroiditis (*painless*)
Struma ovarii (ovarian teratoma with thyroid)
Factitious thyrotoxicosis (exogenous thyroxine intake)

TSH, thyroid-stimulating hormone.
*Associated with increased TSH; all other causes of thyrotoxicosis associated with decreased TSH.

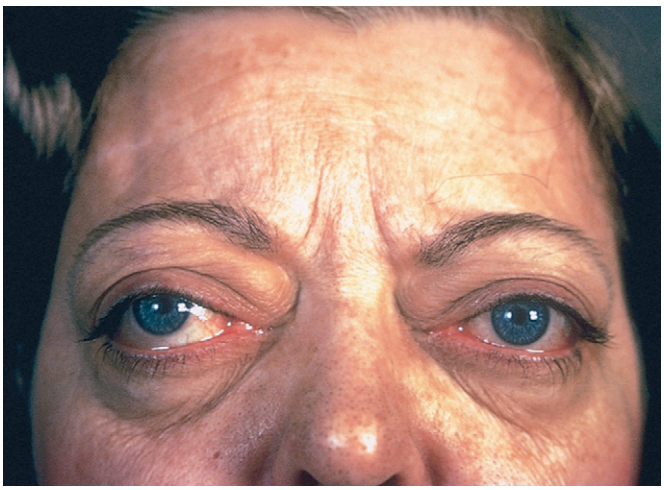


Figure 19–6 Patient with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system, is one of the classic features of this disorder. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue behind the orbits also adds to the protuberant appearance of the eyes.

as a consequence of aggravation of preexisting heart disease.

- *Neuromuscular*: Patients frequently experience nervousness, tremor, and irritability. Nearly 50% develop proximal muscle weakness (*thyroid myopathy*).
- *Ocular manifestations*: a wide, staring gaze and lid lag are present because of sympathetic overstimulation of the levator palpebrae superioris (Fig. 19–6). However, true *thyroid ophthalmopathy* associated with proptosis is a feature seen only in Graves disease (discussed later).
- *Thyroid storm* is used to designate the abrupt onset of severe hyperthyroidism. This condition occurs most commonly in patients with underlying Graves disease, probably resulting from an acute elevation in catecholamine levels, as might be encountered during stress. Thyroid storm constitutes a medical emergency: A significant number of untreated patients die of cardiac arrhythmias.
- *Apathetic hyperthyroidism* refers to thyrotoxicosis occurring in elderly persons, in whom the typical features of thyroid hormone excess seen in younger patients are blunted. In these patients the diagnosis is often made during laboratory workup for unexplained weight loss or worsening cardiovascular disease.

The diagnosis of hyperthyroidism is based on clinical features and laboratory data. *The measurement of serum TSH is the most useful single screening test for hyperthyroidism,* because TSH levels are decreased even at the earliest stages, when the disease may still be subclinical. In rare cases of pituitary- or hypothalamus-associated (secondary) hyperthyroidism, TSH levels are either normal or raised. A low TSH value usually is associated with increased levels of free T_4. In the occasional patient, hyperthyroidism results predominantly from increased circulating levels of T_3 (T_3 toxicosis). In such cases, free T_4 levels may be decreased, and direct measurement of serum T_3 may be useful. Once the diagnosis of thyrotoxicosis has been confirmed by a combination of TSH and free thyroid hormone assays, measurement of radioactive iodine uptake by the thyroid gland often is valuable in determining the etiology. For example, such scans may show diffusely increased (whole-gland) uptake in Graves disease, increased uptake in a solitary nodule in toxic adenoma, or decreased uptake in thyroiditis.

HYPOTHYROIDISM

Hypothyroidism is caused by any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone. As in the case of hyperthyroidism, this disorder is sometimes divided into primary and secondary categories, depending on whether the hypothyroidism arises from an intrinsic abnormality in the thyroid or from hypothalamic or pituitary disease (Table 19–3). Worldwide, the most common cause of hypothyroidism is dietary deficiency of iodine (see further on), while in most developed nations, autoimmune causes predominate. Genetic defects that perturb thyroid development itself (*thyroid dysgenesis*) or the synthesis of thyroid hormone (*dyshormonogenetic goiter*) are relatively rare.

The clinical manifestations of hypothyroidism include cretinism and myxedema.

- *Cretinism* refers to hypothyroidism developing in infancy or early childhood. This disorder formerly was fairly common in areas of the world where dietary iodine deficiency is endemic, including mountainous areas such as the Himalayas and the Andes (*endemic cretinism*). It is now much less frequent because of the widespread supplementation of foods with iodine. By contrast, enzyme defects that interfere with thyroid hormone synthesis are a cause of *sporadic cretinism.* Clinical features of cretinism include impaired development of the skeletal system and central nervous system, with severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia. The severity of the

Table 19–3 Causes of Hypothyroidism

Primary
Rare developmental abnormalities (thyroid dysgenesis): mutations in *PAX8, FOXE1*
Congenital biosynthetic defect (dyshormonogenetic goiter)*
Postablative
Surgery, radioiodine therapy, or external irradiation
Autoimmune hypothyroidism
Hashimoto thyroiditis*
Iodine deficiency*
Drugs (lithium, iodides, *p*-aminosalicylic acid)*
Secondary (Central)
Pituitary failure
Hypothalamic failure (rare)

FOXE1, forkhead box E1 gene; *PAX8*, paired box 8 gene.
*Associated with enlargement of thyroid ("goitrous hypothyroidism"). Hashimoto thyroiditis and postablative hypothyroidism account for a majority of cases of hypothyroidism in developed countries.

mental impairment in cretinism seems to be directly influenced by the timing of onset of the deficient state in utero. Normally, maternal hormones that are critical to fetal brain development, including T_3 and T_4, cross the placenta. If maternal thyroid deficiency is present before the development of the fetal thyroid gland, mental retardation is severe. By contrast, reduction in maternal thyroid hormones later in pregnancy, after the fetal thyroid has developed, allows normal brain development.

- Hypothyroidism developing in older children and adults results in a condition known as *myxedema.* Myxedema, or Gull disease, was first linked with thyroid dysfunction in 1873 by Sir William Gull in a paper addressing the development of a *cretinoid state* in adults. Manifestations of myxedema include generalized apathy and mental sluggishness that in the early stages of disease may mimic depression. Patients with myxedema are listless, cold intolerant, and often obese. Mucopolysaccharide-rich edematous fluid accumulates in skin, subcutaneous tissue, and a number of visceral sites, with resultant broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice. Bowel motility is decreased, resulting in constipation. Pericardial effusions are common; in later stages, the heart is enlarged, and heart failure may supervene.

Laboratory evaluation has a vital role in the diagnosis of suspected hypothyroidism. As in the case of hyperthyroidism, *measurement of serum TSH is the most sensitive screening test for this disorder.* The serum TSH is increased in primary hypothyroidism because of a loss of feedback inhibition of thyrotropin-releasing hormone (TRH) and TSH production by the hypothalamus and pituitary, respectively. The TSH concentration is not increased in persons with hypothyroidism caused by primary hypothalamic or pituitary disease. Serum T_4 is decreased in patients with hypothyroidism of any origin.

THYROIDITIS

Thyroiditis, or inflammation of the thyroid gland, encompasses a diverse group of disorders characterized by some form of thyroid inflammation. These diseases include conditions that result in acute illness with severe thyroid pain (e.g., infectious thyroiditis, granulomatous [de Quervain] thyroiditis) and disorders in which relatively little inflammation occurs and the illness is manifested primarily by thyroid dysfunction (subacute lymphocytic ["painless"] thyroiditis and fibrous [Reidel] thyroiditis). This section focuses on the more common and clinically significant types of thyroiditis: (1) Hashimoto thyroiditis (or chronic lymphocytic thyroiditis); (2) granulomatous (de Quervain) thyroiditis; and (3) subacute lymphocytic thyroiditis.

Chronic Lymphocytic (Hashimoto) Thyroiditis

Hashimoto thyroiditis is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient. It is characterized by gradual thyroid failure secondary to autoimmune destruction of the thyroid gland. It is most prevalent between the ages of 45 and 65 years and is more common in women than in men, with female predominance in a ratio of 10:1 to 20:1. Although it is primarily a disease of older women, it can occur in children and is a major cause of nonendemic goiter in children.

PATHOGENESIS

Hashimoto thyroiditis is caused by a breakdown in **self-tolerance** (Chapter 4) to thyroid autoantigens. Thus, circulating autoantibodies against thyroid antigens are present in the vast majority of patients, who demonstrate progressive depletion of thyroid epithelial cells (thyrocytes) and their replacement by mononuclear cell infiltration and fibrosis. The inciting events leading to breakdown in self-tolerance have not been fully elucidated, but multiple immunologic mechanisms that may contribute to thyrocyte damage have been identified (Fig. 19–7), including

- **CD8+ cytotoxic T cell–mediated cell death:** CD8+ cytotoxic T cells may cause thyrocyte destruction.
- **Cytokine-mediated cell death:** Excessive T cell activation leads to the production of inflammatory cytokines such as interferon-γ in the thyroid gland, with resultant recruitment and activation of macrophages and damage to follicles.
- Binding of **antithyroid antibodies** (antithyroglobulin, and antithyroid peroxidase antibodies), followed by antibody-dependent cell–mediated cytotoxicity (Chapter 4).

A significant genetic component to the disease pathogenesis is supported by the concordance of disease in as many as 40% of monozygotic twins, as well as the presence of circulating antithyroid antibodies in approximately 50% of asymptomatic siblings of affected patients. Increased susceptibility to Hashimoto thyroiditis is associated with polymorphisms in multiple immune regulation–associated genes, the most significant of which is the linkage to **cytotoxic T lymphocyte–associated antigen-4** gene (*CTLA4*), which codes for a negative regulator of T cell function (Chapter 4).

MORPHOLOGY

The thyroid usually is diffusely and symmetrically enlarged, although more localized enlargement may be seen in some cases. The cut surface is pale and gray-tan in appearance, and the tissue is firm and somewhat friable. Microscopic examination reveals widespread infiltration of the parenchyma by a **mononuclear inflammatory infiltrate** containing small lymphocytes, plasma cells, and well-developed **germinal centers** (Fig. 19–8). The thyroid follicles are atrophic and are lined in many areas by epithelial cells distinguished by the presence of abundant eosinophilic, granular cytoplasm, termed **Hürthle,** or **oxyphil, cells.** This is a metaplastic response of the normally low cuboidal follicular epithelium to ongoing injury; on ultrastructural examination, the Hürthle cells are characterized by numerous prominent

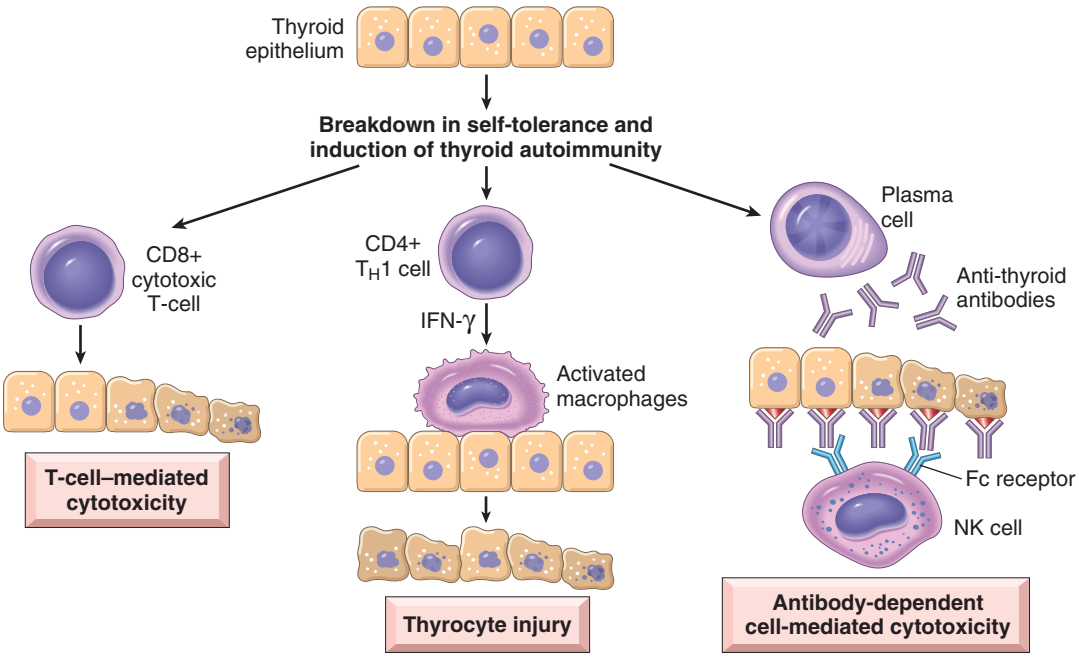


Figure 19–7 Pathogenesis of Hashimoto thyroiditis. Breakdown of immune tolerance to thyroid autoantigens results in progressive autoimmune destruction of thyrocytes by infiltrating cytotoxic T cells, locally released cytokines, or antibody-dependent cytotoxicity.

mitochondria. Interstitial connective tissue is increased and may be abundant. Less commonly, the thyroid is small and atrophic as a result of more extensive fibrosis **(fibrosing variant).** Unlike in Reidel thyroiditis, the fibrosis does not extend beyond the capsule of the gland.

Clinical Features

Hashimoto thyroiditis comes to clinical attention as *painless enlargement of the thyroid, usually associated with some degree of hypothyroidism,* in a middle-aged woman. The enlargement of the gland usually is symmetric and diffuse, but in some cases it may be sufficiently localized to raise suspicion for neoplasm. In the usual clinical course, hypothyroidism develops gradually. In some cases, however, it *may be preceded by transient thyrotoxicosis* caused by disruption of thyroid follicles, with secondary release of thyroid hormones (*hashitoxicosis*). During this phase, free T_4 and T_3 concentrations are elevated, TSH is diminished, and radioactive iodine uptake is decreased. As hypothyroidism supervenes, T_4 and T_3 levels progressively fall, accompanied by a compensatory increase in TSH. Patients with Hashimoto thyroiditis often have *other autoimmune diseases* and are at *increased risk for the development of B cell non-Hodgkin lymphomas* (Chapter 11), which typically arise within the thyroid gland. The relationship between Hashimoto disease and thyroid epithelial cancers remains controversial, with some morphologic and molecular studies suggesting a predisposition to papillary carcinomas.

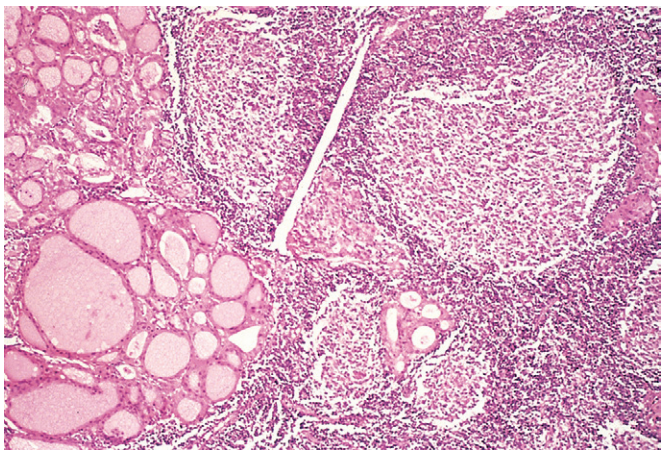


Figure 19–8 Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells also are seen.

Subacute Granulomatous (de Quervain) Thyroiditis

Subacute granulomatous thyroiditis, also known as de Quervain thyroiditis, is much less common than Hashimoto disease. De Quervain thyroiditis is most common between the ages of 30 and 50 and, like other forms of thyroiditis, occurs more frequently in women than in men. Subacute thyroiditis is believed to be caused by a viral infection or an inflammatory process triggered by viral infections. A majority of patients have a history of an upper respiratory infection just before the onset of thyroiditis. By contrast with autoimmune thyroid disease, the immune response is not self-perpetuating, so the process is limited.

MORPHOLOGY

The gland is firm, with an intact capsule, and may be unilaterally or bilaterally enlarged. Histologic examination reveals disruption of thyroid follicles, with extravasation of colloid leading to a polymorphonuclear infiltrate, which is replaced over time by lymphocytes, plasma cells, and macrophages. The extravasated colloid provokes an exuberant granulomatous reaction with giant cells, some containing fragments of colloid. Healing occurs by resolution of inflammation and fibrosis.

Clinical Features

The onset of this form of thyroiditis often is acute, characterized by *pain* in the neck (particularly with swallowing), fever, malaise, and variable enlargement of the thyroid. Transient hyperthyroidism may occur, as in other cases of thyroiditis, as a result of disruption of thyroid follicles and release of excessive thyroid hormone. The leukocyte count and erythrocyte sedimentation rates are increased. With progression of disease and gland destruction, a transient hypothyroid phase may ensue. The condition typically is self-limited, with most patients returning to a euthyroid state within 6 to 8 weeks.

Subacute Lymphocytic Thyroiditis

Subacute lymphocytic thyroiditis also is known as *silent* or *painless* thyroiditis; in a subset of patients the onset of disease follows pregnancy (*postpartum thyroiditis*). This disease is most likely to be autoimmune in etiology, because circulating antithyroid antibodies are found in a majority of patients. It mostly affects middle-aged women, who present with a *painless* neck mass or features of thyroid hormone excess. The initial phase of thyrotoxicosis (which is likely to be secondary to thyroid tissue damage) is followed by return to a euthyroid state within a few months. In a minority of affected persons the condition eventually progresses to hypothyroidism. Except for possible mild symmetric enlargement, the thyroid appears normal on gross inspection. The histologic features consist of lymphocytic infiltration and hyperplastic germinal centers within the thyroid parenchyma.

Other Forms of Thyroiditis

Riedel thyroiditis, a rare disorder of unknown etiology, is characterized by extensive fibrosis involving the thyroid and contiguous neck structures. Clinical evaluation demonstrates a hard and fixed thyroid mass, simulating a thyroid neoplasm. It may be associated with idiopathic fibrosis in other sites in the body, such as the retroperitoneum. The presence of circulating antithyroid antibodies in most patients suggests an autoimmune etiology.

SUMMARY

Thyroiditis

- Chronic lymphocytic (Hashimoto) thyroiditis is the most common cause of hypothyroidism in regions where dietary iodine levels are sufficient.
- Hashimoto thyroiditis is an autoimmune disease characterized by progressive destruction of thyroid parenchyma, Hürthle cell change, and mononuclear (lymphoplasmacytic) infiltrates, with or without extensive fibrosis.
- Multiple autoimmune mechanisms account for Hashimoto disease, including cytotoxicity mediated by CD8+ T cells, cytokines (IFN-γ), and antithyroid antibodies.
- Subacute granulomatous (de Quervain) thyroiditis is a self-limited disease, probably secondary to a viral infection, and is characterized by pain and the presence of a granulomatous inflammation in the thyroid.
- Subacute lymphocytic thyroiditis is a self-limited disease that often occurs after a pregnancy (postpartum thyroiditis), typically is painless, and is characterized by lymphocytic inflammation in the thyroid.

GRAVES DISEASE

In 1835 Robert Graves reported on his observations of a disease characterized by "violent and long continued palpitations in females" associated with enlargement of the thyroid gland. *Graves disease is the most common cause of endogenous hyperthyroidism.* It is characterized by a triad of manifestations:

- *Thyrotoxicosis,* caused by a diffusely enlarged, hyperfunctional thyroid, is present in all cases.
- An infiltrative *ophthalmopathy* with resultant exophthalmos is noted in as many as 40% of patients.
- A localized, infiltrative *dermopathy* (sometimes designated *pretibial myxedema*) is seen in a minority of cases.

Graves disease has a peak incidence between the ages of 20 and 40, with *women being affected up to seven times more commonly than men.* This very common disorder is estimated to affect 1.5% to 2.0% of women in the United States. Genetic factors are important in the causation of Graves disease; the incidence is increased in relatives of affected patients, and the concordance rate in monozygotic twins is as high as 60%. As with other autoimmune disorders, a genetic susceptibility to Graves disease is associated with the presence of certain human leukocyte antigen (HLA) haplotypes, specifically HLA-DR3, and polymorphisms in genes encoding the inhibitory T cell receptor CTLA-4 and the tyrosine phosphatase PTPN22.

PATHOGENESIS

Graves disease is characterized by a breakdown in self-tolerance to thyroid autoantigens, of which the most important is the TSH receptor. The result is the production of multiple autoantibodies, including:

- **Thyroid-stimulating immunoglobulin:** An IgG antibody that binds to the TSH receptor and mimics the action of TSH, stimulating adenyl cyclase, with resultant increased release of thyroid hormones. Almost all persons with Graves disease have detectable amounts of this autoantibody, which is relatively specific for Graves disease.
- **Thyroid growth-stimulating immunoglobulins:** Also directed against the TSH receptor, these antibodies

have been implicated in the proliferation of thyroid follicular epithelium.

- **TSH-binding inhibitor immunoglobulins:** These anti-TSH receptor antibodies prevent TSH from binding to its receptor on thyroid epithelial cells and in so doing may actually **inhibit** thyroid cell function. The coexistence of stimulating *and* inhibiting immunoglobulins in the serum of the same patient is not unusual—a finding that may explain why some patients with Graves disease spontaneously develop episodes of hypothyroidism.

A T cell–mediated autoimmune phenomenon also is involved in the development of the **infiltrative ophthalmopathy** characteristic of Graves disease. In Graves ophthalmopathy, the volume of the retroorbital connective tissues and extraocular muscles is increased as a result of several causes, including (1) marked infiltration of the retroorbital space by mononuclear cells, predominantly T cells; (2) inflammatory edema and swelling of extraocular muscles; (3) accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate; and (4) increased numbers of adipocytes (fatty infiltration). These changes displace the eyeball forward, potentially interfering with the function of the extraocular muscles.

Autoimmune disorders of the thyroid thus span a continuum on which Graves disease, characterized by hyperfunction of the thyroid, lies at one extreme and Hashimoto disease, manifesting as hypothyroidism, occupies the other end. Sometimes hyperthyroidism may supervene on preexisting Hashimoto thyroiditis (*hashitoxicosis*), while at other times persons with Graves disease may spontaneously develop thyroid hypofunction; occasionally, Hashimoto thyroiditis and Graves disease may coexist within an affected kindred. Not surprisingly, there is also an element of histologic overlap between the autoimmune thyroid disorders (most characteristically, prominent intrathyroidal lymphoid cell infiltrates with germinal center formation). In both disorders, the frequency of other autoimmune diseases, such as systemic lupus erythematosus, pernicious anemia, type 1 diabetes, and Addison disease, is increased.

MORPHOLOGY

In the typical case of Graves disease, the thyroid gland is enlarged (usually symmetrically) due to **diffuse hypertrophy and hyperplasia** of thyroid follicular epithelial cells. The gland is usually smooth and soft, and its capsule is intact. On microscopic examination, the follicular epithelial cells in untreated cases are tall, columnar, and more crowded than usual. This crowding often results in the formation of small papillae, which project into the follicular lumen (Fig. 19–9). Such papillae lack fibrovascular cores, in contrast with those of papillary carcinoma. The colloid within the follicular lumen is pale, with scalloped margins. Lymphoid infiltrates, consisting predominantly of T cells, with fewer B cells and mature plasma cells, are present throughout the interstitium; germinal centers are common.

Changes in extrathyroidal tissues include generalized lymphoid hyperplasia. In persons with ophthalmopathy, the tissues of the orbit are edematous because of the presence of hydrophilic glycosaminoglycans. In addition, there is infiltration by lymphocytes, mostly T cells. Orbital muscles initially are edematous but may undergo fibrosis late in the course of the disease. The dermopathy, if present, is characterized by thickening of the dermis, as a result of deposition of glycosaminoglycans and lymphocyte infiltration.

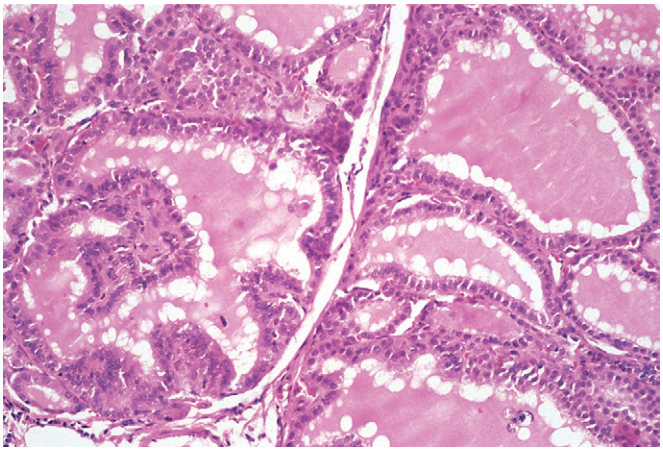


Figure 19–9 Graves disease. The thyroid is diffusely hyperplastic. The follicles are lined by tall columnar epithelial cells that project into the lumina. These cells actively resorb the colloid in the centers of the follicles, resulting in the "scalloped" appearance of the edges of the colloid.

Clinical Features

The clinical manifestations of Graves disease include those common to all forms of thyrotoxicosis (discussed earlier), as well as those associated uniquely with Graves disease: *diffuse hyperplasia of the thyroid, ophthalmopathy,* and *dermopathy*. The degree of thyrotoxicosis varies from case to case, and the related changes may sometimes be less conspicuous than other manifestations of the disease. Increased flow of blood through the hyperactive gland often produces an audible bruit. Sympathetic overactivity produces a characteristic wide, staring gaze and lid lag. The ophthalmopathy of Graves disease results in abnormal protrusion of the eyeball (exophthalmos). The extraocular muscles often are weak. The exophthalmos may persist or progress despite successful treatment of the thyrotoxicosis, sometimes resulting in corneal injury. The infiltrative dermopathy, or pretibial myxedema, most commonly involves the skin overlying the shins, where it manifests as scaly thickening and induration of the skin. The skin lesions may be slightly pigmented papules or nodules and often have an orange peel texture. Laboratory findings in Graves disease include elevated serum free T_4 and T_3 and depressed serum TSH. Because of ongoing stimulation of the thyroid follicles by TSIs, radioactive iodine uptake is increased, and radioiodine scans show a *diffuse uptake* of iodine.

SUMMARY

Graves Disease

- Graves disease, the most common cause of endogenous hyperthyroidism, is characterized by the triad of thyrotoxicosis, ophthalmopathy, and dermopathy.

- Graves disease is an autoimmune disorder caused by autoantibodies to the TSH receptor that mimic TSH action and activate TSH receptors on thyroid epithelial cells.
- The thyroid in Graves disease is characterized by diffuse hypertrophy and hyperplasia of follicles and lymphoid infiltrates; glycosaminoglycan deposition and lymphoid infiltrates are responsible for the ophthalmopathy and dermopathy.
- Laboratory features include elevations in serum free T_3 and T_4 and decreased serum TSH.

DIFFUSE AND MULTINODULAR GOITER

Enlargement of the thyroid, or *goiter,* is the most common manifestation of thyroid disease. *Diffuse and multinodular goiters reflect impaired synthesis of thyroid hormone,* most often caused by dietary iodine deficiency. Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH, which in turn causes hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, gross enlargement of the thyroid gland. The compensatory increase in functional mass of the gland is enough to overcome the hormone deficiency, ensuring a *euthyroid* metabolic state in the vast majority of affected persons. If the underlying disorder is sufficiently severe (e.g., a congenital biosynthetic defect), the compensatory responses may be inadequate to overcome the impairment in hormone synthesis, resulting in *goitrous hypothyroidism.* The degree of thyroid enlargement is proportional to the level and duration of thyroid hormone deficiency.

Goiters can be endemic or sporadic.

- *Endemic goiter* occurs in geographic areas where the soil, water, and food supply contain little iodine. The designation *endemic* is used when goiters are present in more than 10% of the population in a given region. Such conditions are particularly common in mountainous areas of the world, including the Himalayas and the Andes. With increasing availability of dietary iodine supplementation, the frequency and severity of endemic goiter have declined significantly.
- *Sporadic goiter* occurs less commonly than endemic goiter. The condition is more common in females than in males, with a peak incidence in puberty or young adulthood, when there is an increased physiologic demand for T_4. Sporadic goiter may be caused by several conditions, including the ingestion of substances that interfere with thyroid hormone synthesis at some level, such as excessive calcium and vegetables belonging to the Brassicaceae (also called Cruciferae) family (e.g., cabbage, cauliflower, Brussels sprouts, turnips). In other instances, goiter may result from hereditary enzymatic defects that interfere with thyroid hormone synthesis *(dyshormonogenetic goiter).* In most cases, however, the cause of sporadic goiter is not apparent.

MORPHOLOGY

In most cases, TSH-induced hypertrophy and hyperplasia of thyroid follicular cells result initially in diffuse, symmetric enlargement of the gland **(diffuse goiter).** The follicles are lined by crowded columnar cells, which may pile up and form projections similar to those seen in Graves disease. If dietary iodine subsequently increases, or if the demands for thyroid hormone decrease, the stimulated follicular epithelium involutes to form an enlarged, colloid-rich gland **(colloid goiter).** The cut surface of the thyroid in such cases usually is brown, somewhat glassy-appearing, and translucent. On microscopic examination, the follicular epithelium may be hyperplastic in the early stages of disease or flattened and cuboidal during periods of involution. Colloid is abundant during the latter periods. With time, recurrent episodes of hyperplasia and involution combine to produce a more irregular enlargement of the thyroid, termed **multinodular goiter.** Virtually all long-standing diffuse goiters convert into multinodular goiters. Multinodular goiters typically are hormonally silent, although a minority (approximately 10% over 10 years) can manifest with thyrotoxicosis secondary to the development of **autonomous** nodules that produce thyroid hormone independent of TSH stimulation. This condition, known as toxic multinodular goiter or **Plummer syndrome,** is not accompanied by the infiltrative ophthalmopathy and dermopathy of Graves disease–associated thyrotoxicosis.

Multinodular goiters are multilobulate, asymmetrically enlarged glands, which may attain massive size. On cut surface, irregular nodules containing variable amounts of brown, gelatinous colloid are evident (Fig. 19–10, *A*). Older lesions often show areas of fibrosis, hemorrhage, calcification, and cystic change. The microscopic appearance includes colloid-rich follicles lined by flattened, inactive epithelium and areas of follicular epithelial hypertrophy and hyperplasia, accompanied by the regressive changes just noted (Fig. 19–10, *B*).

Clinical Features

The dominant clinical features of goiter are those caused by the *mass effects* of the enlarged gland. In addition to the obvious cosmetic problem of a large neck mass, goiters also may cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax (so-called *superior vena cava syndrome*). As stated, a hyperfunctioning (*toxic*) nodule may develop within a long-standing goiter, resulting in *hyperthyroidism.* The incidence of malignancy in long-standing multinodular goiters is low (less than 5%) but not zero, and concern for malignancy arises with goiters that demonstrate sudden changes in size or associated symptoms (e.g., hoarseness).

NEOPLASMS OF THE THYROID

The thyroid gland gives rise to a variety of neoplasms, ranging from circumscribed, benign adenomas to highly aggressive, anaplastic carcinomas. From a clinical standpoint, the possibility of a tumor is of major concern in patients who present with *thyroid nodules.* Fortunately, the overwhelming majority of solitary nodules of the thyroid

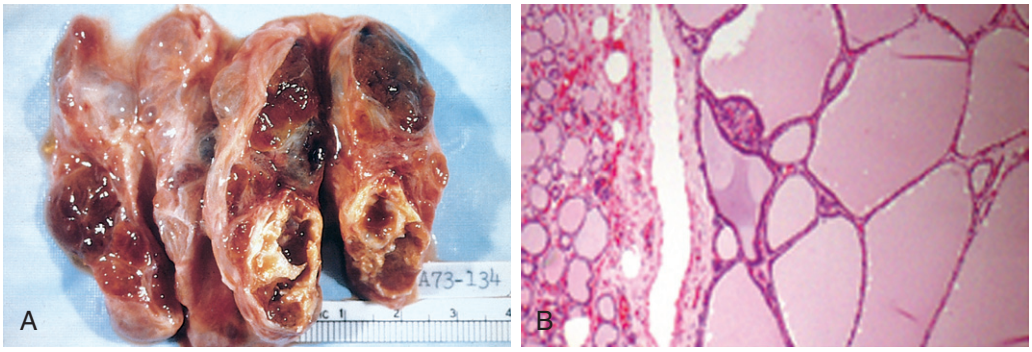


Figure 19–10 Multinodular goiter. **A,** Gross morphologic appearance. The coarsely nodular gland contains areas of fibrosis and cystic change. **B,** Photomicrograph of specimen from a hyperplastic nodule, with compressed residual thyroid parenchyma on the periphery. The hyperplastic follicles contain abundant pink "colloid" within their lumina. Note the absence of a prominent capsule, a feature distinguishing such lesions from neoplasms of the thyroid.

(B, Courtesy of Dr. William Westra, Department of Pathology, Johns Hopkins University, Baltimore, Maryland.)

prove to be either follicular adenomas or localized, non-neoplastic conditions (e.g., a dominant nodule in multinodular goiter, simple cysts, or foci of thyroiditis). Carcinomas of the thyroid, by contrast, are uncommon, accounting for much less than 1% of solitary thyroid nodules. Several clinical criteria provide a clue to the nature of a given thyroid nodule:

- *Solitary nodules,* in general, are more likely to be neoplastic than are multiple nodules.
- *Nodules in younger patients* are more likely to be neoplastic than are those in older patients.
- *Nodules in males* are more likely to be neoplastic than are those in females.
- A history of *radiation* treatment to the head and neck region is associated with an increased incidence of thyroid malignancy.
- Nodules that take up radioactive iodine in imaging studies (*hot nodules*) are more likely to be benign than malignant, reflecting well-differentiated cells.

Such statistics and general trends, however, are of little significance in the evaluation of a given patient, in whom the timely recognition of a malignancy, however uncommon, can be lifesaving. Ultimately, it is the morphologic evaluation of a given thyroid nodule by fine needle aspiration, combined with histologic study of surgically resected thyroid parenchyma, that provides the most definitive information about its nature. This section presents an overview of the major thyroid neoplasms, including adenomas and carcinomas of various types.

Adenomas

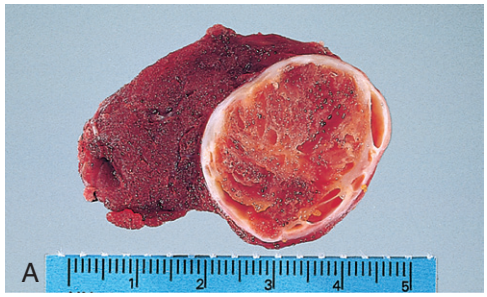
Adenomas of the thyroid are benign neoplasms derived from follicular epithelium. As in the case of all thyroid neoplasms, follicular adenomas usually are solitary. On clinical and morphologic grounds, they may be difficult to distinguish from a dominant nodule in multinodular goiter, for example, or from the less common follicular carcinomas. Although the vast majority of adenomas are nonfunctional, a small proportion produce thyroid hormones (*toxic adenomas*), causing clinically apparent thyrotoxicosis. In general, follicular adenomas are *not* forerunners to carcinomas; nevertheless, shared genetic alterations support the possibility that at least a subset of follicular carcinomas arise in preexisting adenomas (see further on).

PATHOGENESIS

The TSH receptor signaling pathway plays an important role in the pathogenesis of toxic adenomas. Activating (gain-of-function) somatic mutations in one of two components of this signaling system—most often the gene encoding the TSH receptor itself (TSHR) and, less commonly, the α-subunit of G_s (GNAS)—allow follicular cells to secrete thyroid hormone independent of TSH stimulation (thyroid autonomy). The result of this overabundance is symptomatic hyperthyroidism, with a "hot" thyroid nodule seen on imaging studies. Overall, somatic mutations in the TSH receptor signaling pathway seem to be present in slightly over half of toxic adenomas. Not surprisingly, such mutations also are observed in a subset of autonomous nodules that give rise to toxic multinodular goiters, as described earlier. A minority of nonfunctioning follicular adenomas (less than 20%) exhibit mutations of RAS or phosphatidylinositol-3-kinase (PIK3CA), or bear a *PAX8/PPARG* fusion gene, all of which are genetic alterations shared with follicular carcinomas. These are discussed in further detail under "Carcinomas" (see further on).

MORPHOLOGY

The typical thyroid adenoma is a **solitary,** spherical lesion that compresses the adjacent non-neoplastic thyroid. The neoplastic cells are demarcated from the adjacent parenchyma by a **well-defined, intact capsule** (Fig. 19–11, *A*). **These features are important in making the distinction from multinodular goiters,** which contain multiple nodules on their cut surface (even though the patient may present clinically with a solitary dominant nodule), do not demonstrate compression of the adjacent thyroid parenchyma, and lack a well-formed capsule. On microscopic examination, the constituent cells are arranged in uniform follicles that contain colloid (Fig. 19–11, *B*). Papillary growth



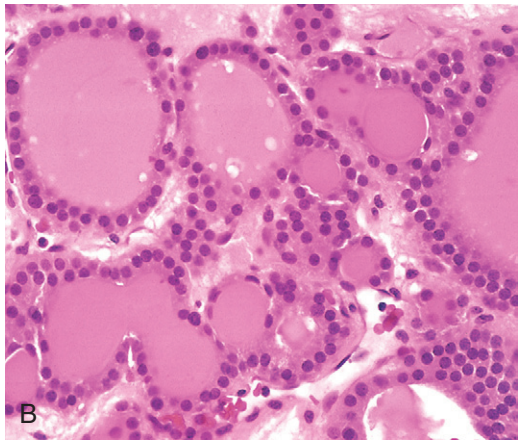


Figure 19–11 Follicular adenoma of the thyroid. **A,** A solitary, well-circumscribed nodule is visible in this gross specimen. **B,** The photomicrograph shows well-differentiated follicles resembling those of normal thyroid parenchyma.

patterns, if present, should raise suspicion for an encapsulated papillary carcinoma (discussed later). Occasionally, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (oxyphil or Hürthle cell change) (Fig. 19–12); the clinical presentation and behavior of a **Hürthle cell adenoma** are no different from those of a conventional adenoma. Similar to endocrine tumors at other anatomic sites, even benign follicular adenomas may, on occasion, exhibit focal nuclear pleomorphism, atypia, and prominent nucleoli **(endocrine atypia);** by themselves, these features do not constitute evidence of malignancy. The hallmark of all follicular adenomas is the presence of an intact well-formed capsule encircling the tumor. **Careful evaluation of the integrity of the capsule is therefore critical in distinguishing follicular adenomas from follicular carcinomas,** which demonstrate capsular and/or vascular invasion (see later).

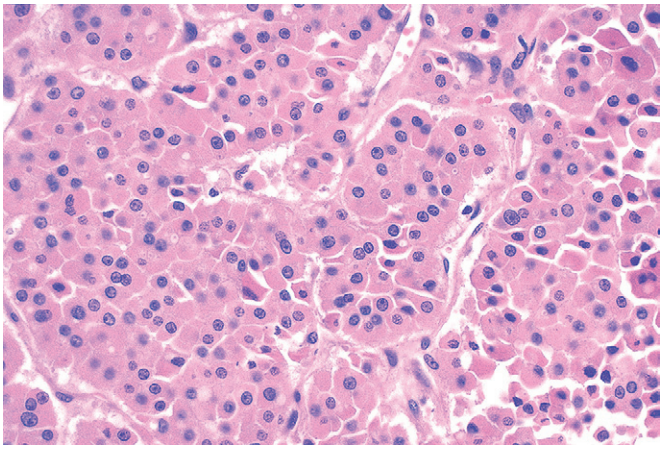


Figure 19–12 Hürthle cell adenoma. On this high-power view, the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei.
(Courtesy of Dr. Mary Sunday, Brigham and Women's Hospital, Boston, Massachusetts.)

Clinical Features

Most adenomas of the thyroid manifest as painless nodules, often discovered during a routine physical examination. Larger masses may produce local symptoms such as difficulty in swallowing. As previously stated, persons with toxic adenomas can present with features of thyrotoxicosis. After injection of radioactive iodine, most adenomas take up iodine less avidly than normal thyroid parenchyma. On radionuclide scanning, therefore, adenomas appear as *cold* nodules relative to the adjacent normal thyroid gland. Toxic adenomas, however, will appear as *warm* or *hot* nodules in the scan. As many as 10% of *cold* nodules eventually prove to be malignant. By contrast, malignancy is rare in *hot* nodules. Essential techniques used in the preoperative evaluation of suspected adenomas are ultrasonography and fine needle aspiration biopsy. Because of the need for evaluating capsular integrity, *the definitive diagnosis of thyroid adenoma can be made only after careful histologic examination of the resected specimen.* Suspected adenomas of the thyroid are therefore removed surgically to exclude malignancy. Thyroid adenomas carry an excellent prognosis and do not recur or metastasize.

Carcinomas

Carcinomas of the thyroid are relatively uncommon in the United States, accounting for about 1.5% of all cancers. A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years. By contrast, cases manifesting in childhood and late adult life are distributed equally between males and females. Most thyroid carcinomas (except medullary carcinomas) are derived from the thyroid follicular epithelium, and of these, the vast majority are well-differentiated lesions. The major subtypes of thyroid carcinoma and their relative frequencies are

- Papillary carcinoma (accounting for more than 85% of cases)
- Follicular carcinoma (5% to 15% of cases)
- Anaplastic (undifferentiated) carcinoma (less than 5% of cases)
- Medullary carcinoma (5% of cases)

Because of the unique clinical and biologic features associated with each variant of thyroid carcinoma, these subtypes are described separately. Presented next is an overview of the molecular pathogenesis of all thyroid cancers.

PATHOGENESIS

Both genetic and environmental factors are implicated in the pathogenesis of thyroid cancers.

Genetic Factors. Distinct molecular events are involved in the pathogenesis of the four major variants of thyroid cancer. As stated, medullary carcinomas do not arise from the follicular epithelium. Genetic alterations in the three follicular cell–derived malignancies are clustered along two oncogenic pathways—the mitogen-activated protein (MAP) kinase pathway and the phosphatidylinositol-3-kinase (PI-3K)/AKT pathway (Fig. 19–13). In normal cells, these pathways are transiently activated by binding of soluble growth factor ligands to the extracellular domain of receptor tyrosine kinases, which results in autophosphorylation of the cytoplasmic domain of the receptor, permitting intracellular signal transduction. In thyroid carcinomas, as with many solid cancers (Chapter 5), gain-of-function mutations along components of these pathways lead to constitutive activation even in the absence of ligand, thus promoting carcinogenesis.

- **Papillary thyroid carcinomas: Activation of the MAP kinase pathway is a feature of most papillary carcinomas** and can occur by one of two major mechanisms. The first mechanism involves rearrangements of *RET* or *NTRK1* (neurotrophic tyrosine kinase receptor 1), both of which encode transmembrane receptor tyrosine kinases, and the second mechanism involves activating point mutations in *BRAF*, whose product is an intermediate signaling component in the MAP kinase pathway (Fig. 19–13). The *RET* gene is not normally expressed in thyroid follicular cells. In papillary cancers, chromosomal rearrangements place the tyrosine kinase domain of *RET* under the transcriptional control of genes that are constitutively expressed in the thyroid epithelium. The novel fusion proteins that are so formed are known as RET/PTC (papillary thyroid carcinoma) and are present in approximately 20% to 40% of papillary thyroid cancers. The frequency of *RET/PTC* rearrangements is significantly higher in papillary cancers arising in the backdrop of radiation exposure. Similarly, rearrangements of *NTRK1* are present in 5% to 10% of papillary thyroid cancers, and the resultant fusion proteins are constitutively expressed in thyroid cells, leading to activation of MAP kinase pathways. One third to one half of papillary thyroid carcinomas harbor a gain-of-function mutation in the *BRAF* gene, which most commonly is a valine-to-glutamate change on codon 600 ($BRAF^{V600E}$). Since chromosomal rearrangements of the *RET* or *NTRK1* genes and mutations of *BRAF* have redundant effects on the thyroid epithelium (both mechanisms result in activation of the MAP kinase signaling pathway), papillary thyroid carcinomas demonstrate either one or the other molecular abnormality, but not both. *RET/PTC* rearrangements and *BRAF* point mutations are not observed in follicular adenomas or carcinomas.
- **Follicular thyroid carcinomas:** Approximately one third to one half of follicular thyroid carcinomas harbor **mutations in the PI-3K/AKT signaling pathway,** resulting in constitutive activation of this oncogenic pathway. This subset of tumors includes those with gain-of-function point mutations of *RAS* and *PIK3CA,* those with amplification of *PIK3CA,* and those with loss-of-function mutations of *PTEN,* a tumor suppressor gene and negative regulator of this pathway. The progressive increase in the prevalence of *RAS* and *PIK3CA* mutations from benign follicular adenomas to follicular carcinomas to anaplastic carcinomas (see next) suggests a shared histogenesis and molecular evolution among these follicular cell–derived tumors. A unique (2;3)(q13;p25) translocation has been described in one third to one half of follicular carcinomas. This translocation creates a fusion gene composed of portions of *PAX8*, a paired homeobox gene that is important in thyroid development, and the peroxisome proliferator–activated receptor gene (*PPARG*), whose gene product is a nuclear hormone receptor implicated in terminal differentiation of cells. Less than 10% of follicular adenomas harbor ***PAX8/PPARG* fusion genes,** and thus far these have not been documented in other thyroid neoplasms.
- **Anaplastic carcinomas:** These highly aggressive and lethal tumors can arise de novo or, more commonly, by **dedifferentiation** of a well-differentiated papillary or follicular carcinoma. Molecular alterations present in anaplastic carcinomas include those also seen in well-differentiated carcinomas (e.g., *RAS* or *PIK3CA* mutations), albeit at a significantly higher rate, suggesting that the presence of these mutations might predispose existing thyroid neoplasms to transform. Other genetic *hits,* such as inactivation of *TP53*, are essentially restricted to anaplastic carcinomas and may also relate to their aggressive behavior.
- **Medullary thyroid carcinomas:** In contrast with the subtypes described earlier, these neoplasms arise from the

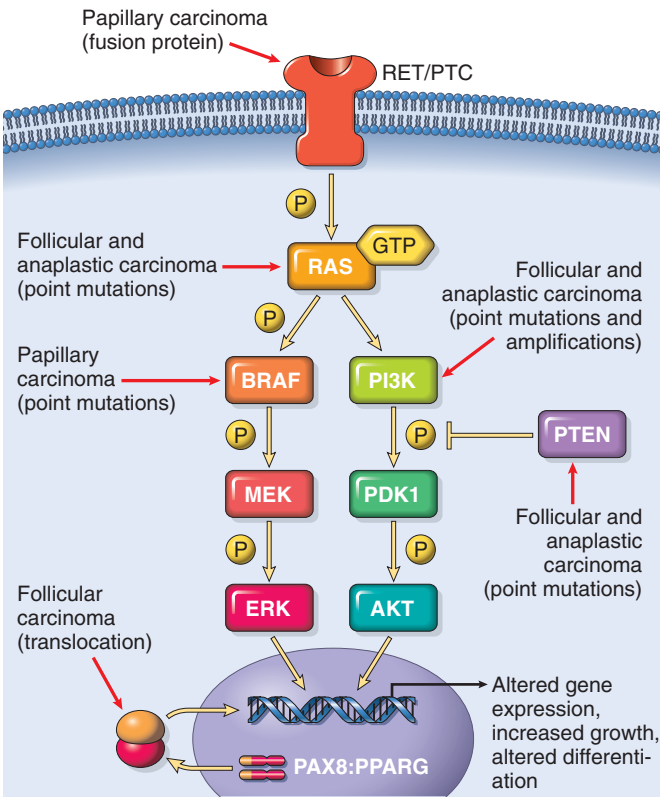


Figure 19–13 Genetic alterations in follicular cell–derived malignancies of the thyroid gland.

parafollicular C cells, rather than the follicular epithelium. Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) (see later) and are associated with germline ***RET* proto-oncogene mutations** that lead to constitutive activation of the receptor. *RET* mutations are also seen in approximately one half of nonfamilial (sporadic) medullary thyroid cancers. Chromosomal rearrangements involving *RET,* such as the *RET/PTC* translocations reported in papillary cancers, are not seen in medullary carcinomas.

Environmental Factors. The major risk factor predisposing to thyroid cancer is exposure to **ionizing radiation,** particularly during the first 2 decades of life. In keeping with this finding, there was a marked increase in the incidence of papillary carcinomas among children exposed to ionizing radiation after the Chernobyl nuclear disaster in 1986. **Deficiency of dietary iodine** (and by extension, an association with goiter) is linked with a higher frequency of follicular carcinomas.

Papillary Carcinoma

As mentioned earlier, papillary carcinomas represent the most common form of thyroid cancer. These tumors may occur at any age, and they account for the vast majority of thyroid carcinomas associated with previous exposure to ionizing radiation.

MORPHOLOGY

Papillary carcinomas may manifest as solitary or multifocal lesions within the thyroid. In some cases, they may be well circumscribed and even encapsulated; in other instances, they infiltrate the adjacent parenchyma with ill-defined margins. The lesions may contain areas of fibrosis and calcification and often are cystic. On cut surface, they may appear granular and sometimes contain grossly discernible papillary foci (Fig. 19–14, *A*). The definitive diagnosis of papillary carcinoma can be made only after microscopic examination. In current practice, **the diagnosis of papillary carcinoma is based on nuclear features** even in the absence of a papillary architecture. The nuclei of papillary carcinoma cells contain very finely dispersed chromatin, which imparts an **optically clear** appearance, giving rise to the designation **ground glass** or "Orphan Annie eye" nuclei (Fig. 19–14, *C* and *D*). In addition, invaginations of the cytoplasm may give the appearance of intranuclear inclusions (hence the designation **pseudoinclusions**) in cross-sections. A **papillary architecture** is common (Fig. 19–14, *B*); unlike hyperplastic papillary lesions seen in Graves disease, the neoplastic papillae have dense fibrovascular cores. Concentrically calcified structures termed **psammoma bodies** often are present within the papillae. Foci of lymphatic permeation by tumor cells are often present, but invasion of blood vessels is relatively uncommon, particularly in smaller lesions. Metastases to adjacent cervical lymph nodes are estimated to occur in about half of

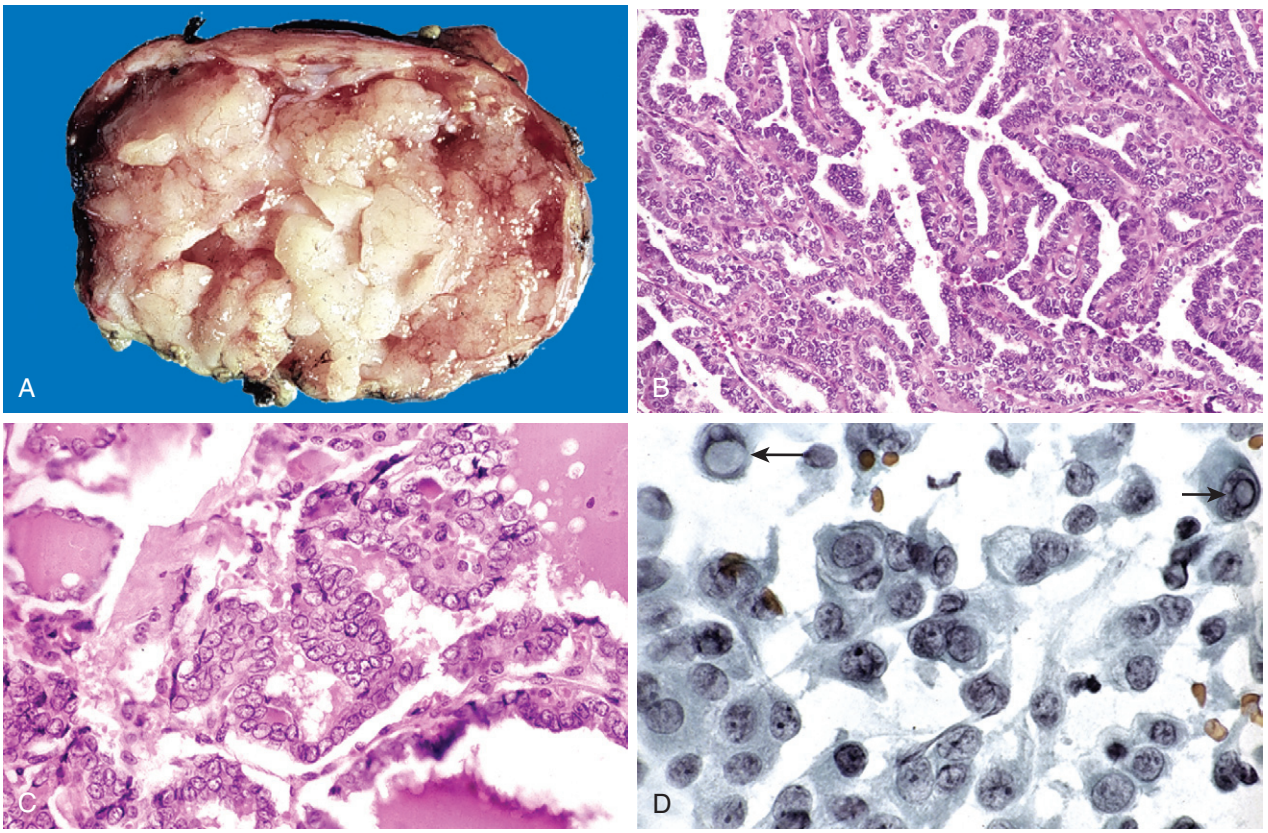


Figure 19–14 Papillary carcinoma of the thyroid. **A–C,** A papillary carcinoma with grossly discernible papillary structures. In this particular example, well-formed papillae (**B**) are lined by cells with characteristic empty-appearing nuclei, sometimes termed "Orphan Annie eye" nuclei (**C**). **D,** Cells obtained by fine-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells (*arrows*).
(Courtesy of Dr. S. Gokasalan, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

cases. There are over a dozen variants of papillary thyroid carcinoma, but the most common is one composed predominantly or exclusively of follicles (**follicular variant** of papillary thyroid carcinoma). The follicular variant more frequently is encapsulated and is associated with a lower incidence of lymph node metastases and extrathyroidal extension than that typical for conventional papillary carcinomas.

Clinical Features

Papillary carcinomas are nonfunctional tumors, so they manifest most often as a painless mass in the neck, either within the thyroid or as metastasis in a cervical lymph node. A preoperative diagnosis usually can be established by fine-needle aspiration on the basis of the characteristic nuclear features described earlier. Papillary carcinomas are indolent lesions, with 10-year survival rates in excess of 95%. Of interest, the presence of isolated cervical nodal metastases does not seem to have a significant influence on the generally good prognosis of these lesions. In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly to the lung. The long-term survival of patients with papillary thyroid cancer is dependent on several factors, including age (in general, the prognosis is less favorable among patients older than 40 years), the presence of extrathyroidal extension, and presence of distant metastases (stage).

Follicular Carcinoma

Follicular carcinomas account for 5% to 15% of primary thyroid cancers. They are more common in women (occurring in a ratio of 3:1) and manifest at an older age than that typical for papillary carcinomas, with a peak incidence between the ages of 40 and 60 years. Follicular carcinoma is more frequent in areas with dietary iodine deficiency (accounting for 25% to 40% of thyroid cancers), while its incidence has either decreased or remained stable in iodine-sufficient areas of the world.

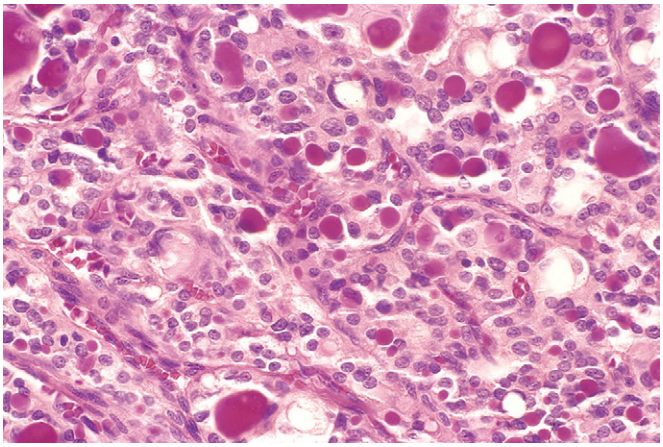


Figure 19–15 Follicular carcinoma of the thyroid. A few of the glandular lumina contain recognizable colloid.

MORPHOLOGY

On microscopic examination, most follicular carcinomas are composed of fairly uniform cells forming small follicles, reminiscent of normal thyroid (Fig. 19–15); in other cases, follicular differentiation may be less apparent. As with follicular adenomas, Hürthle cell variants of follicular carcinomas may be seen. Follicular carcinomas may be **widely invasive,** infiltrating the thyroid parenchyma and extrathyroidal soft tissues, or **minimally invasive.** The latter type are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination. **This distinction requires extensive histologic sampling of the tumor capsule–thyroid interface, to exclude capsular and/or vascular invasion** (Fig. 19–16). As mentioned earlier, follicular lesions in which the nuclear features are typical of papillary carcinomas should be regarded as follicular variants of papillary cancers.

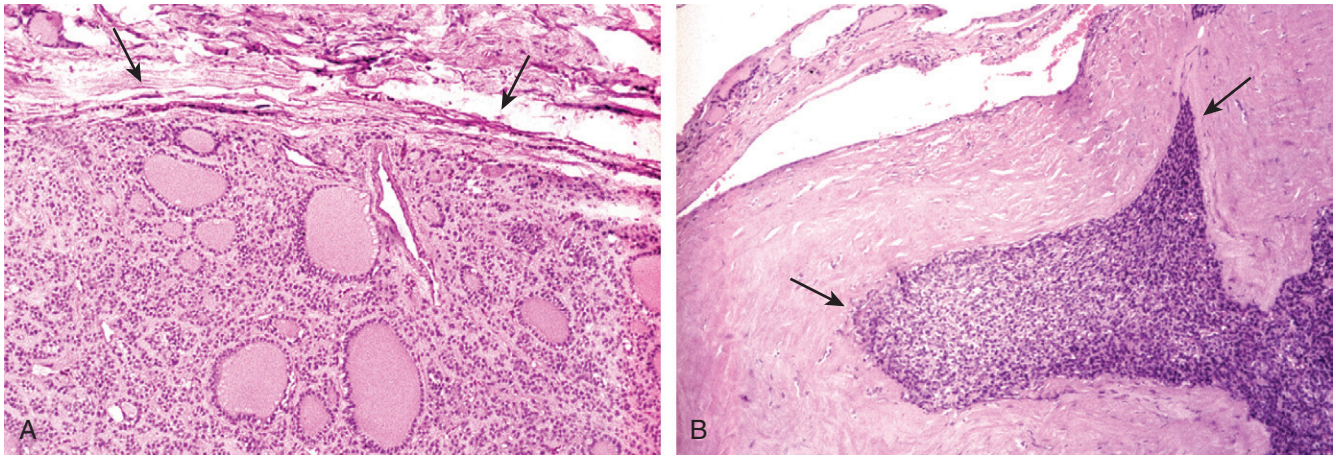


Figure 19–16 Capsular invasion in follicular carcinoma. Evaluating the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas. **A,** In adenomas, a fibrous capsule, usually thin but occasionally more prominent, surrounds the neoplastic follicles and no capsular invasion is seen (*arrows*); compressed normal thyroid parenchyma usually is present external to the capsule (*top*). **B,** By contrast, follicular carcinomas demonstrate capsular invasion (*arrows*) that may be minimal, as in this case, or widespread, with extension into local structures of the neck.

Clinical Features

Follicular carcinomas manifest most frequently as solitary *cold thyroid nodules*. In rare cases, they may be hyperfunctional. These neoplasms tend to metastasize through the bloodstream (*hematogenous dissemination*) to the lungs, bone, and liver. In contrast with papillary carcinomas, regional nodal metastases are uncommon. As many as half of patients with widely invasive carcinomas succumb to their disease within 10 years, while less than 10% of patients with minimally invasive follicular carcinomas die within the same time span. Follicular carcinomas are treated with surgical excision. Well-differentiated metastases may take up radioactive iodine, which can be used to identify and also ablate such lesions. Because better-differentiated lesions may be stimulated by TSH, patients usually are placed on a thyroid hormone regimen after surgery to suppress endogenous TSH.

Anaplastic Carcinoma

Anaplastic carcinomas are undifferentiated tumors of the thyroid follicular epithelium, accounting for less than 5% of thyroid tumors. They are aggressive, with a mortality rate approaching 100%. Patients with anaplastic carcinoma are older than those with other types of thyroid cancer, with a mean age of 65 years. Approximately a quarter of patients with anaplastic thyroid carcinomas have a past history of a well-differentiated thyroid carcinoma, and another quarter harbor a concurrent well-differentiated tumor in the resected specimen.

MORPHOLOGY

Anaplastic carcinomas manifest as bulky masses that typically grow rapidly beyond the thyroid capsule into adjacent neck structures. On microscopic examination, these neoplasms are composed of highly anaplastic cells, which may take on any of several histologic patterns, including those populated by

- Large, pleomorphic giant cells
- Spindle cells with a sarcomatous appearance
- Mixed spindle and giant cell lesions

Foci of papillary or follicular differentiation may be present in some tumors, suggesting origin from a better-differentiated carcinoma.

Clinical Features

Anaplastic carcinomas grow with wild abandon despite therapy. Metastases to distant sites are common, but in most cases death occurs in less than 1 year as a result of aggressive local growth and compromise of vital structures in the neck.

Medullary Carcinoma

Medullary carcinomas of the thyroid are neuroendocrine neoplasms derived from the parafollicular cells, or C cells, of the thyroid. Like normal C cells, medullary carcinomas secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up evaluation of patients. In some cases, the tumor cells elaborate other polypeptide hormones such as somatostatin, serotonin, and vasoactive intestinal peptide (VIP). Medullary carcinomas arise *sporadically* in about 70% of cases. The remaining 30% are *familial* cases occurring in the setting of MEN syndrome 2A or 2B, or familial medullary thyroid carcinoma without an associated MEN syndrome, as discussed later. Of note, both familial and sporadic medullary forms demonstrate activating *RET* mutations. Sporadic medullary carcinomas, as well as familial cases without an associated MEN syndrome, occur in adults, with a peak incidence in the fifth and sixth decades. Cases associated with MEN-2A or MEN-2B, by contrast, have been reported in younger patients, including children.

MORPHOLOGY

Medullary carcinomas may arise as a solitary nodule or may manifest as multiple lesions involving both lobes of the thyroid. **Multicentricity** is particularly common in familial cases. Larger lesions often contain areas of necrosis and hemorrhage and may extend through the capsule of the thyroid. On microscopic examination, medullary carcinomas are composed of polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles. **Amyloid deposits,** derived from altered calcitonin molecules, are present in the adjacent stroma in many cases (Fig. 19–17) and are a distinctive feature. Calcitonin is readily demonstrable both within the cytoplasm of the tumor cells and in the stromal amyloid by immunohistochemical methods. Electron microscopy reveals variable numbers of intracytoplasmic membrane-bound, electron-dense granules (Fig. 19–18). One of the peculiar features of familial medullary carcinomas is the presence of **multicentric C cell hyperplasia** in the surrounding thyroid parenchyma, a feature usually absent in sporadic lesions. Foci of C cell hyperplasia are believed to represent the precursor lesions from which medullary carcinomas arise.

Clinical Features

In the sporadic cases, medullary carcinoma manifests most often as a mass in the neck, sometimes associated with compression effects such as dysphagia or hoarseness. In

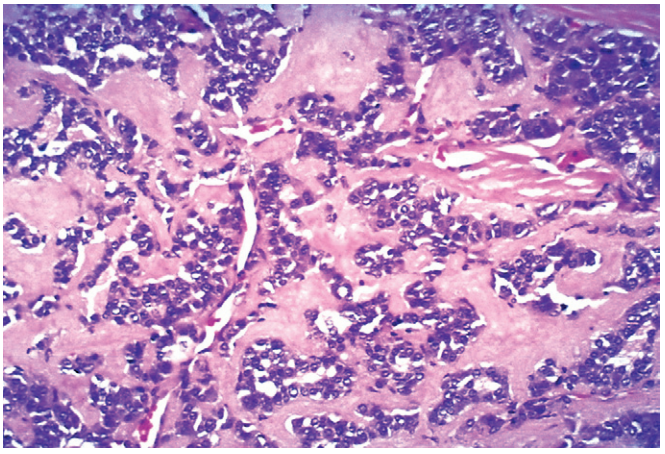


Figure 19–17 Medullary carcinoma of the thyroid. These tumors typically contain amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells.

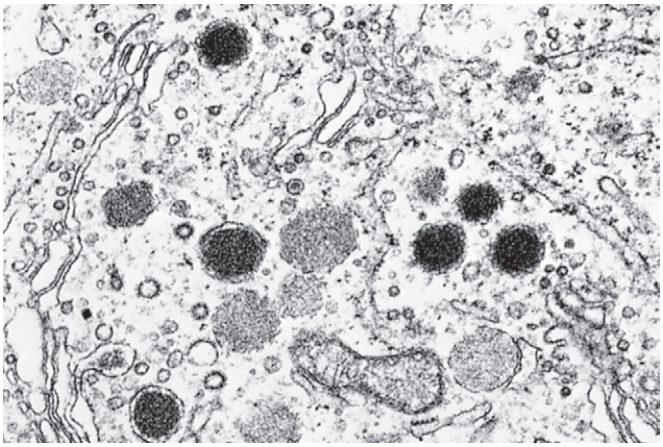


Figure 19–18 Electron micrograph of medullary thyroid carcinoma. These cells contain membrane-bound secretory granules, which are the sites of storage of calcitonin and other peptides. (Original magnification ×30,000.)

some instances, the initial manifestations are caused by the secretion of a peptide hormone (e.g., diarrhea caused by the secretion of VIP). Screening of the patient's relatives for elevated calcitonin levels or *RET* mutations permits early detection of tumors in familial cases. As discussed at the end of this chapter, all members of MEN-2 kindreds carrying *RET* mutations are offered prophylactic thyroidectomies to preempt the development of medullary carcinomas; often, the only histologic finding in the resected thyroid of these asymptomatic carriers is the presence of C cell hyperplasia or small (less than 1 cm) *micromedullary* carcinomas. Recent studies have shown that specific *RET* mutations correlate with an aggressive behavior in medullary carcinomas.

SUMMARY

Thyroid Neoplasms

- Most thyroid neoplasms manifest as *solitary thyroid nodules*, but only 1% of all thyroid nodules are neoplastic.
- *Follicular adenomas* are the most common benign neoplasms, while papillary carcinoma is the most common malignancy.
- Multiple genetic pathways are involved in *thyroid carcinogenesis*. Some of the genetic abnormalities that are fairly unique to thyroid cancers include *PAX8/PPARG* fusion (in follicular carcinoma), chromosomal rearrangements involving the *RET* oncogene (in papillary cancers), and mutations of *RET* (in medullary carcinomas).
- *Follicular adenomas and carcinomas* both are composed of well-differentiated follicular epithelial cells; the latter are distinguished by evidence of capsular and/or vascular invasion.
- *Papillary carcinomas* are recognized based on nuclear features (ground glass nuclei, pseudoinclusions) even in the absence of papillae. These neoplasms typically metastasize by way of lymphatics, but the prognosis is excellent.
- *Anaplastic carcinomas* are thought to arise by dedifferentiation of more differentiated neoplasms. They are highly aggressive, uniformly lethal cancers.
- *Medullary cancers* are nonepithelial neoplasms arising from the parafollicular C cells and can occur in either sporadic (70%) or familial (30%) settings. Multicentricity and C cell hyperplasia are features of familial cases. Amyloid deposits are a characteristic histologic finding.

PARATHYROID GLANDS

The parathyroid glands are derived from the developing pharyngeal pouches that also give rise to the thymus. They normally lie in close proximity to the upper and lower poles of each thyroid lobe but may be found anywhere along the pathway of descent of the pharyngeal pouches, including the carotid sheath and the thymus and elsewhere in the anterior mediastinum. Most of the gland is composed of *chief cells.* On hematoxylin-eosin (H&E) staining, the chief cells range from light to dark pink, depending on their glycogen content. They contain secretory granules of *parathyroid hormone* (PTH). *Oxyphil cells* are found throughout the normal parathyroid either singly or in small clusters. They are slightly larger than the chief cells, have acidophilic cytoplasm, and are tightly packed with mitochondria. *The activity of the parathyroid glands is controlled by the level of free (ionized) calcium in the bloodstream, rather than by trophic hormones secreted by the hypothalamus and pituitary.* Normally, decreased levels of free calcium stimulate the synthesis and secretion of PTH, with the following effects:

- Increase in renal tubular reabsorption of calcium
- Increase in urinary phosphate excretion, thereby lowering serum phosphate levels (since phosphate binds to ionized calcium)
- Increase in the conversion of vitamin D to its active dihydroxy form in the kidneys, which in turn augments gastrointestinal calcium absorption
- Enhancement of osteoclastic activity (i.e., bone resorption, thus releasing ionized calcium), mediated indirectly by promoting the differentiation of osteoclast progenitor cells into mature osteoclasts

The net result of these activities is an increase in the level of free calcium, which inhibits further PTH secretion. Abnormalities of the parathyroids include both hyperfunction and hypofunction. *Tumors of the parathyroid glands, unlike thyroid tumors, usually come to attention because of excessive secretion of PTH, rather than mass effects.*

HYPERPARATHYROIDISM

Hyperparathyroidism occurs in two major forms, *primary* and *secondary,* and, less commonly, as *tertiary* hyperparathyroidism. The first condition represents an autonomous, spontaneous overproduction of PTH, while the latter two conditions typically occur as secondary phenomena in patients with chronic renal insufficiency.

Primary Hyperparathyroidism

Primary hyperparathyroidism is a common endocrine disorder, and an important cause of *hypercalcemia.* There has been a dramatic increase in the detection of cases in the latter half of the last century, mainly as a result of the routine inclusion of serum calcium assays in testing for a variety of clinical conditions that bring a patient to the hospital. The frequency of occurrence of the various parathyroid lesions underlying the hyperfunction is as follows:

- Adenoma—85% to 95%
- Primary hyperplasia (diffuse or nodular)—5% to 10%
- Parathyroid carcinoma—1%

In more than 95% of cases, primary hyperparathyroidism is caused by a sporadic parathyroid adenoma or sporadic hyperplasia. The genetic defects identified in *familial primary hyperparathyroidism* include multiple endocrine neoplasia syndromes, specifically MEN-1 and MEN-2A (see further on). *Familial hypocalciuric hypercalcemia* is a rare cause of hyperparathyroidism, caused by inactivating mutations in the calcium-sensing receptor gene on parathyroid cells, leading to constitutive PTH secretion.

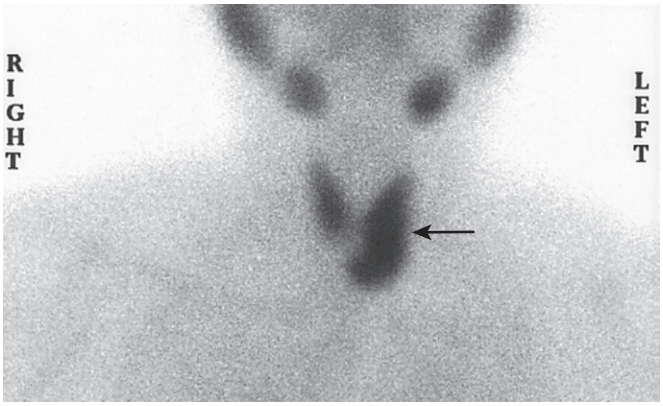


Figure 19–19 Technetium-99 radionuclide scan demonstrates an area of increased uptake corresponding to the left inferior parathyroid gland (*arrow*). This proved to be a parathyroid adenoma. Preoperative scintigraphy is useful in localizing and distinguishing adenomas from parathyroid hyperplasia, in which more than one gland will demonstrate increased uptake.

PATHOGENESIS

Although the details of genetic alterations in sporadic parathyroid tumors are beyond the scope of this discussion, abnormalities in two specific genes are commonly associated with these tumors:

- **Cyclin D1 gene inversions:** Cyclin D1 is a positive regulator of the cell cycle. A **chromosomal inversion** on chromosome 11 results in relocation of the *cyclin D1* gene (normally on 11q), so that it is now positioned adjacent to the 5′-flanking region of the *PTH* gene (on 11p), leading to abnormal expression of cyclin D1 protein and increased proliferation. Between 10% and 20% of adenomas have this clonal genetic defect. In addition, cyclin D1 is overexpressed in approximately 40% of parathyroid adenomas, suggesting that mechanisms other than *cyclin D1* gene inversion can lead to its overexpression.
- **MEN1 mutations:** Approximately 20% to 30% of parathyroid tumors not associated with the MEN-1 syndrome have mutations in both copies of the *MEN1* gene (see later). The spectrum of *MEN1* mutations in the sporadic tumors is virtually identical to that in familial parathyroid adenomas.

MORPHOLOGY

The morphologic changes seen in primary hyperparathyroidism include those in the parathyroid glands as well as those in other organs affected by elevated levels of calcium. In 75% to 80% of cases, one of the parathyroids harbors a solitary **adenoma,** which, like the normal parathyroids, may lie in close proximity to the thyroid gland or in an ectopic site (e.g., the mediastinum). The typical parathyroid adenoma is a well-circumscribed, soft, tan nodule, invested by a delicate capsule. **By definition, parathyroid adenomas are almost invariably confined to single glands** (Fig. 19–19), and the remaining glands are normal in size or somewhat shrunken, as a result of feedback inhibition by elevated serum calcium. Most parathyroid adenomas weigh between 0.5 and 5 g. On microscopic examination, parathyroid adenomas are composed predominantly of chief cells (Fig. 19–20). In most cases, at least a few nests of larger oxyphil cells also are present. A rim of compressed, non-neoplastic parathyroid tissue, generally separated by a fibrous capsule, often is visible at the edge of the adenoma. This finding constitutes a helpful internal control, since the chief cells of the adenoma are larger and show greater nuclear size variability than that typical for the normal chief cells. Cells with bizarre and pleomorphic nuclei are often seen within adenomas (so-called **endocrine atypia**) and must not be taken as a sign of malignancy. Mitotic figures are rare. In contrast with the normal parathyroid parenchyma, adipose tissue is inconspicuous within adenomas.

Parathyroid hyperplasia is typically a multiglandular process. In some cases, however, enlargement may be grossly apparent in only one or two glands, complicating the distinction between hyperplasia and adenoma. The combined weight of all glands rarely exceeds 1.0 g and often is less. Microscopically, the most common pattern seen is that of chief cell hyperplasia, which may involve the glands in a diffuse or multinodular pattern. Less commonly, the constituent cells contain abundant clear cytoplasm as a consequence of accumulation of glycogen—a condition designated "water-clear cell hyperplasia." As in the case of adenomas, stromal fat is inconspicuous within foci of hyperplasia.

Parathyroid carcinomas may be circumscribed lesions that are difficult to distinguish from adenomas, or they may be clearly invasive neoplasms. These tumors enlarge one parathyroid gland and consist of gray-white, irregular masses that sometimes exceed 10 g in weight. The cells usually are uniform and resemble normal parathyroid cells. They are arrayed in nodular or trabecular patterns with a dense, fibrous capsule enclosing the mass. There is general agreement that a **diagnosis of carcinoma based on cytologic detail is unreliable, and invasion of surrounding tissues and metastasis are the only definitive**

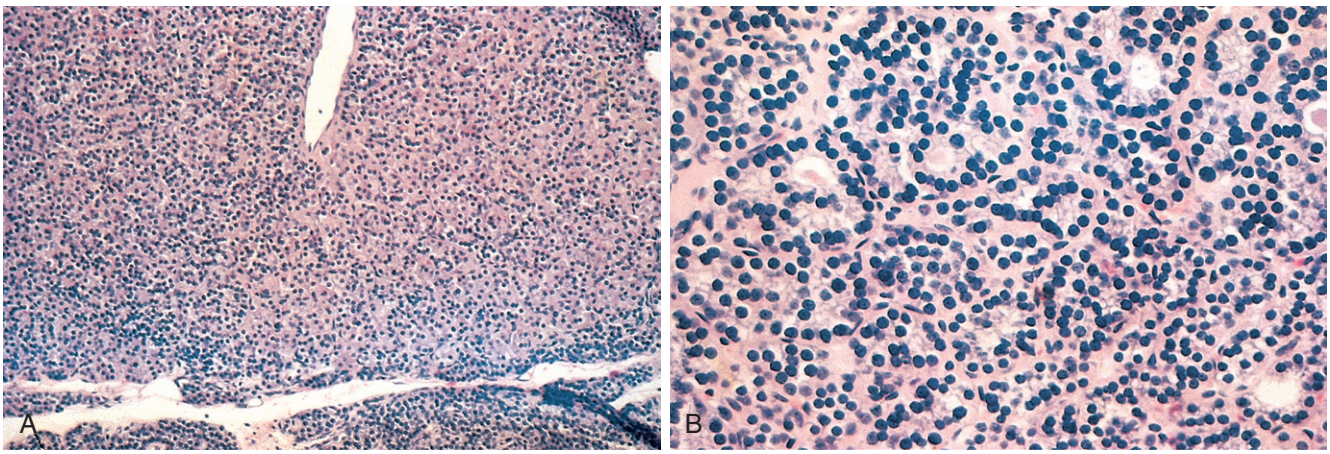


Figure 19–20 Chief cell parathyroid adenoma. **A,** On this low-power view, a solitary adenoma is clearly delineated from the residual gland below. **B,** High-power detail shows slight variation in nuclear size and tendency to follicular formation but no anaplasia.

criteria. Local recurrence occurs in one third of cases, and more distant dissemination occurs in another third.

Morphologic changes in other organs deserving special mention are found in the skeleton and kidneys. **Skeletal changes** include increased osteoclastic activity, which results in erosion of bone matrix and mobilization of calcium salts, particularly in the metaphyses of long tubular bones. Bone resorption is accompanied by increased osteoblastic activity and the formation of new bone trabeculae. In more severe cases the cortex is grossly thinned and the marrow contains increased amounts of fibrous tissue accompanied by foci of hemorrhage and cysts **(osteitis fibrosa cystica)** (Chapter 20). Aggregates of osteoclasts, reactive giant cells, and hemorrhagic debris occasionally form masses that may be mistaken for neoplasms (**brown tumors** of hyperparathyroidism). PTH-induced hypercalcemia favors the formation of urinary tract stones (nephrolithiasis) as well as calcification of the renal interstitium and tubules (nephrocalcinosis). Metastatic calcification secondary to hypercalcemia also may be seen in other sites, including the stomach, lungs, myocardium, and blood vessels.

Table 19–4 Causes of Hypercalcemia

Raised PTH	Decreased PTH
Hyperparathyroidism	Hypercalcemia of malignancy
Primary (adenoma > hyperplasia)*	Osteolytic metastases
Secondary†	PTH-rP–mediated
Tertiary†	Vitamin D toxicity
Familial hypocalciuric hypercalcemia	Immobilization
	Drugs (thiazide diuretics)
	Granulomatous diseases (sarcoidosis)

PTH, parathyroid hormone; PTH-rP, PTH-related protein.
*Primary hyperparathyroidism is the most common cause of hypercalcemia overall. Malignancy is the most common cause of *symptomatic* hypercalcemia. Primary hyperparathyroidism and malignancy together account for nearly 90% of cases of hypercalcemia.
†Secondary and tertiary hyperparathyroidism are most commonly associated with progressive renal failure.

Clinical Features

Primary hyperparathyroidism usually is a disease of adults and is much more common in women than in men (gender ratio of nearly 4:1). *The most common manifestation of primary hyperparathyroidism is an increase in serum ionized calcium.* In fact, primary hyperparathyroidism is the most common cause of *clinically silent hypercalcemia.* Of note, other conditions also may produce hypercalcemia (Table 19–4). The most common cause of clinically apparent hypercalcemia in adults is paraneoplastic syndromes associated with *malignancy* and bone metastases (Chapter 5). The prognosis for patients with malignancy-associated hypercalcemia is poor, because it often occurs in those with advanced cancers. In persons with hypercalcemia caused by parathyroid hyperfunction, serum PTH is inappropriately elevated, whereas serum PTH is low to undetectable in those with hypercalcemia caused by nonparathyroid diseases, including malignancy. Other laboratory alterations referable to PTH excess include hypophosphatemia and increased urinary excretion of both calcium and phosphate.

Primary hyperparathyroidism traditionally has been associated with a constellation of symptoms that included "painful bones, renal stones, abdominal groans, and psychic moans." Pain, secondary to fractures of bones weakened by osteoporosis or osteitis fibrosa cystica and resulting from renal stones, with obstructive uropathy, was at one time a prominent manifestation of primary hyperparathyroidism. Because serum calcium is now routinely assessed in the workup of most patients who need blood tests for unrelated conditions, clinically silent hyperparathyroidism is detected early. Hence, many of the classic clinical manifestations, particularly those referable to bone and renal disease, are seen much less frequently. Additional signs and symptoms that may be encountered in some cases include

- *Gastrointestinal disturbances,* including constipation, nausea, peptic ulcers, pancreatitis, and gallstones
- *Central nervous system alterations,* including depression, lethargy, and seizures
- *Neuromuscular abnormalities,* including weakness and hypotonia
- *Polyuria* and secondary polydipsia

Although some of these alterations, for example, polyuria and muscle weakness, are clearly related to hypercalcemia,

the pathogenesis of many of the other manifestations of the disorder remains poorly understood.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is caused by any condition associated with a chronic depression in the serum calcium level, because low serum calcium leads to compensatory overactivity of the parathyroids. *Renal failure is by far the most common cause of secondary hyperparathyroidism.* The mechanisms by which chronic renal failure induces secondary hyperparathyroidism are complex and not fully understood. Chronic renal insufficiency is associated with decreased phosphate excretion, which in turn results in hyperphosphatemia. The elevated serum phosphate levels directly depress serum calcium levels and thereby stimulate parathyroid gland activity. In addition, loss of renal substances reduces the availability of α_1-hydroxylase enzyme necessary for the synthesis of the active form of vitamin D, which in turn reduces intestinal absorption of calcium (Chapter 7).

MORPHOLOGY

The parathyroid glands in secondary hyperparathyroidism are hyperplastic. As in the case of primary hyperplasia, the degree of glandular enlargement is not necessarily symmetric. On microscopic examination, the hyperplastic glands contain an increased number of chief cells, or cells with more abundant, clear cytoplasm **(water-clear cells),** in a diffuse or multinodular distribution. Fat cells are decreased in number. **Bone changes** similar to those seen in primary hyperparathyroidism also may be present. **Metastatic calcification** may be seen in many tissues.

Clinical Features

The clinical manifestations of secondary hyperparathyroidism usually are dominated by those related to chronic renal failure. Bone abnormalities (*renal osteodystrophy*) and other changes associated with PTH excess are, in general, less severe than those seen in primary hyperparathyroidism. Serum calcium remains near normal because the compensatory increase in PTH levels sustains serum calcium. The metastatic calcification of blood vessels (secondary to hyperphosphatemia) occasionally may result in significant ischemic damage to skin and other organs—a process sometimes referred to as *calciphylaxis.* In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia—a process sometimes termed *tertiary hyperparathyroidism.* Parathyroidectomy may be necessary to control the hyperparathyroidism in such patients.

SUMMARY

Hyperparathyroidism

- Primary hyperparathyroidism is the most common cause of asymptomatic hypercalcemia.
- In a majority of cases, primary hyperparathyroidism is caused by a sporadic parathyroid adenoma and, less commonly, by parathyroid hyperplasia.
- Parathyroid adenomas are solitary, while hyperplasia typically is a multiglandular process.
- Skeletal manifestations of hyperparathyroidism include bone resorption, *osteitis fibrosa cystica,* and *brown tumors.* Renal changes include nephrolithiasis (stones) and nephrocalcinosis.
- The clinical manifestations of hyperparathyroidism can be summarized as "painful bones, renal stones, abdominal groans, and psychic moans."
- Secondary hyperparathyroidism most often is caused by renal failure, and the parathyroid glands are hyperplastic.
- Malignancies are the most important cause of symptomatic hypercalcemia, which results from osteolytic metastases or release of PTH-related protein from nonparathyroid tumors.

HYPOPARATHYROIDISM

Hypoparathyroidism is far less common than hyperparathyroidism. The major causes of hypoparathyroidism include the following:

- *Surgically induced hypoparathyroidism*: The most common cause is inadvertent removal of parathyroids during thyroidectomy or other surgical neck dissections.
- *Congenital absence*: This occurs in conjunction with thymic aplasia (Di George syndrome) and cardiac defects, secondary to deletions on chromosome 22q11.2 (Chapter 6)
- *Autoimmune hypoparathyroidism*: This is a hereditary polyglandular deficiency syndrome arising from autoantibodies to multiple endocrine organs (parathyroid, thyroid, adrenals, and pancreas). Chronic fungal infections involving the skin and mucous membranes (mucocutaneous candidiasis) are sometimes encountered in affected persons. This condition is caused by mutations in the *autoimmune regulator* gene (*AIRE*) and is discussed more extensively later on, in the context of autoimmune adrenalitis. As one consequence of the failure of self-tolerance, some of these patients make autoantibodies against their own IL-17, accounting for the increased susceptibility to *Candida* infections (in which the T_H17 response plays an important protective role).

The major clinical manifestations of hypoparathyroidism are secondary to hypocalcemia and include *increased neuromuscular irritability* (*tingling, muscle spasms, facial grimacing,* and *sustained carpopedal spasm or tetany*), cardiac arrhythmias, and, on occasion, *increased intracranial pressures* and *seizures.* Morphologic changes generally are inconspicuous but may include cataracts, calcification of the cerebral basal ganglia, and dental abnormalities.

ENDOCRINE PANCREAS

The endocrine pancreas consists of about 1 million microscopic clusters of cells, the islets of Langerhans, which contain four major cell types—beta, alpha, delta, and PP (pancreatic polypeptide) cells. The cells can be differentiated morphologically by their staining properties, by the ultrastructural characteristics of their granules, and by their hormone content. *The beta cell produces insulin,* which is the most potent anabolic hormone known, with multiple synthetic and growth-promoting effects; *the alpha cell secretes glucagon,* inducing hyperglycemia by its glycogenolytic activity in the liver; *delta cells contain somatostatin,* which suppresses both insulin and glucagon release; and *PP cells contain a unique pancreatic polypeptide,* VIP, that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes and inhibition of intestinal motility. The most important disease of the endocrine pancreas is diabetes mellitus, caused by deficient production or action of insulin.

DIABETES MELLITUS

Diabetes mellitus is not a single disease entity but rather a *group of metabolic disorders sharing the common underlying feature of hyperglycemia.* Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both. The chronic hyperglycemia and attendant metabolic deregulation of diabetes mellitus may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels. According to the American Diabetes Association, diabetes affects over 20 million children and adults, or 7% of the population, in the United States, nearly a third of whom are currently unaware that they have hyperglycemia. Approximately 1.5 million new cases of diabetes are diagnosed each year in the United States, and diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower extremity amputations. A staggering 54 million adults in this country have *prediabetes*, which is defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes (discussed next); persons with prediabetes have an elevated risk for development of frank diabetes.

Diagnosis

Blood glucose levels normally are maintained in a very narrow range, usually 70 to 120 mg/dL. The diagnosis of diabetes is established by elevation of blood glucose by any one of three criteria:

1. A random blood glucose concentration of 200 mg/dL or higher, with classical signs and symptoms (discussed next)
2. A fasting glucose concentration of 126 mg/dL or higher on more than one occasion
3. An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is 200 mg/dL or higher 2 hours after a standard carbohydrate load (75 g of glucose).

Derangements in carbohydrate metabolism proceed along a continuum. Persons with serum fasting glucose values less than 110 mg/dL, or less than 140 mg/dL for an OGTT, are considered to be euglycemic. However, those with serum fasting glucose greater than 110 but less than 126 mg/dL, or OGTT values of greater than 140 but less than 200 mg/dL, are considered to have *impaired glucose tolerance,* also known as *prediabetes.* Persons with impaired glucose tolerance have a significant risk for progression to overt diabetes over time, with as many as 5% to 10% advancing to full-fledged diabetes mellitus per year. In addition, those with impaired glucose tolerance are at *risk for cardiovascular disease,* as a consequence of abnormal carbohydrate metabolism and the coexistence of other risk factors (Chapter 9).

Classification

Although all forms of diabetes mellitus share hyperglycemia as a common feature, the underlying causes of hyperglycemia vary widely. *The vast majority of cases of diabetes fall into one of two broad classes*:

- *Type 1 diabetes (T1D)* is characterized by an absolute deficiency of insulin secretion caused by pancreatic beta cell destruction, usually resulting from an autoimmune attack. Type 1 diabetes accounts for approximately 10% of all cases.
- *Type 2 diabetes (T2D)* is caused by a combination of peripheral resistance to insulin action and an inadequate compensatory response of insulin secretion by the pancreatic beta cells (*relative insulin deficiency*). Approximately 80% to 90% of patients have type 2 diabetes.

A variety of monogenic and secondary causes make up the remaining cases of diabetes (Table 19–5). An important point is that although the major types of diabetes arise by different pathogenic mechanisms, *the long-term complications in kidneys, eyes, nerves, and blood vessels are the same and are the principal causes of morbidity and death.*

Normal Insulin Physiology and Glucose Homeostasis

Before discussing the pathogenesis of the two major types of diabetes, we briefly review normal insulin physiology and glucose metabolism. *Normal glucose homeostasis is tightly regulated by three interrelated processes*: (1) glucose production in the liver, (2) glucose uptake and utilization by peripheral tissues, chiefly skeletal muscle, and (3) actions of insulin and counterregulatory hormones (e.g., glucagon).

The principal metabolic function of insulin is to increase the rate of glucose transport into certain cells in the body (Fig. 19–21). These are the *striated* muscle cells (including myocardial cells) and, to a lesser extent, *adipocytes,* representing collectively about two thirds of total body weight. Glucose uptake in other peripheral tissues, most notably the brain, is insulin-independent. In muscle cells, glucose is then

Table 19–5 Classification of Diabetes Mellitus

1. Type 1 Diabetes
Beta cell destruction, usually leading to absolute insulin deficiency
2. Type 2 Diabetes
Combination of insulin resistance and beta cell dysfunction
3. Genetic Defects of Beta Cell Function
Maturity-onset diabetes of the young (MODY), caused by mutations in: Hepatocyte nuclear factor 4α gene (*HNF4A*)—MODY1 Glucokinase gene (*GCK*)—MODY2 Hepatocyte nuclear factor 1α gene (*HNF1A*)—MODY3 Pancreatic and duodenal homeobox 1 gene (*PDX1*)—MODY4 Hepatocyte nuclear factor 1β gene (*HNF1B*)—MODY5 Neurogenic differentiation factor 1 gene (*NEUROD1*)—MODY6
Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (3243A→G)
Defects in proinsulin conversion
Insulin gene mutations
4. Genetic Defects in Insulin Action
Insulin receptor mutations
5. Exocrine Pancreatic Defects
Chronic pancreatitis
Pancreatectomy
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy
6. Endocrinopathies
Growth hormone excess (acromegaly)
Cushing syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
7. Infections
Cytomegalovirus infection
Coxsackievirus B infection
Congenital rubella
8. Drugs
Glucocorticoids
Thyroid hormone
β-Adrenergic agonists
9. Genetic Syndromes Associated with Diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
10. Gestational Diabetes Mellitus
Diabetes associated with pregnancy

Modified from the American Diabetes Association: Position statement from the American Diabetes Association on the diagnosis and classification of diabetes mellitus. Diabetes Care 31(Suppl 1):S55–S60, 2008.

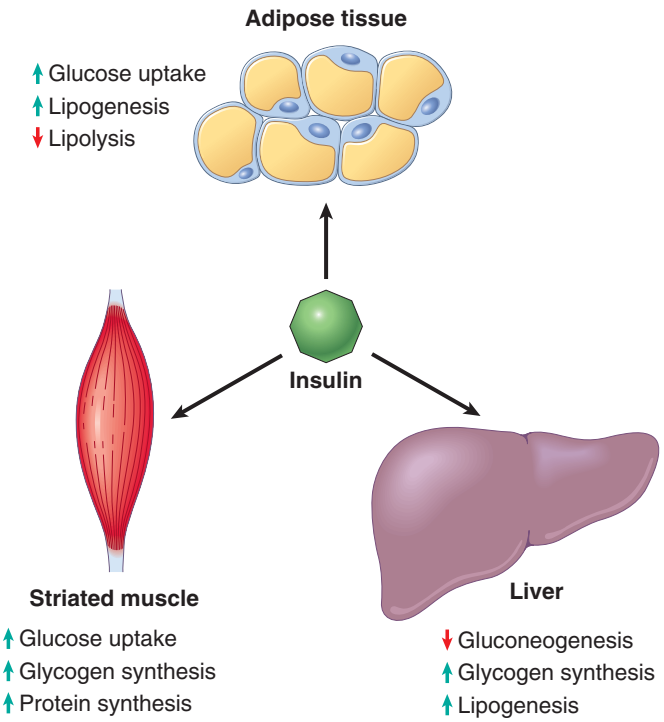


Figure 19–21 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

either stored as glycogen or oxidized to generate adenosine triphosphate (ATP). In adipose tissue, glucose is stored primarily as lipid. Besides promoting lipid synthesis (lipogenesis), insulin also inhibits lipid degradation (lipolysis) in adipocytes. Similarly, insulin promotes amino acid uptake and protein synthesis while inhibiting protein degradation. *Thus, the metabolic effects of insulin can be summarized as anabolic, with increased synthesis and reduced degradation of glycogen, lipid, and protein.* In addition to these metabolic effects, insulin has several *mitogenic* functions, including initiation of DNA synthesis in certain cells and stimulation of their growth and differentiation.

Insulin reduces the production of glucose from the liver. Insulin and glucagon have opposing regulatory effects on glucose homeostasis. During *fasting* states, low insulin and high glucagon levels facilitate hepatic gluconeogenesis and glycogenolysis (glycogen breakdown) while decreasing glycogen synthesis, thereby preventing hypoglycemia. Thus, *fasting* plasma glucose levels are determined primarily by hepatic glucose output. After a meal, insulin levels rise and glucagon levels fall in response to the large glucose load. *The most important stimulus that triggers insulin release is glucose itself, which initiates insulin synthesis in the pancreatic beta cells.* In peripheral tissues (skeletal muscle and adipose tissue), secreted insulin binds to the *insulin receptor,* triggering a number of intracellular responses that promote glucose uptake and postprandial glucose utilization, thereby maintaining glucose homeostasis. Abnormalities at various points along this complex signaling cascade, from synthesis and release of insulin by beta cells to insulin receptor interactions in peripheral tissues, can result in the diabetic phenotype.

PATHOGENESIS

Type 1 Diabetes Mellitus

Type 1 diabetes is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous beta cell antigens. Type 1 diabetes most commonly develops in childhood, becomes manifest at puberty, and progresses with age. Most patients with type 1 diabetes depend on exogenous insulin for survival; without insulin they develop serious metabolic complications such as ketoacidosis and coma.

Although the clinical onset of type 1 diabetes is abrupt, this disease in fact results from a chronic autoimmune attack on beta cells that usually starts many years before the disease becomes evident (Fig. 19–22). The classic manifestations of the disease (hyperglycemia and ketosis) occur late in its course, after more than 90% of the beta cells have been destroyed. **The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells.** This failure of tolerance may be a result of some combination of defective clonal deletion of self-reactive T cells in the thymus, as well as defects in the functions of regulatory T cells or resistance of effector T cells to suppression by regulatory cells. Thus, autoreactive T cells not only survive but are poised to respond to self-antigens. Not surprisingly, **autoantibodies** against a variety of beta cell antigens, including insulin and the beta cell enzyme glutamic acid decarboxylase, are detected in the blood of 70% to 80% of patients. In the rare cases in which the pancreatic lesions have been examined early in the disease process, the islets show necrosis of beta cells and lymphocytic infiltration (so-called insulitis).

As with most autoimmune diseases, the pathogenesis of type 1 diabetes involves the interplay of genetic susceptibility and environmental factors. Genome-wide association studies (Chapter 6) have identified over 20 susceptibility loci for type 1 diabetes. Of these, **the principal susceptibility locus for type 1 diabetes resides in the chromosomal region that encodes the class II MHC molecules on *6p21 (HLA-D)*.** Between 90% and 95% of white patients with type 1 diabetes have *HLA-DR3*, or *DR4*, or both, in contrast with about 40% of normal subjects, and 40% to 50% of patients are *DR3/DR4* heterozygotes, in contrast with 5% of normal subjects. Of note, despite the high relative risk in persons with particular class II alleles, most people who inherit these alleles do not develop diabetes. Several *non-HLA genes* also confer susceptibility to type 1 diabetes, including polymorphisms within the gene encoding insulin itself, as well as *CTLA4* and *PTPN22*. CTLA-4 is an inhibitory receptor of T cells and PTPN-22 is a protein tyrosine phosphatase; both are thought to inhibit T cell responses, so polymorphisms that interfere with their functional activity are expected to set the stage for excessive T cell activation. Polymorphisms in the insulin gene may reduce expression of this protein in the thymus, thus reducing the elimination of T cells reactive with this self protein (Chapter 4). Additional evidence suggests that **environmental factors,** especially infections, may be involved in type 1 diabetes. It has been proposed that certain viruses (mumps, rubella, and coxsackie B viruses, in particular) may be an initiating trigger, perhaps because some viral antigens are antigenically similar to beta cell antigens **(molecular mimicry),** leading to bystander damage to the islets, but this idea is not conclusively established.

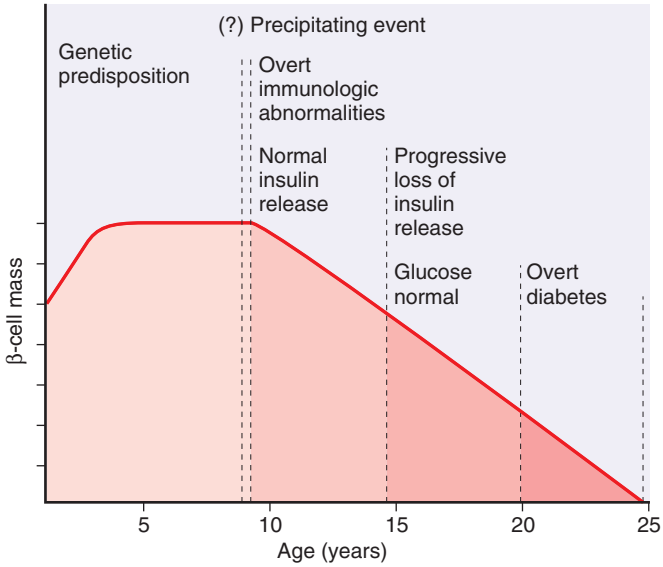


Figure 19–22 Stages in the development of type 1 diabetes mellitus. The stages are listed *from left to right*, and hypothetical beta cell mass is plotted against age.

(From Eisenbarth GE: Type 1 diabetes—a chronic autoimmune disease. N Engl J Med 314:1360, 1986.)

Type 2 Diabetes Mellitus

Type 2 diabetes is a prototypical complex multifactorial disease. Environmental factors, such as a sedentary life style and dietary habits, unequivocally play a role, as described in the subsequent discussion of the association with obesity. Genetic factors are also involved in the pathogenesis, as evidenced by the disease concordance rate of 35% to 60% in monozygotic twins compared with nearly half that in dizygotic twins. Such concordance is even greater than in type 1 diabetes, suggesting perhaps an even larger genetic component in type 2 diabetes. **Additional evidence for a genetic basis has emerged from recent large-scale genome-wide association studies, which have identified more than a dozen susceptibility loci called "diabetogenic" genes.** Unlike type 1 diabetes, however, the disease is not linked to genes involved in immune tolerance and regulation (e.g., *HLA, CTLA4*), and evidence of an autoimmune basis is lacking. The two metabolic defects that characterize type 2 diabetes are (1) a decreased ability of peripheral tissues to respond to insulin (insulin resistance) and (2) beta cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia (Fig. 19–23). Insulin resistance predates the development of hyperglycemia and usually is accompanied by compensatory beta cell hyperfunction and hyperinsulinemia in the early stages of the evolution of diabetes.

Insulin Resistance

Insulin resistance is defined as the failure of target tissues to respond normally to insulin. It leads to decreased uptake of glucose in muscle, reduced glycolysis and fatty acid oxidation in the liver, and an inability to suppress hepatic gluconeogenesis. A variety of functional defects have been

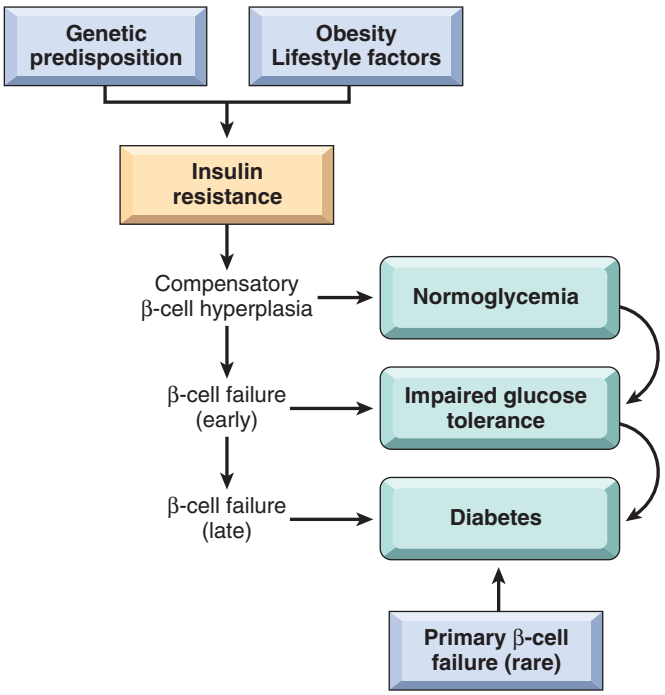


Figure 19–23 Pathogenesis of type 2 diabetes mellitus. Genetic predisposition and environmental influences converge to cause insulin resistance. Compensatory beta cell hyperplasia can maintain normoglycemia, but eventually beta cell secretory dysfunction sets in, leading to impaired glucose tolerance and, ultimately, frank diabetes. Rare instances of primary beta cell failure can lead directly to type 2 diabetes without an intervening state of insulin resistance.

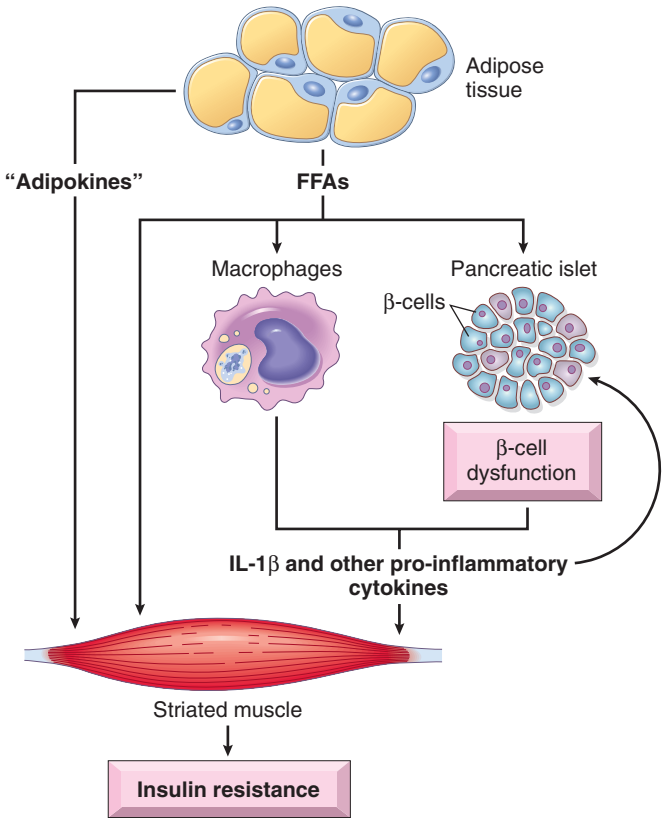


Figure 19–24 Mechanisms of beta cell dysfunction and insulin resistance in type 2 diabetes. Free fatty acids directly cause beta cell dysfunction and induce insulin resistance in target tissues (such as striated muscle, *shown here*), and also induce the secretion of pro-inflammatory cytokines that cause more beta cell dysfunction and insulin resistance.

reported in the insulin signaling pathway in states of insulin resistance (for example, reduced phosphorylation-dependent activation of the insulin receptor and its downstream components), which attenuate signal transduction. *Few factors play as important a role in the development of insulin resistance as obesity.*

Obesity and Insulin Resistance

The association of obesity with type 2 diabetes has been recognized for decades, with visceral obesity being common in a majority of affected patients. Insulin resistance is present even with simple obesity unaccompanied by hyperglycemia, indicating a fundamental abnormality of insulin signaling in states of fatty excess. In fact, the term *metabolic syndrome* has been applied to a constellation of findings dominated by visceral obesity, which is accompanied by insulin resistance, glucose intolerance, and cardiovascular risk factors such as hypertension and abnormal lipid profiles (Chapter 7). In the absence of weight loss and lifestyle modifications, persons with metabolic syndrome are at significant risk for the development of frank type 2 diabetes, underscoring the importance of obesity to the pathogenesis of this disease. The risk of diabetes increases as the body mass index (a measure of body fat content) increases, suggesting a dose-response relationship between body fat and insulin resistance. Although many details of the so-called *adipo-insulin axis* remain to be elucidated, recognition of some of the putative pathways leading to insulin resistance has increased substantially (Fig. 19–24):

- *Role of excess free fatty acids* (FFAs): Cross-sectional studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity. The level of intracellular triglycerides often is markedly increased in muscle and liver tissues in obese persons, presumably because excess circulating FFAs are deposited in these organs. Intracellular triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state. These *lipotoxic* effects of FFAs are mediated through a decrease in activity of key insulin-signaling proteins.
- *Role of inflammation*: Over the past several years, inflammation has emerged as a major player in the pathogenesis of type 2 diabetes. It is now known that a permissive inflammatory milieu (mediated *not* by an autoimmune process as in type 1 diabetes but rather by pro-inflammatory cytokines that are secreted in response to excess nutrients such as FFAs) results in both peripheral insulin resistance and beta cell dysfunction (see later). Excess FFAs within macrophages and beta cells can engage the *inflammasome*, a multiprotein cytoplasmic complex that leads to secretion of the cytokine interleukin IL-1β (Chapter 2). IL-1β, in turn, mediates the

secretion of additional pro-inflammatory cytokines from macrophages, islets, and other cells that are released into the circulation and act on the major sites of insulin action to promote insulin resistance. Thus, excess FFAs can impede insulin signaling directly within peripheral tissues, as well as indirectly through the release of pro-inflammatory cytokines. Not surprisingly, there are now several ongoing trials of cytokine antagonists (particularly of IL-1β) in patients with type 2 diabetes.

- *Role of adipokines*: Adipose tissue is not merely a passive storage depot for fat; it can operate as a functional endocrine organ, releasing so-called *adipokines* in response to extracellular stimuli or changes in metabolic status. Thus, adipocytes also release IL-1β and other pro-inflammatory cytokines into the circulation in response to excess FFAs, which promote peripheral insulin resistance. By contrast, *adiponectin* is an adipokine with insulin sensitizing activity, which probably acts by dampening the inflammatory response.
- *Peroxisome proliferator-activated receptor-γ* (PPARγ): PPARγ is a nuclear receptor and transcription factor expressed in adipose tissue and plays a seminal role in adipocyte differentiation. A class of antidiabetic medications known as thiazolidinediones acts as agonist ligands for PPARγ and improves insulin sensitivity. Activation of PPARγ promotes secretion of antihyperglycemic adipokines such as adiponectin, and shifts the deposition of FFAs toward adipose tissue and away from liver and skeletal muscle.

Beta Cell Dysfunction

Beta cell dysfunction in type 2 diabetes reflects the inability of these cells to adapt themselves to the long-term demands of peripheral insulin resistance and increased insulin secretion. In states of insulin resistance, insulin secretion initially is higher for each level of glucose than in controls. This hyperinsulinemic state is a compensation for peripheral resistance and often can maintain normal plasma glucose for years. Eventually, however, beta cell compensation becomes inadequate, and there is progression to hyperglycemia, which is accompanied by an absolute loss in beta cell mass. The molecular mechanisms underlying beta cell dysfunction in type 2 diabetes are multifactorial and in many instances overlap with those implicated in insulin resistance. Thus, excess nutrients such as FFAs and glucose can promote the secretion of pro-inflammatory cytokines from beta cells, which leads to recruitment of mononuclear cells (macrophages and T cells) into the islets, resulting in more local cytokine production. The consequences of this abnormal inflammatory microenvironment are beta cell dysfunction and, ultimately, beta cell death. Amyloid replacement of islets is a characteristic finding in persons with *long-standing* type 2 diabetes and is present in more than 90% of diabetic islets examined (see later). The islet amyloid polypeptide (IAPP), also known as amylin, is secreted by the beta cells in conjunction with insulin, and its abnormal aggregation results in amyloid. IAPP also engages the inflammasome and promotes IL-1β secretion, thus sustaining the inflammatory onslaught on surviving beta cells even late in the disease.

Monogenic Forms of Diabetes

Type 1 and type 2 diabetes are genetically complex, and despite the associations with multiple susceptibility loci, no single-gene defect (mutation) can account for predisposition to these entities. By contrast, monogenic forms of diabetes (Table 19–5) are uncommon examples of the *diabetic phenotype occurring as a result of loss-of-function mutations within a single gene.* Monogenic causes of diabetes include either a primary defect in beta cell function or a defect in insulin receptor signaling. The largest subgroup of patients in this category traditionally was designated as having *maturity-onset diabetes of the young (MODY)* because of its superficial resemblance to type 2 diabetes and its occurrence in younger patients; MODY can be the result of inactivating mutations in one of six genes. Other uncommon causes include *maternally inherited diabetes and bilateral deafness,* secondary to mitochondrial DNA mutations, and mutations within the *insulin* gene itself, which most commonly manifests with diabetes in the neonatal period. Finally, rare instances of *insulin receptor* mutations that affect receptor synthesis, insulin binding, or downstream signal transduction can cause severe insulin resistance, accompanied by hyperinsulinemia and diabetes.

Complications of Diabetes

Diabetes can be a devastating disease because the abnormal glucose metabolism and other metabolic derangements have serious pathologic effects on virtually all the systems of the body. The most significant complications of diabetes are vascular abnormalities, renal damage, and lesions affecting the peripheral nerves and eyes (Fig. 19–25). The pathologic findings in these tissues and their clinical consequences are described below. There is extreme variability among patients in the time of onset of these complications, their severity, and the particular organ or organs involved. In persons with tight control of their diabetes, the onset may be delayed.

The pathogenesis of the long-term complications of diabetes is multifactorial, although persistent hyperglycemia (glucotoxicity) seems to be a key mediator. At least three distinct metabolic pathways seem to be involved in the pathogenesis of long-term complications; it is likely that all of them play a role in a tissue-specific manner.

1. *Formation of advanced glycation end products* (AGEs). AGEs are formed as a result of nonenzymatic reactions between intracellular glucose-derived precursors (glyoxal, methylglyoxal, and 3-deoxyglucosone) with the amino groups of both intracellular and extracellular proteins. The natural rate of AGE formation is greatly accelerated in the presence of hyperglycemia. AGEs bind to a specific receptor (RAGE), which is expressed on inflammatory cells (macrophages and T cells) and in endothelium and vascular smooth muscle. The detrimental effects of the AGE-RAGE signaling axis within the vascular compartment include
   - Release of pro-inflammatory *cytokines and growth factors* from intimal macrophages
   - Generation of *reactive oxygen species* in endothelial cells

- Increased *procoagulant activity* on endothelial cells and macrophages
- Enhanced *proliferation of vascular smooth muscle cells and synthesis of extracellular matrix*

  In addition to receptor-mediated effects, *AGEs can directly cross-link extracellular matrix proteins,* which decreases protein removal while enhancing protein deposition. AGEs cross-linked proteins can *trap* other plasma or interstitial proteins; for example, low-density lipoprotein (LDL) gets trapped within AGE-modified large vessel walls, accelerating atherosclerosis (Chapter 9), while albumin can get trapped within capillaries, accounting in part for the basement membrane thickening that is characteristic of diabetic microangiopathy (see later).

2. *Activation of protein kinase C.* Activation of intracellular protein kinase C (PKC) by calcium ions and the second messenger diacylglycerol (DAG) is an important signal transduction pathway in many cellular systems. Intracellular hyperglycemia can stimulate the de novo synthesis of DAG from glycolytic intermediates and hence cause activation of PKC. The downstream effects of PKC activation are numerous and include production of *pro-angiogenic molecules* such as vascular endothelial growth factor (VEGF), implicated in the neovascularization seen in diabetic retinopathy, and profibrogenic molecules such as transforming growth factor-β, leading to increased deposition of extracellular matrix and basement membrane material.
3. *Disturbances in polyol pathways.* In some tissues that do not require insulin for glucose transport (e.g., nerves, lens, kidneys, blood vessels), hyperglycemia leads to an increase in intracellular glucose that is then metabolized by the enzyme *aldose reductase* to sorbitol, a polyol, and eventually to fructose, in a reaction that uses NADPH (the reduced form of nicotinamide dinucleotide phosphate) as a cofactor. NADPH is also required by the enzyme glutathione reductase in a reaction that regenerates reduced glutathione (GSH). As described in Chapter 1, GSH is one of the important antioxidant mechanisms in the cell, and any reduction in GSH increases cellular susceptibility to *oxidative stress.* In neurons, persistent hyperglycemia appears to be the major underlying cause of diabetic neuropathy (*glucose neurotoxicity*).

MORPHOLOGY

Diabetes and Its Late Complications

Pathologic findings in the diabetic pancreas are variable and not necessarily dramatic. The important morphologic changes are related to the many late systemic complications of diabetes. In most patients, morphologic changes are likely to be found in arteries **(macrovascular disease),** basement membranes of small vessels **(microangiopathy),** kidneys **(diabetic nephropathy),** retina **(retinopathy),** nerves **(neuropathy),** and other tissues. These changes are seen in both type 1 and type 2 diabetes (Fig. 19–25).

Pancreas. Lesions in the pancreas are inconstant and rarely of diagnostic value. One or more of the following alterations may be present:

- **Reduction in the number and size of islets.** This change most often is seen in type 1 diabetes, particularly with rapidly advancing disease. Most of the islets are small, inconspicuous, and not easily detected.
- **Leukocytic infiltration of the islets,** which are principally composed of mononuclear cells (lymphocytes and macrophages) (Fig. 19–26, *A*). Of note, both type 1 and type 2 diabetes may demonstrate islet inflammation early in the disease, although it is typically more severe in T1D. In both types inflammation is often absent by the time the disease is clinically evident.
- **Amyloid replacement of islets in long-standing type 2 diabetes,** appearing as deposition of pink, amorphous material beginning in and around capillaries and between cells. At advanced stages the islets may be virtually obliterated (Fig. 19–26, *B*); fibrosis also may be observed. While inflammation is observed early in the natural history of type 2 diabetes, amyloid deposition occurs in long-standing cases.
- **An increase in the number and size of islets, especially characteristic of nondiabetic newborns of diabetic mothers.** Presumably, fetal islets undergo hyperplasia in response to the maternal hyperglycemia.

Diabetic Macrovascular Disease. Diabetes exacts a heavy toll on the vascular system. The hallmark of diabetic macrovascular disease is accelerated atherosclerosis affecting the aorta and large and medium-sized arteries. Except for its greater severity and earlier age at onset, atherosclerosis in diabetics is indistinguishable from that in nondiabetics (Chapter 9). Myocardial infarction, caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetics. Significantly, it is almost as common in diabetic women as in diabetic men. By contrast, myocardial infarction is uncommon in nondiabetic women of reproductive age. Gangrene of the lower extremities, as a result of advanced vascular disease, is about 100 times more common in persons with diabetes than in the general population. The larger renal arteries also are subject to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation, as discussed later on.

Hyaline arteriolosclerosis, the vascular lesion associated with hypertension (Chapters 9 and 13), is both more prevalent and more severe in diabetics than in nondiabetics, but it is not specific for diabetes and may be seen in elderly persons who do not suffer from either diabetes or hypertension. It takes the form of an amorphous, hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen (Fig. 19–27). Not surprisingly, in diabetic patients, its severity is related not only to the duration of the disease but also to the presence or absence of hypertension.

Diabetic Microangiopathy. One of the most consistent morphologic features of diabetes is **diffuse thickening of basement membranes.** The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla. However, it also may be seen in such nonvascular structures as renal tubules, the Bowman

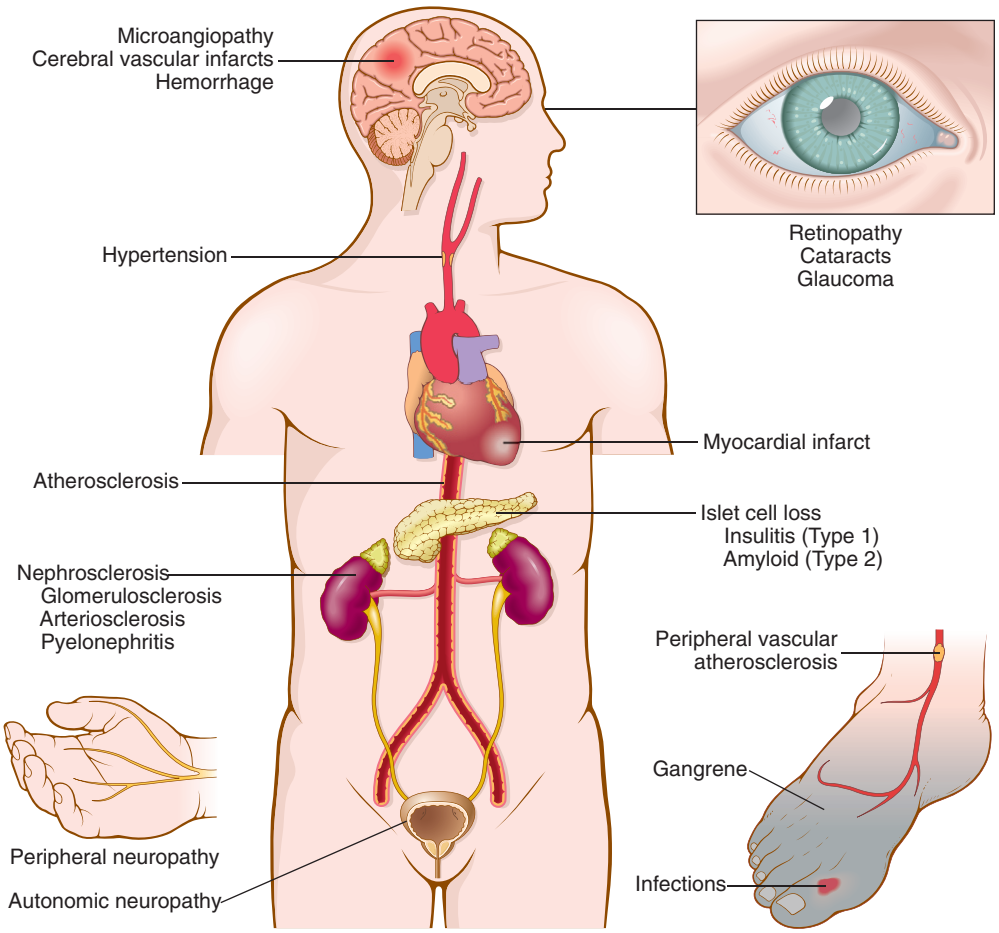


Figure 19–25 Long-term complications of diabetes.

capsule, peripheral nerves, and placenta. By both light and electron microscopy, the basal lamina separating parenchymal or endothelial cells from the surrounding tissue is markedly thickened by concentric layers of hyaline material composed predominantly of type IV collagen (Fig. 19–28).

Of note, **despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins. The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of**

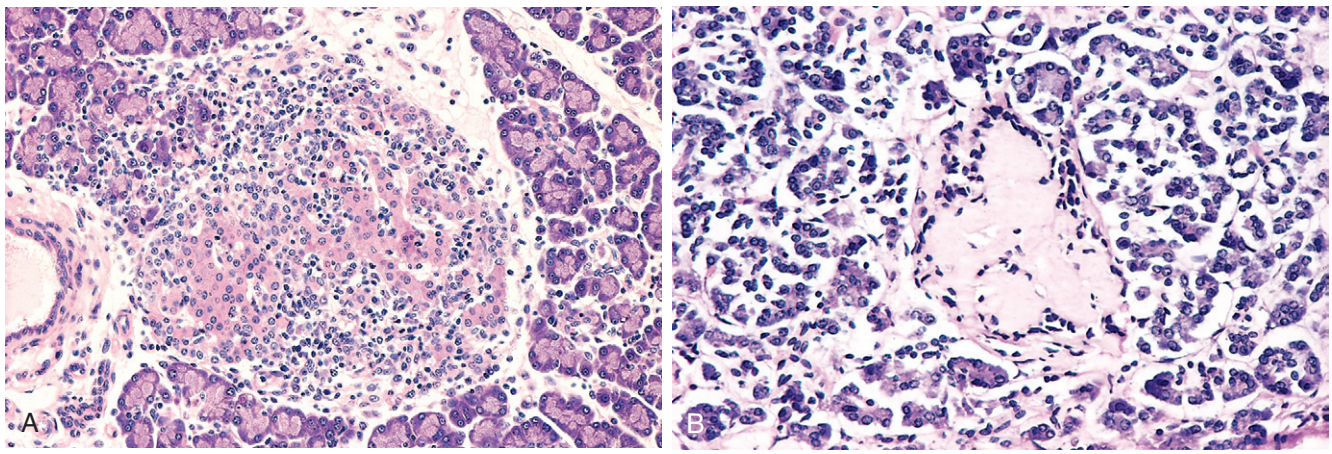


Figure 19–26 A, Autoimmune insulitis in a rat (BB) model of autoimmune diabetes. This disorder also is seen in type 1 human diabetes. **B,** Amyloidosis of a pancreatic islet in type 2 diabetes. Amyloidosis typically is observed late in the natural history of this form of diabetes, with islet inflammation noted at earlier observations.

(A, Courtesy of Dr. Arthur Like, University of Massachusetts, Worcester, Massachusetts.)

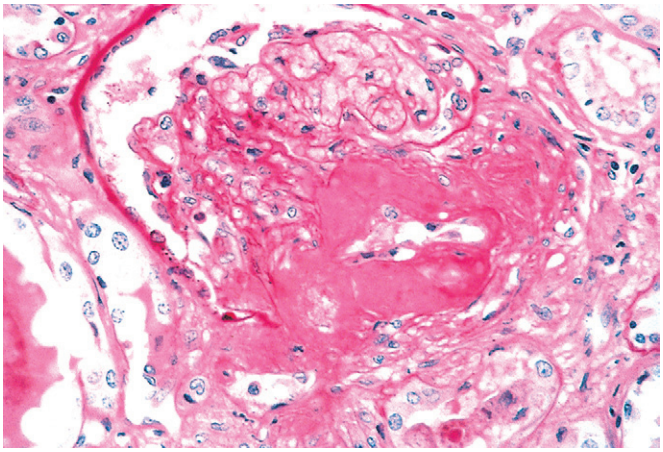


Figure 19–27 Severe renal hyaline arteriolosclerosis in a periodic acid–Schiff stained specimen. Note the markedly thickened, tortuous afferent arteriole. The amorphous nature of the thickened vascular wall is evident.
(Courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas Health Science Center, San Antonio, Texas.)

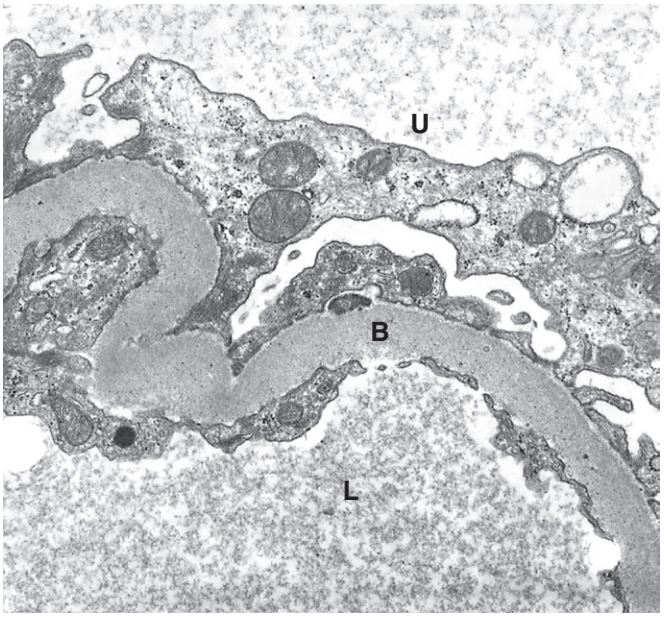


Figure 19–29 Renal glomerulus showing markedly thickened glomerular basement membrane (B) in a diabetic. L, glomerular capillary lumen; U, urinary space.
(Courtesy of Dr. Michael Kashgarian, Department of Pathology, Yale University School of Medicine, New Haven, Connecticut.)

neuropathy. An indistinguishable microangiopathy can be found in aged nondiabetic patients, but rarely to the extent seen in persons with long-standing diabetes.

Diabetic Nephropathy. The kidneys are prime targets of diabetes (see also Chapter 13). Renal failure is second only to myocardial infarction as a cause of death from this disease. Three lesions are encountered: (1) glomerular lesions; (2) renal vascular lesions, principally arteriolosclerosis; and (3) pyelonephritis, including necrotizing papillitis.

The most important glomerular lesions are capillary basement membrane thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis. The glomerular capillary basement membranes are thickened along their entire length. This change can be detected by electron microscopy within a few years of the onset of diabetes, sometimes without any associated change in renal function (Fig. 19–29).

Diffuse mesangial sclerosis consists of a diffuse increase in mesangial matrix along with mesangial cell proliferation and is always associated with basement membrane thickening. It is found in most individuals with disease of more than 10 years' duration. When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema (Chapter 13).

Nodular glomerulosclerosis describes a glomerular lesion made distinctive by ball-like deposits of a laminated matrix situated in the periphery of the glomerulus (Fig. 19–30). These nodules are PAS-positive and usually contain trapped mesangial cells. This distinctive change has been called the **Kimmelstiel-Wilson lesion,** after the two pathologists who first described it. Nodular glomerulosclerosis is encountered in approximately 15% to 30% of persons with long-term diabetes and is a major contributor to

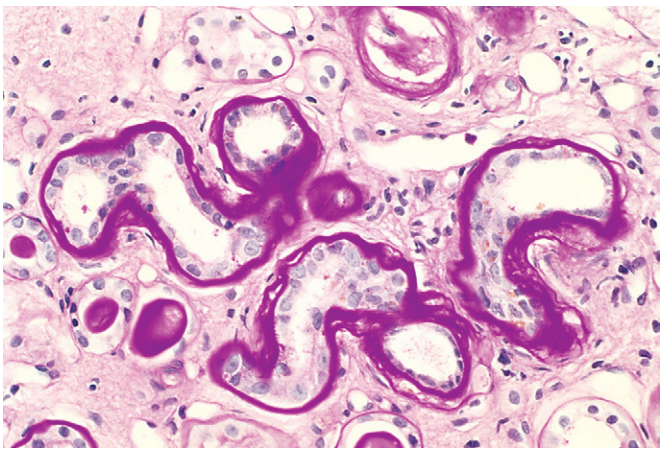


Figure 19–28 Renal cortex showing thickening of tubular basement membranes in a specimen from a diabetic patient. Periodic acid–Schiff stain.

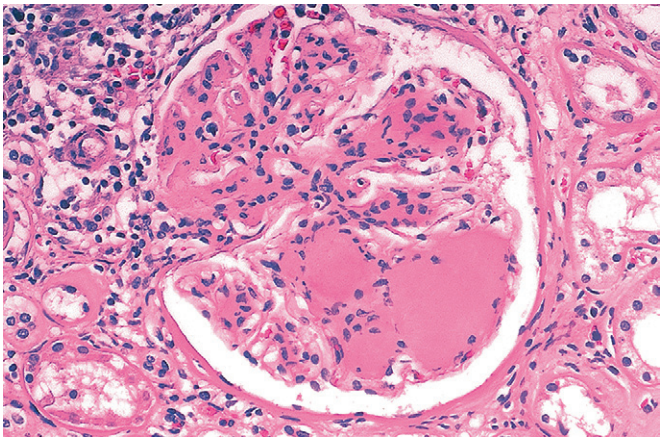


Figure 19–30 Nodular glomerulosclerosis in a renal specimen from a patient with long-standing diabetes.
(Courtesy of Dr. Lisa Yerian, Department of Pathology, University of Chicago, Chicago, Illinois.)

morbidity and mortality. Diffuse mesangial sclerosis also may be seen in association with old age and hypertension; by contrast, the nodular form of glomerulosclerosis, once certain unusual forms of nephropathies have been excluded (Chapter 13), is essentially pathognomonic of diabetes. Both the diffuse and the nodular forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular-appearing cortical surface (Fig. 19–31).

Renal atherosclerosis and arteriolosclerosis constitute part of the macrovascular disease seen in diabetics. The kidney is one of the most frequently and severely affected organs; however, the changes in the arteries and arterioles are similar to those found throughout the body. **Hyaline arteriolosclerosis affects not only the afferent but also the efferent arterioles.** Such efferent arteriolosclerosis is rarely if ever encountered in persons who do not have diabetes.

Pyelonephritis is an acute or chronic inflammation of the kidneys that usually begins in the interstitial tissue and then spreads to involve the tubules. Both the acute and chronic forms of this disease occur in nondiabetics as well as in diabetics but are more common in persons with diabetes than in the general population; once affected, diabetics tend to have more severe involvement. One special pattern of acute pyelonephritis, **necrotizing papillitis** (or papillary necrosis), is much more prevalent in diabetics than in nondiabetics.

Ocular Complications of Diabetes. Visual impairment, sometimes even total blindness, is one of the more feared consequences of long-standing diabetes. **The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma.** Retinopathy, the most common pattern, consists of a constellation of changes that together are considered by many ophthalmologists to be virtually diagnostic of the disease. **The lesion in the retina takes two forms: nonproliferative (background) retinopathy and proliferative retinopathy.**

Nonproliferative retinopathy includes intraretinal or preretinal hemorrhages, retinal exudates, microaneurysms, venous dilations, edema, and, most importantly, thickening of the retinal capillaries (microangiopathy). The retinal exudates can be either "soft" (microinfarcts) or "hard" (deposits of plasma proteins and lipids) (Fig. 19–32). The microaneurysms are discrete saccular dilations of retinal choroidal capillaries that appear through the ophthalmoscope as small red dots. Dilations tend to occur at focal points of weakening, resulting from loss of pericytes. Retinal edema presumably results from excessive capillary permeability. Underlying all of these changes is the microangiopathy, which is thought to lead to loss of capillary pericytes and hence to focal weakening of capillary structure.

The so-called proliferative retinopathy is a process of neovascularization and fibrosis. This lesion leads to serious consequences, including blindness, especially if it involves the macula. Vitreous hemorrhages can result from rupture of newly formed capillaries; the subsequent organization of the hemorrhage can pull the retina off its substratum (retinal detachment).

Diabetic Neuropathy. The central and peripheral nervous systems are not spared by diabetes. The most frequent pattern of involvement is that of a peripheral, symmetric neuropathy of the lower extremities affecting both motor and sensory function, particularly the latter. Other forms include autonomic neuropathy, which produces disturbances in bowel and bladder function and sometimes sexual

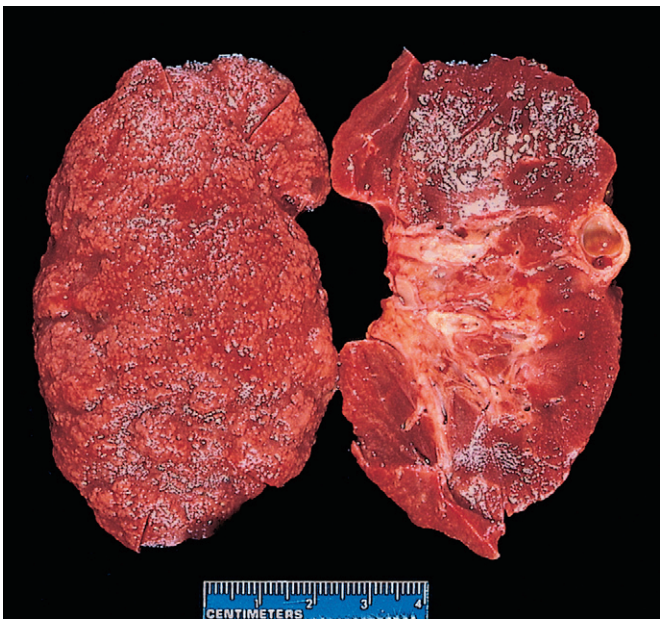


Figure 19–31 Nephrosclerosis in a patient with long-standing diabetes. The kidney has been bisected to demonstrate both diffuse granular transformation of the surface (*left*) and marked thinning of the cortical tissue (*right*). Additional features include some irregular depressions, the result of pyelonephritis, and an incidental cortical cyst (*far right*).

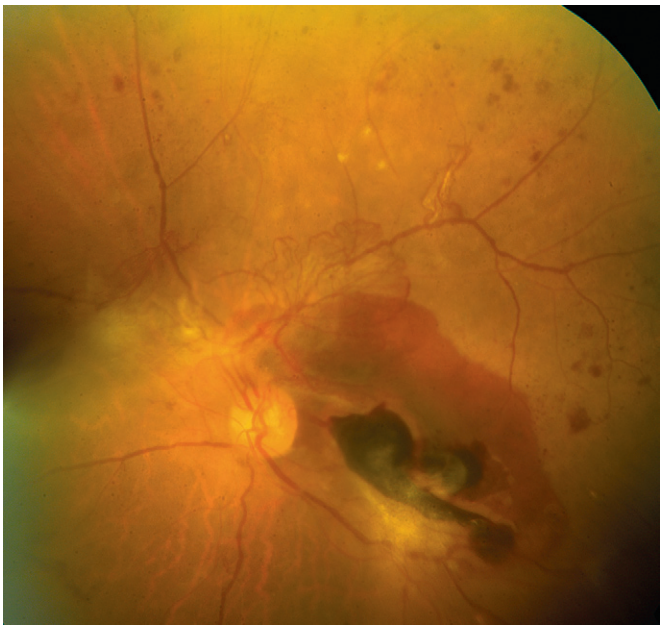


Figure 19–32 Characteristic morphologic changes of diabetic retinopathy. Features include advanced proliferative retinopathy with retinal hemorrhages, exudates, neovascularization, and tractional retinal detachment (*lower right corner*).
(Courtesy of Dr. Rajendra Apte, Washington University School of Medicine, St. Louis, Missouri.)

impotence, and diabetic mononeuropathy, which may manifest as sudden footdrop or wristdrop or isolated cranial nerve palsies. The neurologic changes may be the result of microangiopathy and increased permeability of the capillaries that supply the nerves, as well as direct axonal damage.

Clinical Features

It is difficult to discuss with brevity the diverse clinical presentations of diabetes mellitus. Only a few characteristic patterns are presented here. In the initial 1 or 2 years after manifestation of overt *type 1 diabetes* (referred to as the "honeymoon period"), exogenous insulin requirements may be minimal to none because of residual ongoing endogenous insulin secretion, but thereafter the beta cell reserve is exhausted and insulin requirements increase dramatically. Although beta cell destruction is a gradual process, the transition from impaired glucose tolerance to overt diabetes may be abrupt, heralded by an event associated with increased insulin requirements such as infection. The onset is marked by polyuria, polydipsia, polyphagia, and in severe cases, ketoacidosis, all resulting from metabolic derangements (Fig. 19–33).

Since insulin is a major anabolic hormone in the body, *deficiency of insulin results in a catabolic state that affects not only glucose metabolism but also fat and protein metabolism.* The assimilation of glucose into muscle and adipose tissue is sharply diminished or abolished. Not only does storage of glycogen in liver and muscle cease, but also reserves are depleted by glycogenolysis. The resultant hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria ensues. The glycosuria induces an osmotic diuresis and, consequently, *polyuria,* causing a profound loss of water and electrolytes. The obligatory renal water loss combined with the hyperosmolarity resulting from the increased levels of glucose in the blood tends to deplete intracellular water, triggering the osmoreceptors of the thirst centers of the brain. This sequence of events generates intense thirst (*polydipsia*). With a deficiency of insulin, the scales swing from insulin-promoted anabolism to catabolism of proteins and fats. Proteolysis follows, and the gluconeogenic amino acids are removed by the liver and used as building blocks for glucose. The catabolism of proteins and fats tends to induce a negative energy balance, which in turn leads to increasing appetite (*polyphagia*), thus completing the classic triad of diabetes: *polyuria, polydipsia,* and *polyphagia.* Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle weakness. The combination of polyphagia and weight loss is paradoxical and should always point to the diagnostic possibility of diabetes.

In patients with type 1 diabetes, deviations from normal dietary intake, unusual physical activity, infection, or any other forms of stress may rapidly influence the treacherously fragile metabolic balance, predisposing the affected person to *diabetic ketoacidosis.* The plasma glucose usually is in the range of 500 to 700 mg/dL as a result of absolute insulin deficiency and unopposed effects of counterregulatory hormones (epinephrine, glucagon). The marked hyperglycemia causes an osmotic diuresis and dehydration characteristic of the ketoacidotic state. The second major effect is activation of the ketogenic machinery. Insulin deficiency leads to activation of lipoprotein lipase, with resultant excessive breakdown of adipose stores, giving rise to increased FFAs, which are oxidized by the liver to produce *ketones.* Ketogenesis is an adaptive phenomenon in times of starvation, generating ketones as a source of energy for consumption by vital organs (e.g., brain). The rate at which ketones are formed may exceed the rate at which they can be used by peripheral tissues, leading to *ketonemia* and *ketonuria.* If the urinary excretion of ketones is compromised by dehydration, the accumulating ketones decrease blood pH, resulting in metabolic ketoacidosis.

Type 2 diabetes mellitus also may manifest with polyuria and polydipsia, but unlike in type 1 diabetes, patients often are older than 40 years and frequently are obese. Unfortunately, with the increase in obesity and sedentary life style in Western society, type 2 diabetes is now seen in children and adolescents with increasing frequency. In some cases, medical attention is sought because of unexplained weakness or weight loss. *Most frequently, however, the diagnosis is made after routine blood or urine testing in asymptomatic persons.*

In the decompensated state, patients with type 2 diabetes may develop *hyperosmolar nonketotic coma.* This syndrome is engendered by severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia. Typically, the affected person is an elderly diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake. The absence of ketoacidosis and its symptoms (nausea, vomiting, respiratory difficulties) delays recognition of the seriousness of the situation until the onset of severe dehydration and coma. Table 19–6 summarizes some of the pertinent clinical, genetic, and histopathologic features that distinguish between type 1 and type 2 diabetes.

As previously discussed, it is the long-term effects of diabetes, more than the acute metabolic complications, which are responsible for the overwhelming preponderance of morbidity and mortality attributable to this disease. In most instances, these complications appear approximately 15 to 20 years after the onset of hyperglycemia.

- In both forms of long-standing diabetes, cardiovascular events such as myocardial infarction, renal vascular insufficiency, and stroke (cerebrovascular accident) are the most common contributors to mortality. The impact of cardiovascular disease can be gauged by its involvement in as many as 80% of deaths among persons with type 2 diabetes; in fact, diabetics have a 3 to 7.5 times greater incidence of death from cardiovascular causes than nondiabetic populations. The hallmark of cardiovascular disease is accelerated atherosclerosis of the large and medium-sized arteries (i.e., macrovascular disease). The importance of obesity in the pathogenesis of insulin resistance has already been discussed, but it also is an independent risk factor for development of atherosclerosis.
- Diabetic nephropathy is a leading cause of end-stage renal disease in the United States. The earliest manifestation of diabetic nephropathy is the appearance of small amounts of albumin in the urine (greater than 30 but less than 300 mg/day—i.e., microalbuminuria). Without specific interventions, approximately 80% of patients with type 1 diabetes and 20% to 40% of those with type

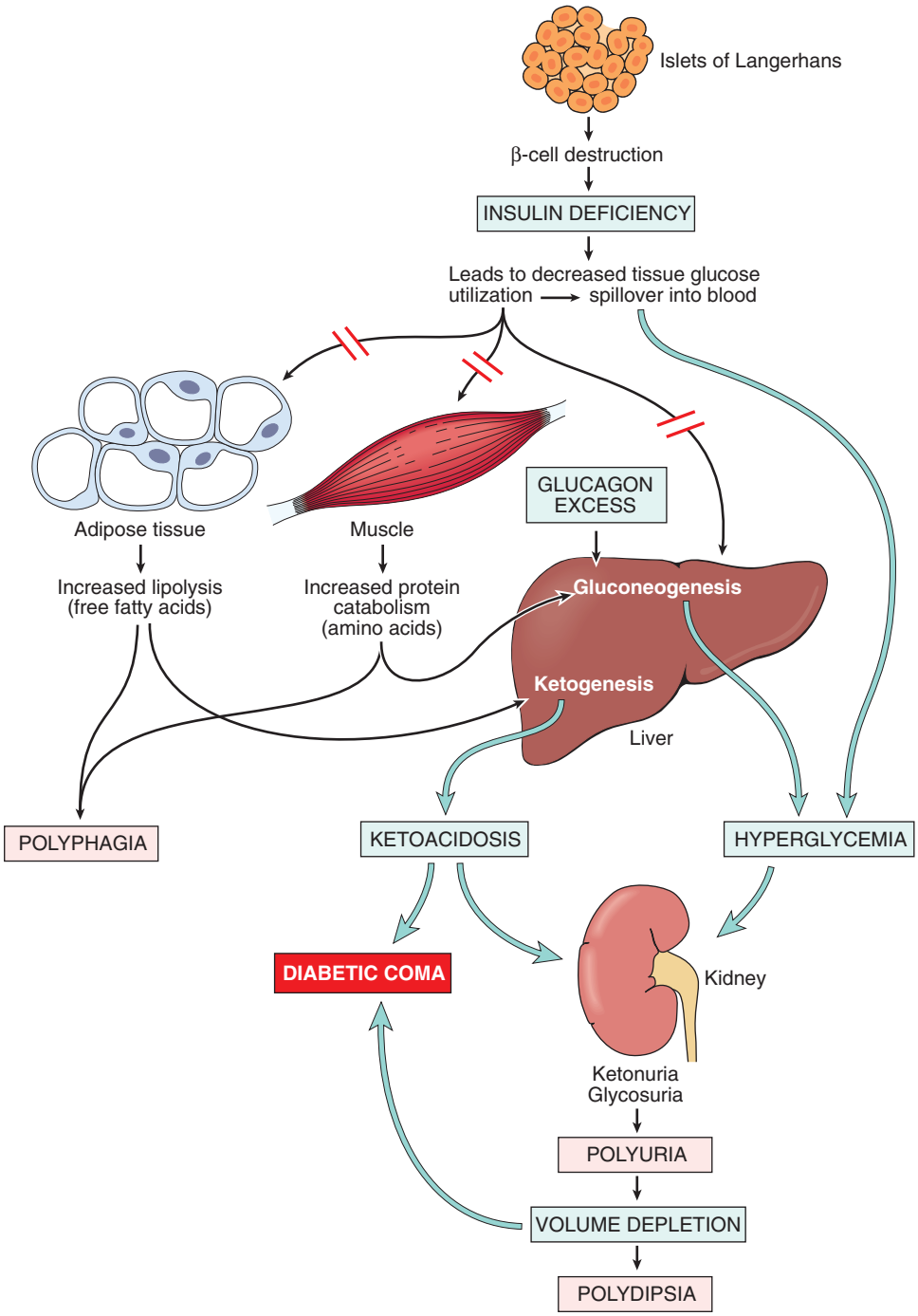


Figure 19–33 Sequence of metabolic derangements leading to diabetic coma in type 1 diabetes mellitus. An absolute insulin deficiency leads to a catabolic state, eventuating in ketoacidosis and severe volume depletion. These derangements bring about sufficient central nervous system compromise to cause coma and, eventually, death if left untreated.

2 diabetes will develop overt nephropathy with macroalbuminuria (excretion of more than 300 mg/day) over the succeeding 10 to 15 years, usually accompanied by the appearance of hypertension. The progression from overt nephropathy to end-stage renal disease can be highly variable and is evidenced by a progressive drop in glomerular filtration rate. By 20 years after diagnosis, more than 75% of persons with type 1 diabetes and about 20% of those with type 2 diabetes with overt nephropathy will develop end-stage renal disease, necessitating dialysis or renal transplantation.

- Visual impairment, sometimes even total blindness, is one of the more feared consequences of long-standing diabetes. This disease currently is the fourth leading cause of acquired blindness in the United States. Approximately 60% to 80% of patients develop some form of diabetic retinopathy approximately 15 to 20 years after diagnosis. In addition to retinopathy, diabetic patients

Table 19–6 Type 1 Versus Type 2 Diabetes Mellitus

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical	
Onset usually in childhood and adolescence	Onset usually in adulthood; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority of patients are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma
Genetics	
Major linkage to MHC class I and II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes
Pathogenesis	
Dysfunction in regulatory T cells (Tregs) leading to breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by beta cells Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
Pathology	
Autoimmune "insulitis"	*Early*: inflammation; *late*: amyloid deposition in islets
Beta cell depletion, islet atrophy	Mild beta cell depletion

HLA, human leukocyte antigen; MHC, major histocompatibility complex.

also have an increased propensity for glaucoma and cataract formation, both of which contribute to visual impairment in diabetes.

- Diabetic neuropathy can elicit a variety of clinical syndromes, afflicting the central nervous system, peripheral sensorimotor nerves, and autonomic nervous system. The most frequent pattern of involvement is a distal symmetric polyneuropathy of the lower extremities that affects both motor and sensory function, particularly the latter (Chapter 21). Over time, the upper extremities may be involved as well, thus approximating a "glove and stocking" pattern of polyneuropathy. Other forms include autonomic neuropathy, which produces disturbances in bowel and bladder function and sometimes sexual impotence, and diabetic mononeuropathy, which may manifest as sudden footdrop, wristdrop, or isolated cranial nerve palsies.
- Diabetic patients are plagued by an enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis. Such infections cause about 5% of diabetes-related deaths. In a person with diabetic neuropathy, a trivial infection in a toe may be the first event in a long succession of complications (gangrene, bacteremia, pneumonia) that may ultimately lead to death.

Several large-scale prospective studies have convincingly demonstrated that the long-term complications, and the associated morbidity and mortality, from diabetes are attenuated by strict glycemic control. For patients with type 1 diabetes, insulin replacement therapy is the mainstay of treatment, while non-pharmacologic approaches such as dietary restrictions and exercise (which improves insulin sensitivity) are often the "first line of defense" for type 2 diabetes. Most patients with type 2 diabetes will eventually require therapeutic intervention to reduce hyperglycemia, which can be achieved by administration of a number of agents that lower glucose levels through several distinct mechanisms of action. Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin, also known as HbA1C, which is formed by non-enzymatic addition of glucose moieties to hemoglobin in red cells. Unlike blood glucose levels, HbA1C is a measure of glycemic control over long periods of time (2 to 3 months) and is relatively unaffected by day-to-day variations. An HbA1C below 7% is taken as evidence of tight glycemic control, but patients with HbA1C levels in this range also have an increased risk of potentially life-threatening episodes of therapy-related hypoglycemia, and "optimal" control of glucose levels in diabetic patients remains an unsettled area of clinical investigation.

SUMMARY

Diabetes Mellitus: Pathogenesis and Long-Term Complications

- Type 1 diabetes is an autoimmune disease characterized by progressive destruction of islet beta cells, leading to absolute insulin deficiency. Both autoreactive T cells and autoantibodies are involved.
- Type 2 diabetes is caused by insulin resistance and beta cell dysfunction, resulting in relative insulin deficiency. Autoimmunity is not involved.
- Obesity has an important relationship with insulin resistance (and hence type 2 diabetes), probably mediated by cytokines released from adipose tissues (adipocytokines). Other players in the *adipo-insulin axis* include FFAs (which may cause *lipotoxicity*) and the PPARγ receptor, which modulates adipocytokine levels.
- Monogenic forms of diabetes are uncommon and are caused by single-gene defects that result in primary beta cell dysfunction (e.g., *glucokinase* mutation) or lead to

abnormalities of insulin–insulin receptor signaling (e.g., insulin receptor gene mutations).

- The long-term complications of diabetes are similar in both types and affect mainly blood vessels, and the kidneys, nerves and eyes. The development of these complications is attributed to three underlying mechanisms: formation of AGEs, activation of PKC, and disturbances in polyol pathways leading to oxidative stress.

PANCREATIC NEUROENDOCRINE TUMORS

Pancreatic neuroendocrine tumors (PanNETs), also known as *islet cell tumors,* are rare in comparison with tumors of the exocrine pancreas, accounting for only 2% of all pancreatic neoplasms. PanNETs are most common in adults and may be single or multifocal; when they are malignant, the liver is the most common site of organ metastases. These tumors have a propensity to elaborate pancreatic hormones, but some are nonfunctional. The latter typically are larger lesions at diagnosis, since they come to clinical attention later in their natural history than functional PanNETs, which often present with symptoms related to excessive hormone production. All PanNETs, with the exception of insulinomas (see later), are regarded as having malignant potential, and in fact, 65% to 80% of PanNETs manifest with overtly malignant features of biologic aggressiveness, such as invasion into local tissues or distant metastases. The *proliferative rate of PanNETs* (measured using either mitotic counts or nuclear labeling with the proliferation marker Ki-67) is one of the best correlates of outcome. Genomic sequencing of sporadic PanNETs has identified recurrent somatic alterations in three major genes or pathways:

- *MEN1*, which causes familial MEN syndrome, type 1 (see later), is also mutated in many sporadic neuroendocrine tumors
- Loss-of-function mutations in tumor suppressor genes such as *PTEN* and *TSC2,* which are negative regulators of the oncogenic mammalian TOR (mTOR) signaling pathway
- Inactivating mutations in two genes, *ATRX* and *DAXX,* which have multiple cellular functions. Of note, nearly half of PanNETs have a somatic mutation in either *ATRX* or *DAXX,* but not both, suggesting that the encoded proteins function in a critical but redundant pathway.

Insulinomas

Beta cell tumors (insulinomas) are the most common type of PanNET and may be responsible for the elaboration of sufficient insulin to induce clinically significant hypoglycemia. The characteristic clinical picture is dominated by attacks of hypoglycemia, which occur when plasma blood glucose levels fall below 50 mg/dL. The attacks consist principally of such central nervous system manifestations as confusion, stupor, and loss of consciousness. They are precipitated by fasting or exercise and are promptly relieved by feeding or parenteral administration of glucose. Most insulinomas are cured by surgical resection.

MORPHOLOGY

Insulinomas exhibit favorable biologic behavior, possibly because the vast majority are identified while they are small (less than 2 cm in diameter) and localized to the pancreas. Most are solitary lesions, although multifocal tumors or tumors ectopic to the pancreas may be encountered. Malignancy in insulinomas, constituting less than 10% of cases, is diagnosed on the basis of local invasion or metastases. On histologic examination, these benign tumors look remarkably like giant islets, with preservation of the regular cords of monotonous cells and their orientation to the vasculature. Not even malignant lesions present much evidence of anaplasia, and they may be deceptively encapsulated. **Deposition of amyloid** in the extracellular tissue is a characteristic feature of many insulinomas (Fig. 19–34, *A*). Under the electron microscope, neoplastic beta cells, like their normal counterparts, display distinctive round granules (Fig. 19–34, *B*).

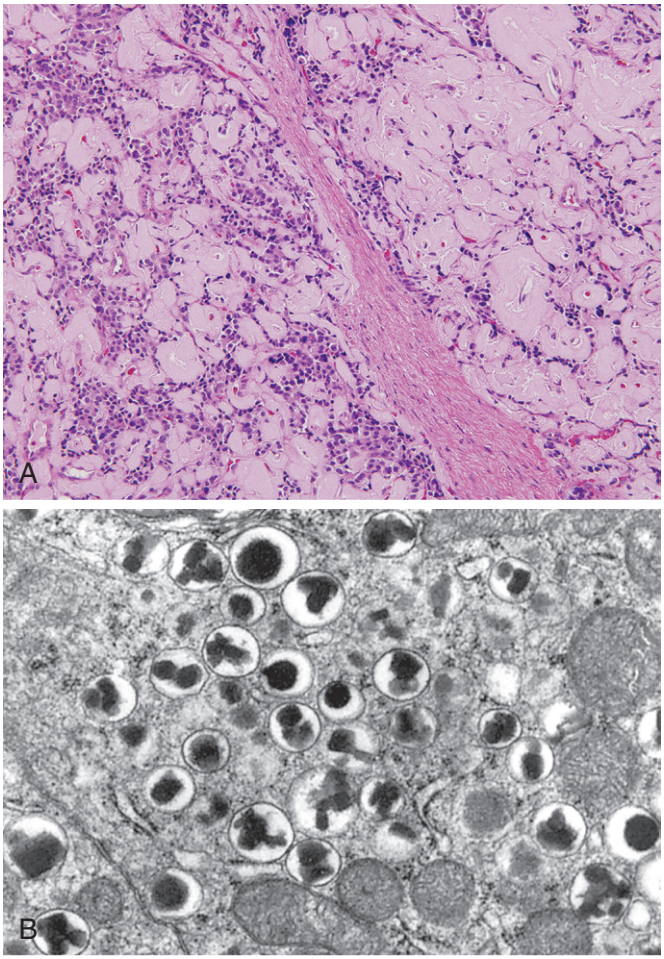


Figure 19–34 Pancreatic neuroendocrine tumor (PanNET), also called islet cell tumor. **A,** The neoplastic cells are monotonous in appearance and demonstrate minimal pleomorphism or mitotic activity. There is abundant amyloid deposition, characteristic of an insulinoma. On clinical evaluation, the patient had episodic hypoglycemia. **B,** Electron micrograph of a normal beta cell shows the characteristic membrane-bound granules, each containing a dense, often rectangular core and distinct halo. Insulinomas contain comparable granules.

Gastrinomas

Marked hypersecretion of gastrin usually has its origin in gastrin-producing tumors (*gastrinomas*), which are just as likely to arise in the duodenum and peripancreatic soft tissues as in the pancreas (the so-called gastrinoma triangle). Zollinger and Ellison first called attention to the *association of pancreatic islet cell lesions with hypersecretion of gastric acid and severe peptic ulceration,* which are present in 90% to 95% of patients with gastrinomas—the clinical hallmark of Zollinger-Ellison syndrome. In this condition, hypergastrinemia from a pancreatic or duodenal tumor stimulates extreme gastric acid secretion, which in turn causes *peptic ulceration.* The duodenal and gastric ulcers often are *multiple*; although they are identical to those found in the general population, they often are *unresponsive* to usual therapy. In addition, ulcers may occur in *unusual locations* such as the jejunum; when intractable jejunal ulcers are found, Zollinger-Ellison syndrome should be considered. More than half of the affected patients have diarrhea; in 30%, it is the presenting manifestation.

MORPHOLOGY

Gastrinomas may arise in the pancreas, the peripancreatic region, or the wall of the duodenum. **Over half of gastrin-producing tumors are locally invasive or have already metastasized at the time of diagnosis.** In approximately 25% of patients, gastrinomas arise in conjunction with other endocrine tumors, thus conforming to the MEN-1 syndrome (see further on); MEN-1–associated gastrinomas frequently are multifocal, while sporadic gastrinomas usually are single. As with insulin-secreting tumors of the pancreas, gastrin-producing tumors are histologically bland and rarely exhibit marked anaplasia.

ADRENAL CORTEX

The *adrenal glands* are paired endocrine organs consisting of two regions, the cortex and medulla, which differ in their development, structure, and function. The *cortex* consists of three layers of distinct cell types. Beneath the capsule of the adrenal is the narrow layer of zona glomerulosa. An equally narrow zona reticularis abuts the medulla. Intervening is the broad zona fasciculata, which makes up about 75% of the total cortex. The adrenal cortex synthesizes three different types of steroids:

- *Glucocorticoids* (principally cortisol), which are synthesized primarily in the zona fasciculata, with a small contribution from the zona reticularis
- *Mineralocorticoids,* the most important being aldosterone, which are generated in the zona glomerulosa
- *Sex steroids* (estrogens and androgens), which are produced largely in the zona reticularis

The *adrenal medulla* is composed of chromaffin cells, which synthesize and secrete *catecholamines,* mainly epinephrine. This section deals first with disorders of the adrenal cortex and then of the medulla. Diseases of the adrenal cortex can be conveniently divided into those associated with cortical hyperfunction and those characterized by cortical hypofunction.

ADRENOCORTICAL HYPERFUNCTION (HYPERADRENALISM)

There are three distinctive hyperadrenal clinical syndromes, each caused by abnormal production of one or more of the hormones produced by the three layers of the cortex: (1) *Cushing syndrome,* characterized by an excess of cortisol; (2) *hyperaldosteronism*; and (3) *adrenogenital* or *virilizing syndromes,* caused by an excess of androgens. The clinical features of some of these syndromes overlap somewhat because of the overlapping functions of some of the adrenal steroids.

Hypercortisolism and Cushing Syndrome

Hypercortisolism, typically manifested as *Cushing syndrome,* is caused by any condition that produces an elevation in glucocorticoid levels. In clinical practice, the vast majority of cases of Cushing syndrome are the result of administration of exogenous glucocorticoids (iatrogenic). The remaining cases are endogenous, and the three most common etiologic disorders are (Fig. 19–35):

- Primary hypothalamic-pituitary diseases associated with hypersecretion of ACTH
- The secretion of ectopic ACTH by non-pituitary neoplasms
- Primary adrenocortical neoplasms (adenoma or carcinoma) and rarely, primary cortical hyperplasia

Primary hypothalamic-pituitary disease associated with hypersecretion of ACTH, also known as *Cushing disease,* accounts for approximately 70% of cases of spontaneous, endogenous Cushing syndrome. The prevalence of this disorder is about four times higher among women than among men, and it occurs most frequently during young adulthood (the 20s and 30s). In the vast majority of cases, the *pituitary gland contains an ACTH-producing microadenoma* that does not produce mass effects in the brain; some corticotroph tumors qualify as macroadenomas (larger than 10 mm across). In the remaining patients, the anterior pituitary contains areas of *corticotroph cell hyperplasia* without a discrete adenoma. Corticotroph cell hyperplasia may be primary or, much less commonly, secondary to excessive ACTH release by a hypothalamic corticotropin-releasing hormone (CRH)–producing tumor. The adrenal glands in patients with Cushing disease are characterized by a variable degree of bilateral nodular cortical hyperplasia (discussed later), secondary to the elevated levels of ACTH ("ACTH-dependent" Cushing syndrome). The cortical hyperplasia is in turn responsible for the hypercortisolism.

Secretion of ectopic ACTH by nonpituitary tumors accounts for about 10% of cases of Cushing syndrome. In

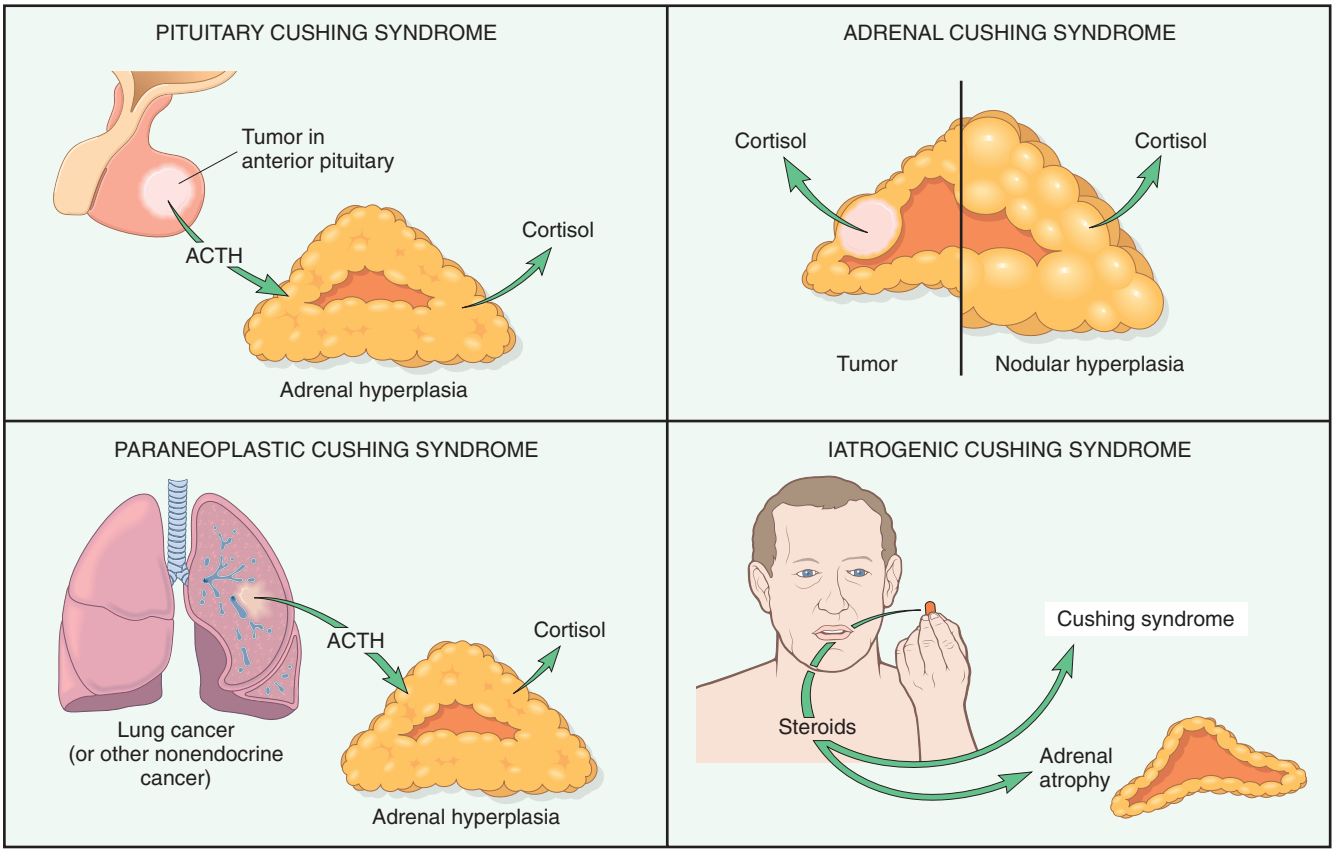


Figure 19–35 Schematic representation of the various forms of Cushing syndrome: The three endogenous forms, as well as the more common exogenous (iatrogenic) form. ACTH, adrenocorticotropic hormone.

many instances the responsible tumor is a *small cell carcinoma of the lung*, although other neoplasms, including carcinoids, medullary carcinomas of the thyroid, and PanNETs, have been associated with the syndrome. In addition to tumors that elaborate ectopic ACTH, an occasional neuroendocrine neoplasm produces ectopic CRH, which in turn causes ACTH secretion and hypercortisolism. As in the pituitary variant, the adrenal glands undergo bilateral cortical hyperplasia secondary to elevated ACTH, but the rapid downhill course of patients with these cancers often cuts short the adrenal enlargement.

Primary adrenal neoplasms, such as adrenal adenoma and carcinoma, and rarely, *primary cortical hyperplasia,* are responsible for about 15% to 20% of cases of endogenous Cushing syndrome. This form of Cushing syndrome is also designated *ACTH-independent Cushing syndrome,* or adrenal Cushing syndrome, because the adrenals function autonomously. The biochemical hallmark of adrenal Cushing syndrome is elevated levels of cortisol with low serum levels of ACTH. In most cases, adrenal Cushing syndrome is caused by a unilateral adrenocortical neoplasm, which may be either benign (adenoma) or malignant (carcinoma). The overwhelming majority of hyperplastic adrenals are ACTH-dependent, and primary cortical hyperplasia of the adrenal cortices is a rare cause of Cushing syndrome. There are two variants of this entity; the first presents as macronodules of varying sizes (3 cm or greater in diameter) and the second as micronodules (1 to 3 mm).

MORPHOLOGY

The main lesions of Cushing syndrome are found in the pituitary and adrenal glands. The **pituitary** in Cushing syndrome shows changes that vary with different causes. The most common alteration, resulting from high levels of endogenous or exogenous glucocorticoids, is termed **Crooke hyaline change.** In this condition, the normal granular, basophilic cytoplasm of the ACTH-producing cells in the anterior pituitary is replaced by homogeneous, lightly basophilic material. This alteration is the result of the accumulation of intermediate keratin filaments in the cytoplasm.

Morphologic changes in the adrenal glands also depend on the cause of the hypercortisolism and include: (1) cortical atrophy, (2) diffuse hyperplasia, (3) macronodular or micronodular hyperplasia, or (4) an adenoma or a carcinoma.

In patients in whom the syndrome results from exogenous glucocorticoids, suppression of endogenous ACTH results in bilateral **cortical atrophy,** due to a lack of stimulation of the zona fasciculata and zona reticularis by ACTH. The zona glomerulosa is of normal thickness in such cases, because this portion of the cortex functions independently of ACTH. In cases of endogenous hypercortisolism, by contrast, the adrenals either are hyperplastic or contain a cortical neoplasm. **Diffuse hyperplasia** is found in patients with ACTH-dependent Cushing syndrome (Fig. 19–36). Both glands are enlarged, either subtly or markedly, each weighing up to

Figure 19–36 Diffuse hyperplasia of the adrenal (*bottom*) contrasted with normal adrenal gland (*top*). In cross-section, the adrenal cortex is yellow and thickened, and a subtle nodularity is evident. The abnormal gland was from a patient with ACTH-dependent Cushing syndrome, in whom both adrenals were diffusely hyperplastic. ACTH, adrenocorticotropic hormone.

30 g. The adrenal cortex is diffusely thickened and variably nodular, although the latter is not as pronounced as in cases of ACTH-independent nodular hyperplasia. The yellow color of diffusely hyperplastic glands derives from presence of **lipid-rich** cells, which appear vacuolated under the microscope. In primary cortical hyperplasia, the cortex is replaced almost entirely by **macro- or micronodules,** with the latter composed of 1- to 3-mm darkly pigmented nodules. The pigment is believed to be lipofuscin, a wear-and-tear pigment (Chapter 1).

Functional adenomas or carcinomas of the adrenal cortex as the source of cortisol are not morphologically distinct from nonfunctioning adrenal neoplasms (described later). Both the benign and the malignant lesions are more common in women in their 30s to 50s. Adrenocortical **adenomas** are yellow tumors surrounded by thin or well-developed capsules, and most weigh less than 30 g (Fig. 19–37, *A*). On microscopic examination, they are composed of cells similar to those encountered in the normal zona fasciculata (Fig. 19–37, *B*). The **carcinomas** associated with Cushing syndrome, by contrast, tend to be larger than the adenomas. These tumors are nonencapsulated masses frequently exceeding 200 to 300 g in weight, having all of the anaplastic characteristics of cancer, as detailed later on. With functioning tumors, both benign and malignant, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic, as a result of suppression of endogenous ACTH by high cortisol levels.

Clinical Features

The signs and symptoms of Cushing syndrome represent an exaggeration of the known actions of glucocorticoids. Cushing syndrome usually develops gradually and, like many other endocrine abnormalities, may be quite subtle in its early stages. A major exception to this insidious onset is with Cushing syndrome associated with small cell carcinomas of the lung, when the rapid course of the underlying disease precludes development of many of the characteristic features. Early manifestations of Cushing syndrome include *hypertension* and *weight gain.* With time, the more characteristic centripetal distribution of adipose tissue becomes apparent, with resultant truncal obesity, "moon facies," and accumulation of fat in the posterior neck and

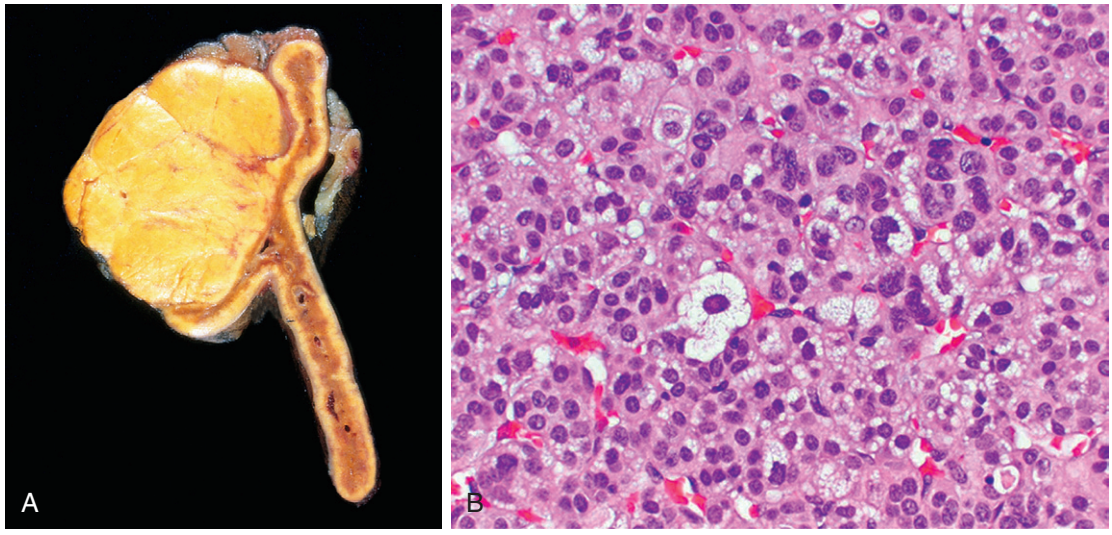


Figure 19–37 Adrenocortical adenoma. **A,** The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature. The functional status of an adrenocortical adenoma cannot be predicted from its gross or microscopic appearance. **B,** Histologic features of an adrenal cortical adenoma. The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid. There is mild nuclear pleomorphism. Mitotic activity and necrosis are not seen.

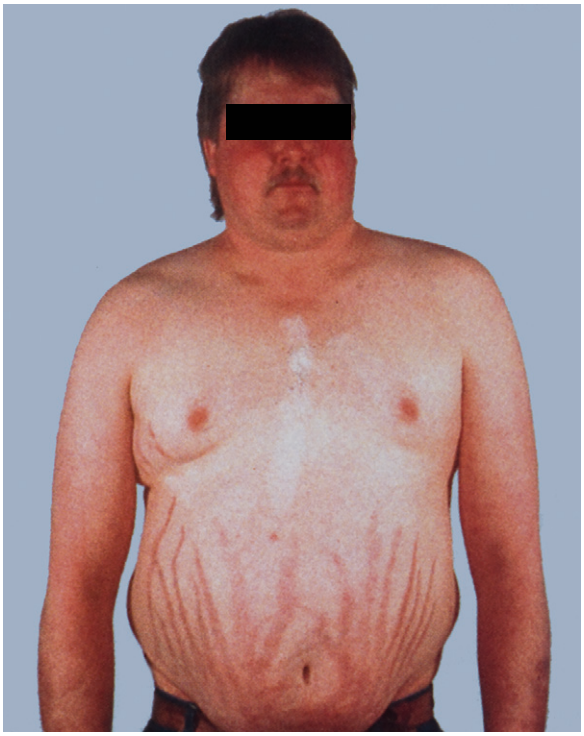


Figure 19–38 A patient with Cushing syndrome. Characteristic features include central obesity, "moon facies," and abdominal striae.
(Reproduced with permission from Lloyd RV, et al: Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)

back ("buffalo hump") (Fig. 19–38). Hypercortisolism causes selective atrophy of fast-twitch (type II) myofibers, with resultant decreased muscle mass and proximal limb weakness. Glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells, with resultant *hyperglycemia, glucosuria,* and *polydipsia,* mimicking diabetes mellitus. The catabolic effects on proteins cause loss of collagen and resorption of bone. Thus, the skin is thin, fragile, and easily bruised; *cutaneous striae* are particularly common in the abdominal area. Bone resorption results in the development of *osteoporosis,* with consequent increased susceptibility to fractures. Because glucocorticoids suppress the immune response, patients with Cushing syndrome also are at increased risk for a variety of infections. Additional manifestations include *hirsutism* and *menstrual abnormalities,* as well as a number of *mental disturbances,* including mood swings, depression, and frank psychosis. Extraadrenal Cushing syndrome caused by pituitary or ectopic ACTH secretion usually is associated with increased skin pigmentation secondary to melanocyte-stimulating activity in the ACTH precursor molecule.

SUMMARY

Hypercortisolism (Cushing Syndrome)

- The most common cause of hypercortisolism is exogenous administration of steroids.
- Endogenous hypercortisolism most often is secondary to an ACTH-producing pituitary microadenoma (*Cushing disease*), followed by primary adrenal neoplasms (*ACTH-independent* hypercortisolism) and paraneoplastic ACTH production by tumors (e.g., small cell lung cancer).
- The morphologic features in the adrenal include bilateral cortical atrophy (in exogenous steroid-induced disease), bilateral diffuse or nodular hyperplasia (most common finding in endogenous Cushing syndrome), or an adrenocortical neoplasm.

Hyperaldosteronism

Hyperaldosteronism is the generic term for a group of closely related conditions characterized by chronic excess aldosterone secretion. Hyperaldosteronism may be primary, or it may be secondary to an extraadrenal cause. In *secondary hyperaldosteronism,* aldosterone release occurs in response to activation of the renin-angiotensin system. This condition is characterized by *increased levels of plasma renin* and is encountered in association with

- Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (caused by estrogen-induced increases in plasma renin substrate)

Primary hyperaldosteronism, by contrast, indicates a primary, autonomous overproduction of aldosterone, with resultant suppression of the renin-angiotensin system and *decreased plasma renin activity.* The potential causes of primary hyperaldosteronism are:

- *Bilateral idiopathic hyperaldosteronism,* characterized by bilateral nodular hyperplasia of the adrenal glands. This mechanism is the most common underlying cause of primary hyperaldosteronism, accounting for about 60% of cases. The pathogenesis is unclear.
- *Adrenocortical neoplasm,* either an aldosterone-producing adenoma (the most common cause) or, rarely, an adrenocortical carcinoma. In approximately 35% of cases, primary hyperaldosteronism is caused by a solitary aldosterone-secreting adenoma, a condition referred to as *Conn syndrome.*
- Rarely, familial hyperaldosteronism may result from a genetic defect that leads to overactivity of the *aldosterone synthase* gene, *CYP11B2.*

MORPHOLOGY

Aldosterone-producing adenomas are almost always solitary, small (less than 2 cm in diameter), well-circumscribed lesions. They are bright yellow on cut section and, surprisingly, are composed of lipid-laden cortical cells more closely resembling fasciculata cells than glomerulosa cells (the normal source of aldosterone). In general, the cells tend to be uniform in size and shape; occasionally there is some nuclear and cellular pleomorphism. A characteristic feature of aldosterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions, known as **spironolactone bodies.** These typically are found after treatment with the antihypertensive agent spironolactone, which is the

drug of choice in primary hyperaldosteronism. In contrast with cortical adenomas associated with Cushing syndrome, those associated with hyperaldosteronism do not usually suppress ACTH secretion. Therefore, the adjacent adrenal cortex and that of the contralateral gland are not atrophic. **Bilateral idiopathic hyperplasia** is marked by diffuse or focal hyperplasia of cells resembling those of the normal zona glomerulosa.

Clinical Features

The clinical hallmark of hyperaldosteronism is hypertension. With an estimated prevalence rate of 5% to 10% among unselected hypertensive patients, primary hyperaldosteronism may be the most common cause of secondary hypertension (i.e., hypertension secondary to an identifiable cause). The long-term effects of hyperaldosteronism-induced hypertension are cardiovascular compromise (e.g., left ventricular hypertrophy and reduced diastolic volumes) and an increase in the prevalence of adverse events such as stroke and myocardial infarction. *Hypokalemia* results from renal potassium wasting and, when present, can cause a variety of neuromuscular manifestations, including weakness, paresthesias, visual disturbances, and occasionally frank tetany. In primary hyperaldosteronism, the therapy varies according to cause. Adenomas are amenable to surgical excision. By contrast, surgical intervention is not very beneficial in patients with primary hyperaldosteronism due to bilateral hyperplasia, which often occurs in children and young adults. These patients are best managed medically with an *aldosterone antagonist* such as spironolactone. The treatment of secondary hyperaldosteronism rests on correcting the underlying cause of the renin-angiotensin system hyperstimulation.

Adrenogenital Syndromes

Excess of androgens may be caused by a number of diseases, including primary gonadal disorders and several primary adrenal disorders. The adrenal cortex secretes two compounds—dehydroepiandrosterone and androstenedione—which require conversion to testosterone in peripheral tissues for their androgenic effects. Unlike gonadal androgens, adrenal androgen formation is regulated by ACTH; thus, excessive secretion can present as an isolated syndrome or in combination with features of Cushing disease. The adrenal causes of androgen excess include *adrenocortical neoplasms* and an uncommon group of disorders collectively designated *congenital adrenal hyperplasia* (CAH). Adrenocortical neoplasms associated with symptoms of androgen excess (*virilization*) are more likely to be carcinomas than adenomas. They are morphologically identical to other functional or nonfunctional cortical neoplasms.

CAH represents a group of autosomal recessive disorders, each characterized by a hereditary defect in an enzyme involved in adrenal steroid biosynthesis, particularly cortisol. In these conditions, decreased cortisol production results in a compensatory increase in ACTH secretion due to absence of feedback inhibition. The resultant adrenal hyperplasia causes increased production of cortisol precursor steroids, which are then channeled into synthesis of androgens with virilizing activity. Certain enzyme defects also may impair aldosterone secretion, adding salt loss to the virilizing syndrome. *The most common enzymatic defect in CAH is 21-hydroxylase deficiency,* which accounts for more than 90% of cases. 21-Hydroxylase deficiency may range in degree from a total lack to a mild loss, depending on the nature of the underlying mutation involving the *CYP21A2* gene, which encodes this enzyme.

MORPHOLOGY

In all cases of CAH, the adrenals are **hyperplastic bilaterally,** sometimes expanding to 10 to 15 times their normal weights. The adrenal cortex is thickened and nodular, and on cut section, the widened cortex appears brown as a result of depletion of all lipid. The proliferating cells mostly are compact, eosinophilic, lipid-depleted cells, intermixed with lipid-laden clear cells. In addition to cortical abnormalities, **adrenomedullary dysplasia** also has recently been reported in patients with the salt-losing 21-hydroxylase deficiency. This is characterized by incomplete migration of the chromaffin cells to the center of the gland, with pronounced intermingling of nests of chromaffin and cortical cells in the periphery. Hyperplasia of corticotroph (ACTH-producing) cells is present in the anterior pituitary in most patients.

Clinical Features

The clinical manifestations of CAH are determined by the specific enzyme deficiency and include abnormalities related to androgen metabolism, sodium homeostasis, and (in severe cases) glucocorticoid deficiency. Depending on the nature and severity of the enzymatic defect, the onset of clinical symptoms may occur in the perinatal period, later childhood, or (less commonly) adulthood.

In 21-hydroxylase deficiency, *excessive androgenic activity* causes signs of masculinization in females, ranging from clitoral hypertrophy and pseudohermaphroditism in infants to oligomenorrhea, hirsutism, and acne in postpubertal girls. In males, androgen excess is associated with enlargement of the external genitalia and other evidence of precocious puberty in prepubertal patients and with oligospermia in older patients. In some forms of CAH (e.g., 11β-hydroxylase deficiency), the accumulated intermediary steroids have mineralocorticoid activity, with resultant *sodium retention* and *hypertension*. In other cases, however, including about one third of persons with 21-hydroxylase deficiency, the enzymatic defect is severe enough to produce mineralocorticoid deficiency, with resultant *salt (sodium) wasting*. Cortisol deficiency places persons with CAH at risk for *acute adrenal insufficiency* (discussed later).

CAH should be suspected in any neonate with ambiguous genitalia; severe enzyme deficiency in infancy can be a life-threatening condition, with vomiting, dehydration, and salt wasting. In the milder variants, women may present with delayed menarche, oligomenorrhea, or hirsutism. In all such cases, an androgen-producing ovarian neoplasm must be excluded. Treatment of CAH is with exogenous glucocorticoids, which, in addition to providing adequate levels of glucocorticoids, also suppress ACTH levels, thereby decreasing the excessive synthesis of the

steroid hormones responsible for many of the clinical abnormalities.

SUMMARY

Adrenogenital Syndromes

- The adrenal cortex can secrete excess androgens in either of two settings: adrenocortical neoplasms (usually *virilizing* carcinomas) or congenital adrenal hyperplasia (CAH).
- CAH consists of a group of autosomal recessive disorders characterized by defects in steroid biosynthesis, usually cortisol; the most common subtype is caused by deficiency of the enzyme 21-hydroxylase.
- Reduction in cortisol production causes a compensatory increase in ACTH secretion, which in turn stimulates androgen production. Androgens have virilizing effects, including masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism), precocious puberty in males, and in some instances, salt (sodium) wasting and hypotension.
- Bilateral hyperplasia of the adrenal cortex is characteristic.

ADRENAL INSUFFICIENCY

Adrenocortical insufficiency, or hypofunction, may be caused by either primary adrenal disease (primary hypoadrenalism) or decreased stimulation of the adrenals resulting from a deficiency of ACTH (secondary hypoadrenalism). The patterns of adrenocortical insufficiency can be divided into three general categories: (1) primary *acute* adrenocortical insufficiency (adrenal crisis); (2) primary *chronic* adrenocortical insufficiency (*Addison disease*); and (3) secondary adrenocortical insufficiency.

Acute Adrenocortical Insufficiency

Acute adrenocortical insufficiency occurs most commonly in the clinical settings listed in Table 19–7. Persons with chronic adrenocortical insufficiency may develop an acute crisis after any stress that taxes their limited physiologic reserves. In patients maintained on exogenous corticosteroids, rapid withdrawal of steroids or failure to increase steroid doses in response to an acute stress may precipitate a similar adrenal crisis, because of the inability of the atrophic adrenals to produce glucocorticoid hormones. *Massive adrenal hemorrhage* may destroy enough of the adrenal cortex to cause acute adrenocortical insufficiency. This condition may occur in patients maintained on anticoagulant therapy, in postoperative patients who develop disseminated intravascular coagulation, during pregnancy, and in patients suffering from overwhelming sepsis; in this last setting it is known as the Waterhouse-Friderichsen syndrome (Fig. 19–39). This catastrophic syndrome is classically associated with *Neisseria meningitidis* septicemia but can also be caused by other organisms, including *Pseudomonas* spp., pneumococci, and *Haemophilus influenzae*. The pathogenesis of the Waterhouse-Friderichsen syndrome remains unclear but probably involves endotoxin-induced vascular injury with associated disseminated intravascular coagulation (Chapter 3).

Table 19–7 Causes of Adrenal Insufficiency

Acute
Waterhouse-Friderichsen syndrome
Sudden withdrawal of long-term corticosteroid therapy
Stress in patients with underlying chronic adrenal insufficiency
Chronic
Autoimmune adrenalitis (60–70% of cases in developed countries)—includes APS1 and APS2
Tuberculosis
Acquired immunodeficiency syndrome
Metastatic disease
Systemic amyloidosis
Fungal infections
Hemochromatosis
Sarcoidosis

APS1, APS2, autoimmune polyendocrine syndrome types 1 and 2.

Chronic Adrenocortical Insufficiency: Addison Disease

Addison disease, or chronic adrenocortical insufficiency, is an uncommon disorder resulting from progressive destruction of the adrenal cortex. More than 90% of all cases are attributable to one of four disorders: *autoimmune adrenalitis, tuberculosis,* the *acquired immune deficiency syndrome* (AIDS), or *metastatic cancer* (Table 19–7).

- *Autoimmune adrenalitis* accounts for 60% to 70% of cases and is by far the most common cause of primary adrenal insufficiency in developed countries. As the name implies, there is autoimmune destruction of steroid-producing cells, and autoantibodies to several key

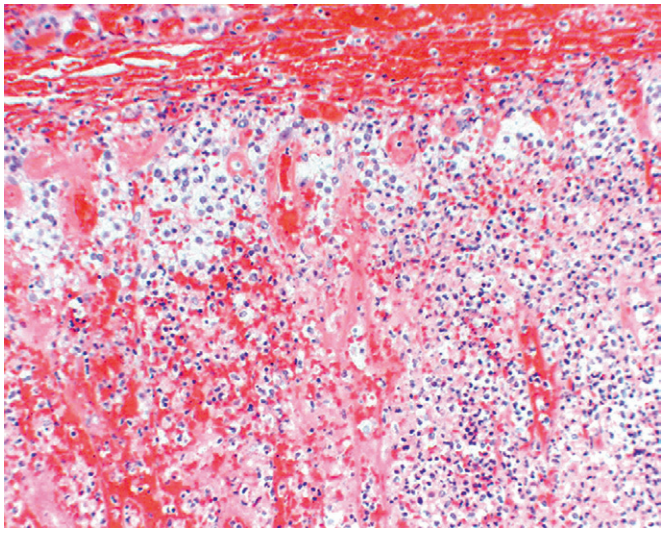


Figure 19–39 Waterhouse-Friderichsen syndrome. Bilateral adrenal hemorrhage in an infant with overwhelming sepsis, resulting in acute adrenal insufficiency. At autopsy, the adrenals were grossly hemorrhagic and shrunken; in this photomicrograph, little residual cortical architecture is discernible.

steroidogenic enzymes have been detected in affected patients. Autoimmune adrenalitis occurs in one of two *a*utoimmune *p*olyendocrine *s*yndromes: APS1, which is caused by mutations in the *autoimmune regulator (AIRE)* gene on chromosome 21 and is characterized by chronic mucocutaneous candidiasis and abnormalities of skin, dental enamel, and nails (ectodermal dystrophy) occurring in association with a combination of organ-specific autoimmune disorders (autoimmune adrenalitis, autoimmune hypoparathyroidism, idiopathic hypogonadism, pernicious anemia) that result in destruction of target organs. The AIRE protein is involved in the expression of tissue antigens in the thymus and the elimination of T cells specific for these antigens (Chapter 4). The second setting is that of APS2, which manifests in early adulthood and manifests as a combination of adrenal insufficiency and autoimmune thyroiditis or type 1 diabetes. Unlike in APS1, in APS2 mucocutaneous candidiasis, ectodermal dysplasia, and autoimmune hypoparathyroidism do not occur.

- *Infections,* particularly tuberculosis and those produced by fungi, also may cause primary chronic adrenocortical insufficiency. Tuberculous adrenalitis, which once accounted for as many as 90% of cases of Addison disease, has become less common with the advent of antituberculosis therapy. With the resurgence of tuberculosis in many urban centers, however, this cause of adrenal deficiency must be borne in mind. When present, tuberculous adrenalitis usually is associated with active infection in other sites, particularly the lungs and genitourinary tract. Among fungi, disseminated infections caused by *Histoplasma capsulatum* and *Coccidioides immitis* also may result in chronic adrenocortical insufficiency. Patients with AIDS are at risk for the development of adrenal insufficiency from several infectious (cytomegalovirus, *Mycobacterium avium-intracellulare*) and noninfectious (Kaposi sarcoma) complications of their disease.
- *Metastatic neoplasms* involving the adrenals are another potential cause of adrenal insufficiency. The adrenals are a fairly common site for metastases in patients with disseminated carcinomas. Although adrenal function is preserved in most such instances, the metastatic growths sometimes destroy sufficient adrenal cortex to produce a degree of adrenal insufficiency. Carcinomas of the lung and breast are the source of a majority of metastases in the adrenals, although many other neoplasms, including gastrointestinal carcinomas, malignant melanomas, and hematopoietic neoplasms, also may metastasize to the organ.

Secondary Adrenocortical Insufficiency

Any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or irradiation, that reduces the output of ACTH leads to a syndrome of hypoadrenalism having many similarities to Addison disease. *With secondary disease, the hyperpigmentation of primary Addison disease is lacking because melanotropic hormone levels are low* (discussed later). ACTH deficiency may occur alone, but in some instances, it is only one part of panhypopituitarism, associated with multiple tropic hormone deficiencies. In patients with primary disease, serum ACTH levels may be normal, but the destruction of the adrenal cortex does not permit a response to exogenously administered ACTH in the form of increased plasma levels of cortisol. By contrast, secondary adrenocortical insufficiency is characterized by low serum ACTH and a prompt rise in plasma cortisol levels in response to ACTH administration.

MORPHOLOGY

The appearance of the adrenal glands varies with the cause of the adrenocortical insufficiency. In **secondary hypoadrenalism** the adrenals are reduced to small, flattened structures that usually retain their yellow color because of a small amount of residual lipid. A uniform, thin rim of atrophic yellow cortex surrounds a central, intact medulla. Histologic evaluation reveals atrophy of cortical cells with loss of cytoplasmic lipid, particularly in the zona fasciculata and zona reticularis. **Primary autoimmune adrenalitis** is characterized by irregularly shrunken glands, which may be exceedingly difficult to identify within the suprarenal adipose tissue. On histologic examination, the cortex contains only scattered residual cortical cells in a collapsed network of connective tissue. A variable lymphoid infiltrate is present in the cortex and may extend into the subjacent medulla (Fig. 19–40). The medulla is otherwise preserved. In **tuberculosis or fungal diseases,** the adrenal architecture may be effaced by a granulomatous inflammatory reaction identical to that encountered in other sites of infection. When hypoadrenalism is caused by **metastatic carcinoma,** the adrenals are enlarged, and their normal architecture is obscured by the infiltrating neoplasm.

Clinical Features

In general, clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised. The initial manifestations often include progressive weakness and easy fatigability, which may be dismissed as nonspecific complaints. *Gastrointestinal disturbances* are common and include anorexia, nausea, vomiting, weight loss, and diarrhea. In patients with primary adrenal disease, increased levels of ACTH precursor hormone stimulate melanocytes, with resultant *hyperpigmentation* of the skin and mucosal surfaces. The

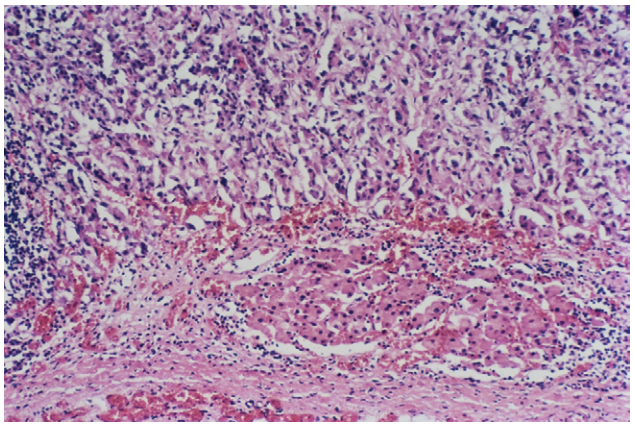


Figure 19–40 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.

face, axillae, nipples, areolae, and perineum are particularly common sites of hyperpigmentation. By contrast, hyperpigmentation is not seen in patients with secondary adrenocortical insufficiency. Decreased mineralocorticoid (aldosterone) activity in patients with primary adrenal insufficiency results in potassium retention and sodium loss, with consequent *hyperkalemia, hyponatremia, volume depletion,* and *hypotension*, whereas secondary hypoadrenalism is characterized by deficient cortisol and androgen output but normal or near-normal aldosterone synthesis. Hypoglycemia occasionally may occur as a result of glucocorticoid deficiency and impaired gluconeogenesis. Stresses such as infections, trauma, or surgical procedures in affected patients may precipitate an acute adrenal crisis, manifested by intractable vomiting, abdominal pain, hypotension, coma, and vascular collapse. Death follows rapidly unless corticosteroids are replaced immediately.

SUMMARY

Adrenocortical Insufficiency (Hypoadrenalism)

- Primary adrenocortical insufficiency can be acute (Waterhouse-Friderichsen syndrome) or chronic (Addison disease).
- Chronic adrenal insufficiency in the Western world most often is secondary to autoimmune adrenalitis, which occurs in the context of one of two autoimmune polyendocrine syndromes: APS1 (caused by mutations in the *AIRE* gene) or APS2.
- Tuberculosis and infections due to opportunistic pathogens associated with the human immunodeficiency virus and tumors metastatic to the adrenals are the other important causes of chronic hypoadrenalism.
- Patients typically present with fatigue, weakness, and gastrointestinal disturbances. Primary adrenocortical insufficiency also is characterized by high ACTH levels with associated skin pigmentation.

ADRENOCORTICAL NEOPLASMS

It should be evident from the discussion of adrenocortical hyperfunction that functional adrenal neoplasms may be responsible for any of the various forms of hyperadrenalism. While functional adenomas are most commonly associated with hyperaldosteronism and with Cushing syndrome, a virilizing neoplasm is more likely to be a carcinoma. Not all adrenocortical neoplasms, however, elaborate steroid hormones. Determination of whether a cortical neoplasm is functional or not is based on clinical evaluation and measurement of the hormone or its metabolites in the laboratory.

MORPHOLOGY

Adrenocortical adenomas were described earlier in the discussions of Cushing syndrome and hyperaldosteronism. Most cortical adenomas do not cause hyperfunction and usually are encountered as incidental findings at the time of autopsy or during abdominal imaging for an unrelated cause. In fact, the half-facetious appellation of **"adrenal incidentaloma"** has crept into the medical lexicon to describe these incidentally discovered tumors. On cut surface, adenomas usually are yellow to yellow-brown, owing to the presence of lipid within the neoplastic cells (Fig. 19–37). As a general rule they are small, averaging 1 to 2 cm in diameter. On microscopic examination, adenomas are composed of cells similar to those populating the normal adrenal cortex. The nuclei tend to be small, although some degree of pleomorphism may be encountered even in benign lesions **(endocrine atypia).** The cytoplasm of the neoplastic cells ranges from eosinophilic to vacuolated, depending on their lipid content; mitotic activity generally is inconspicuous.

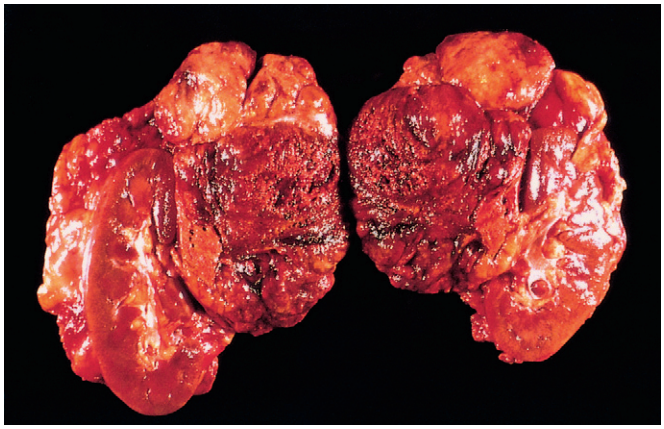


Figure 19–41 Adrenal carcinoma. The tumor dwarfs the kidney and compresses the upper pole. It is largely hemorrhagic and necrotic.

Adrenocortical carcinomas are rare neoplasms that may occur at any age, including in childhood. Two rare inherited causes of adrenal cortical carcinomas are Li-Fraumeni syndrome (Chapter 5) and Beckwith-Wiedemann syndrome (Chapter 6). In most cases, adrenocortical carcinomas are large, invasive lesions that efface the native adrenal gland. On cut surface, adrenocortical carcinomas typically are variegated, poorly demarcated lesions containing areas of necrosis, hemorrhage, and cystic change (Fig. 19–41). Microscopic examination typically shows these tumors to be composed of well-differentiated cells resembling those seen in cortical adenomas or bizarre, pleomorphic cells, which may be difficult to distinguish from those of an undifferentiated carcinoma metastatic to the adrenal (Fig. 19–42). Adrenal

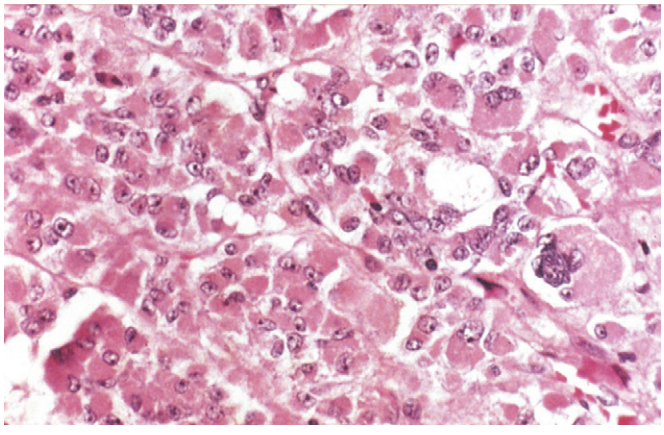


Figure 19–42 Adrenal carcinoma with marked anaplasia.

cancers have a strong tendency to invade the adrenal vein, vena cava, and lymphatics. Metastases to regional and periaortic nodes are common, as is distant hematogenous spread to the lungs and other viscera. Bone metastases are unusual. The median patient survival is about 2 years. Of note, carcinomas metastatic to the adrenal cortex are significantly more frequent than a primary adrenocortical carcinoma.

ADRENAL MEDULLA

The adrenal medulla is embryologically, functionally, and structurally distinct from the adrenal cortex. It is populated by cells derived from the neural crest (*chromaffin cells*) and their supporting (sustentacular) cells. The chromaffin cells, so named because of their brown-black color after exposure to potassium dichromate, synthesize and secrete catecholamines in response to signals from preganglionic nerve fibers in the sympathetic nervous system. Similar collections of cells are distributed throughout the body in the extraadrenal paraganglion system. The most important diseases of the adrenal medulla are neoplasms, which include both neuronal neoplasms (including neuroblastomas and more mature ganglion cell tumors) and neoplasms composed of chromaffin cells (pheochromocytomas).

TUMORS OF THE ADRENAL MEDULLA

Pheochromocytoma

Pheochromocytomas are neoplasms composed of chromaffin cells, which, like their non-neoplastic counterparts, synthesize and release catecholamines and, in some cases, other peptide hormones. These tumors are of special importance because although uncommon, they (like aldosterone-secreting adenomas) give rise to a surgically correctable form of hypertension.

Pheochromocytomas usually subscribe to a convenient "rule of 10s":

- *10% of pheochromocytomas are extraadrenal,* occurring in sites such as the organ of Zuckerkandl and the carotid body, where they usually are called *paragangliomas,* rather than pheochromocytomas.
- *10% of adrenal pheochromocytomas are bilateral*; this proportion may rise to 50% in cases that are associated with familial syndromes.
- *10% of adrenal pheochromocytomas are malignant,* although the associated hypertension represents a serious and potentially lethal complication of even *benign* tumors. Frank malignancy is somewhat more common in tumors arising in extraadrenal sites.
- One "traditional" 10% rule that has since been modified pertains to familial cases. It is now recognized that *as many as 25% of persons with pheochromocytomas and paragangliomas harbor a germ line mutation* in one of at least six known genes, including *RET*, which causes type 2 MEN syndromes (described later); *NF1*, which causes type 1 neurofibromatosis (Chapter 21); *VHL*, which causes von Hippel-Lindau disease (Chapters 13 and 22); and three genes encoding subunits within the succinate dehydrogenase complex (*SDHB, SDHC,* and *SDHD*), which is involved in mitochondrial oxidative phosphorylation.

MORPHOLOGY

Pheochromocytomas range in size from small, circumscribed lesions confined to the adrenal to large, hemorrhagic masses weighing several kilograms. On cut surface, smaller pheochromocytomas are yellow-tan, well-defined lesions that compress the adjacent adrenal (Fig. 19–43). Larger lesions tend to be hemorrhagic, necrotic, and cystic and typically efface the adrenal gland. Incubation of the fresh tissue with potassium dichromate solutions turns the tumor dark brown, as noted previously.

On microscopic examination, pheochromocytomas are composed of polygonal to spindle-shaped chromaffin cells and their supporting cells, compartmentalized into small nests, or **Zellballen,** by a rich vascular network (Fig. 19–44). The cytoplasm of the neoplastic cells often has a finely granular appearance, highlighted by a variety of silver stains, because of the presence of granules containing catecholamines. Electron microscopy reveals variable numbers of membrane-bound, electron-dense granules, representing catecholamines and sometimes other peptides. The nuclei of the neoplastic cells are often quite pleomorphic. Both

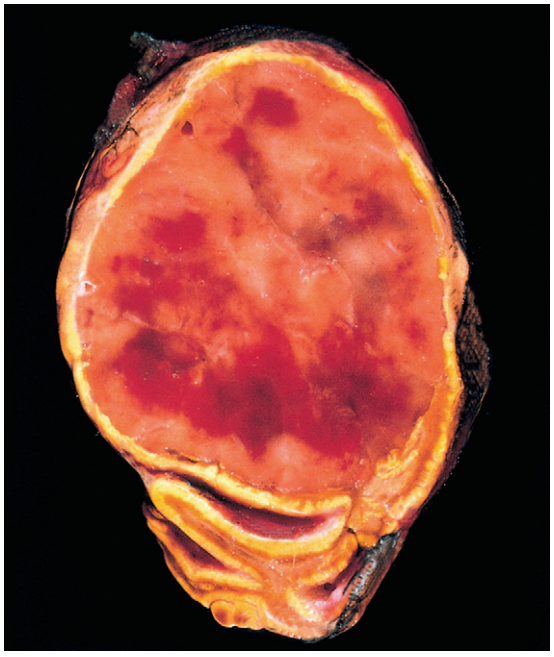


Figure 19–43 Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen *below*.

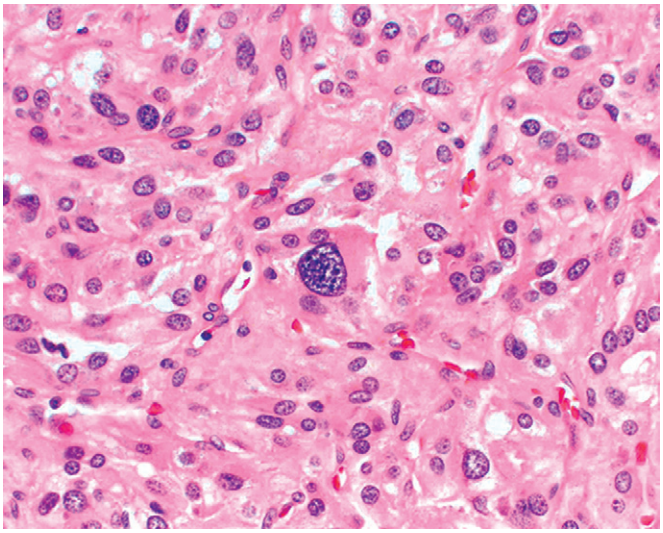


Figure 19–44 Photomicrograph of pheochromocytoma, demonstrating characteristic nests of cells (*Zellballen*) with abundant cytoplasm. Granules containing catecholamine are not visible in this preparation. It is not uncommon to find bizarre cells even in pheochromocytomas that are biologically benign, and this criterion by itself should not be used to diagnose malignancy.

capsular and vascular invasion may be encountered in benign lesions, and the mere presence of mitotic figures does not imply malignancy. **Therefore, the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases.** These may involve regional lymph nodes as well as more distant sites, including liver, lung, and bone.

Clinical Features

The predominant clinical manifestation of pheochromocytoma is *hypertension.* The characteristic presentation with a hypertensive episode is one of abrupt, precipitous elevation in blood pressure, associated with tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension. Such episodes also may be associated with pain in the abdomen or chest, nausea, and vomiting. In clinical practice, *isolated, paroxysmal episodes of hypertension occur in fewer than half of patients* with pheochromocytoma. In about two thirds of patients the hypertension occurs in the form of a chronic, sustained elevation in blood pressure, although an element of labile hypertension often is present as well. Whether sustained or episodic, the hypertension is associated with an increased risk of myocardial ischemia, heart failure, renal injury, and stroke (cerebrovascular accident). Sudden cardiac death may occur, probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias. In some cases, pheochromocytomas secrete other hormones such as ACTH and somatostatin and may therefore be associated with clinical features related to the effects of these and other peptide hormones. The laboratory diagnosis of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines and their metabolites, such as vanillylmandelic acid and metanephrines. Isolated benign pheochromocytomas are treated with surgical excision. With multifocal lesions, long-term medical treatment for hypertension may be required.

Neuroblastoma and Other Neuronal Neoplasms

Neuroblastoma is the most common extracranial solid tumor of childhood. These neoplasms occur most commonly during the first 5 years of life and may arise during infancy. Neuroblastomas may occur anywhere in the sympathetic nervous system and occasionally within the brain, but they are most common in the abdomen; a majority of these tumors arise in either the adrenal medulla or the retroperitoneal sympathetic ganglia. Most neuroblastomas are sporadic, although familial cases also have been described. These tumors are discussed in Chapter 6, along with other pediatric neoplasms.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

The MEN syndromes are a group of inherited diseases resulting in proliferative lesions (hyperplasias, adenomas, and carcinomas) of multiple endocrine organs. Like other inherited cancer disorders (Chapter 5), endocrine tumors arising in the context of MEN syndromes have certain distinctive features that are not shared with their sporadic counterparts:

- These tumors occur at a *younger age* than that typical for sporadic cancers.
- They arise in *multiple endocrine organs,* either *synchronously* or *metachronously.*
- Even in one organ, the tumors often are *multifocal.*
- The tumors usually are preceded by an *asymptomatic stage of endocrine hyperplasia* involving the cell of origin of the tumor (for example, patients with MEN-2 almost universally demonstrate C cell hyperplasia in the thyroid parenchyma adjacent to medullary thyroid carcinomas).
- These tumors are usually *more aggressive* and *recur* in a higher proportion of cases than similar endocrine tumors that occur sporadically.

Unraveling the genetic basis of the MEN syndromes with clinical application of this knowledge in therapeutic decision making has been one of the success stories of translational research. The salient features of the MEN syndromes are discussed next.

Multiple Endocrine Neoplasia Type 1

MEN type 1 is inherited in an autosomal dominant pattern. The gene (*MEN1*) is located at 11q13 and is a tumor suppressor gene; thus, inactivation of both alleles of the gene is believed to be the basis for tumorigenesis. Organs most commonly involved are the parathyroid, the pancreas, and the pituitary—the "3 Ps."

- *Parathyroid*: *Primary hyperparathyroidism* is the most common manifestation of MEN-1 (80% to 95% of patients) and is the initial manifestation of the disorder in most patients, appearing in almost all patients by age 40 to 50. Parathyroid abnormalities include both hyperplasia and adenomas.
- *Pancreas*: Endocrine tumors of the pancreas are the leading cause of death in MEN-1. These tumors usually are aggressive and manifest with metastatic disease. It is not uncommon to find multiple "microadenomas" scattered throughout the pancreas in conjunction with one or two dominant lesions. Pancreatic endocrine tumors often are functional (i.e., secrete hormones). Zollinger-Ellison syndrome, associated with gastrinomas, and hypoglycemia, related to insulinomas, are common endocrine manifestations. Of note, the gastrinomas arising in MEN-1 syndrome are far more likely to be located within the duodenum than in the pancreas.
- *Pituitary*: The most frequent pituitary tumor in patients with MEN-1 is a prolactin-secreting macroadenoma. In some cases, acromegaly develops in association with somatotropin-secreting tumors.

Multiple Endocrine Neoplasia Type 2

MEN type 2 actually comprises two distinct groups of disorders that are unified by the occurrence of activating (i.e., gain-of-function) mutations of the *RET* proto-oncogene at chromosomal locus 10q11.2. A strong *genotype-phenotype correlation* has been recognized for the MEN-2 syndromes, and differences in mutation patterns account for the variable features in the two subtypes. MEN-2 is inherited in an autosomal dominant pattern.

Multiple Endocrine Neoplasia Type 2A

Organs commonly involved in MEN type 2A include

- *Thyroid*: Medullary carcinoma of the thyroid develops in virtually all untreated cases, and the tumors usually occur in the first 2 decades of life. The tumors commonly are multifocal, and foci of C cell hyperplasia can be found in the adjacent thyroid. *Familial medullary thyroid cancer* is a variant of MEN-2A characterized by medullary thyroid cancers, but not the other characteristic manifestations listed here. In comparison with MEN-2, familial medullary carcinoma typically occurs at an older age and follows a more indolent course.
- *Adrenal medulla*: Adrenal pheochromocytomas develop in 50% of the patients; fortunately, no more than 10% of these tumors are malignant.
- *Parathyroid*: Approximately 10% to 20% of patients develop parathyroid gland hyperplasia with manifestations of primary hyperparathyroidism.

Multiple Endocrine Neoplasia Type 2B

Patients with MEN-2B harbor a distinct germline *RET* mutation involving a single–amino acid change. Organs commonly involved include the thyroid and the adrenal medulla. The spectrum of thyroid and adrenal medullary disease is similar to that in MEN-2A, with the following differences:

- *Primary hyperparathyroidism does not develop* in patients with MEN-2B.
- *Extraendocrine manifestations* are characteristic in patients with MEN-2B. These include ganglioneuromas of mucosal sites (gastrointestinal tract, lips, tongue) and a *marfanoid habitus,* in which overly long bones of the axial skeleton give an appearance resembling that in Marfan syndrome (Chapter 6).

Before the advent of genetic testing, relatives of patients with the MEN-2 syndrome were screened with annual biochemical tests, which often lacked sensitivity. Now, routine genetic testing identifies *RET* mutation carriers earlier and more reliably in MEN-2 kindreds; *all persons carrying germline RET mutations are advised to have prophylactic thyroidectomy to prevent the inevitable development of medullary carcinomas.*

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