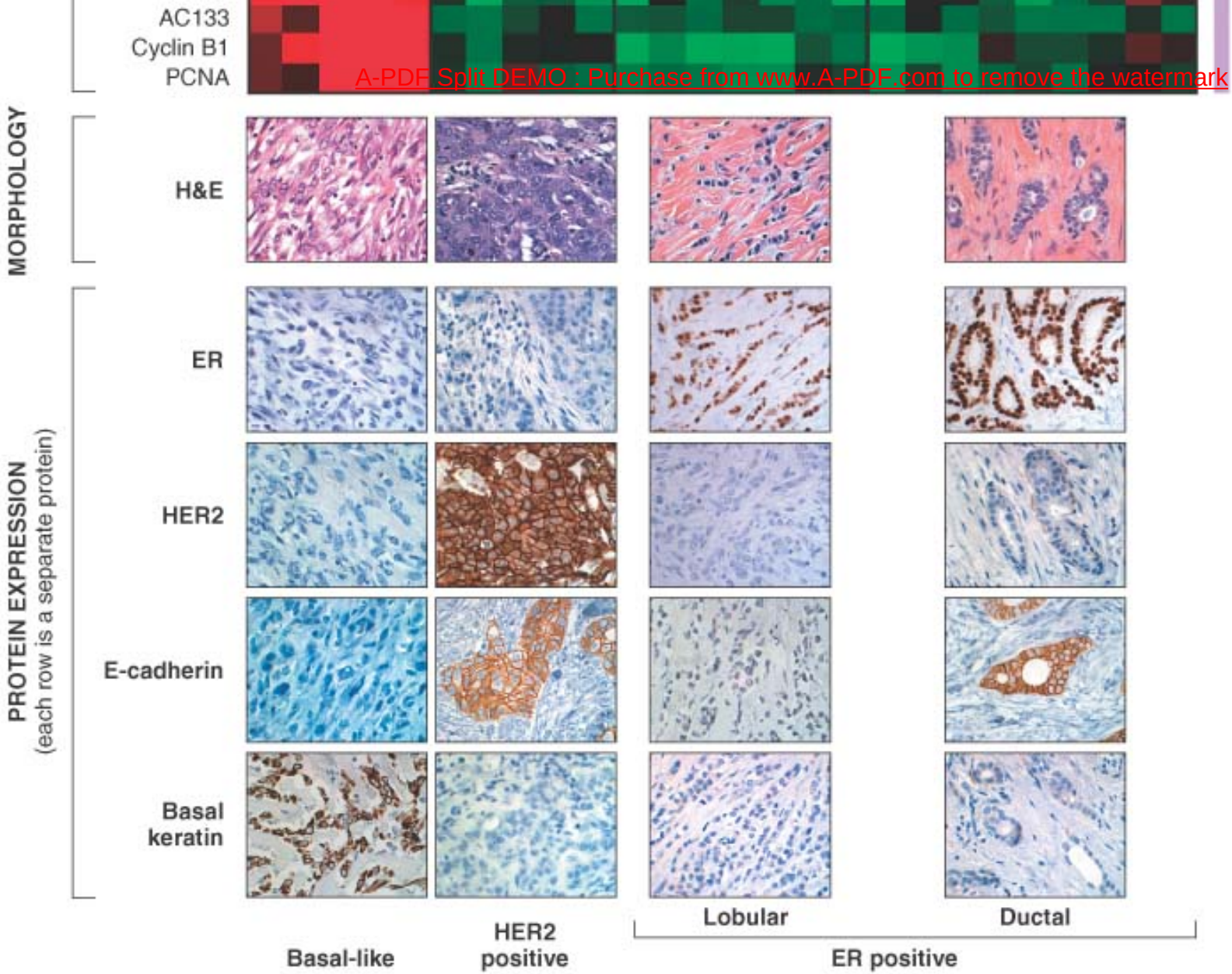


Figure 23-15 The normal breast is maintained by a complex set of interactions among luminal cells, myoepithelial cells, the basement membrane, and stromal cells (illustrated to the left of the figure). Morphologic changes are displayed according to the risk for subsequent invasive carcinoma (top row of pictures). The seven categories of changes in biologic functions

that must occur in successful malignant cells are shown in colored boxes. The changes need not occur in a specific order but accumulate until cells acquire malignant potential. The association of these changes with premalignant breast lesions suggests that the earliest events are related to evasion of growth-inhibiting signals, evasion of apoptosis, and self-sufficiency in growth signals. Hereditary carcinomas arise from cells that have germ line mutations that alter DNA repair and/or normal signals for apoptosis and therefore require fewer acquired changes. Luminal cells likely give rise to the majority of cancers, but myoepithelial cells can also undergo malignant transformation. Changes in the malignant cells are accompanied by alterations in the supporting myoepithelial and stromal cells due to a combination of genetic and epigenetic events and disruption of the normal intercellular signaling pathways. The final alteration, invasion of stroma, is the least well understood. It has been difficult to identify biologic changes that are specific to invasive carcinomas. It is possible that invasion is a result of the loss of the ability of myoepithelial and stromal cells to maintain the basement membrane rather than a gain of function by the malignant cells.

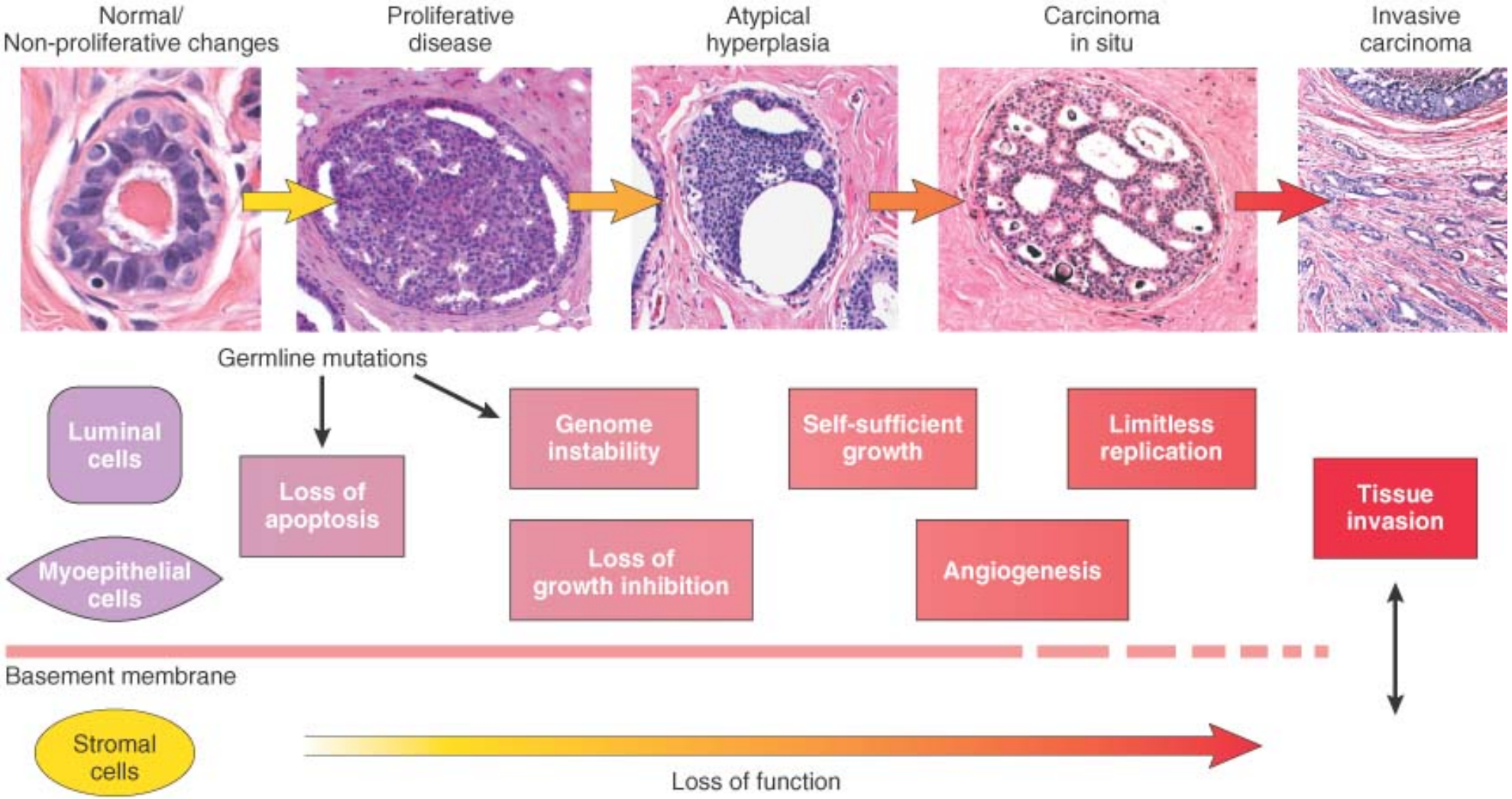


Figure 23-16 *A*, This mammogram reveals multiple clusters of small, irregular calcifications in a segmental distribution. Suspicious calcifications must be biopsied, as 20% to 30% will prove to be due to DCIS. *B*, Comedo DCIS fills several adjacent ducts (or completely replaced lobules) and is characterized by large central zones of necrosis with calcified debris. This type of DCIS is most frequently detected as radiologic calcifications. Less commonly, the surrounding desmoplastic response results in an ill-defined palpable mass or a mammographic density.

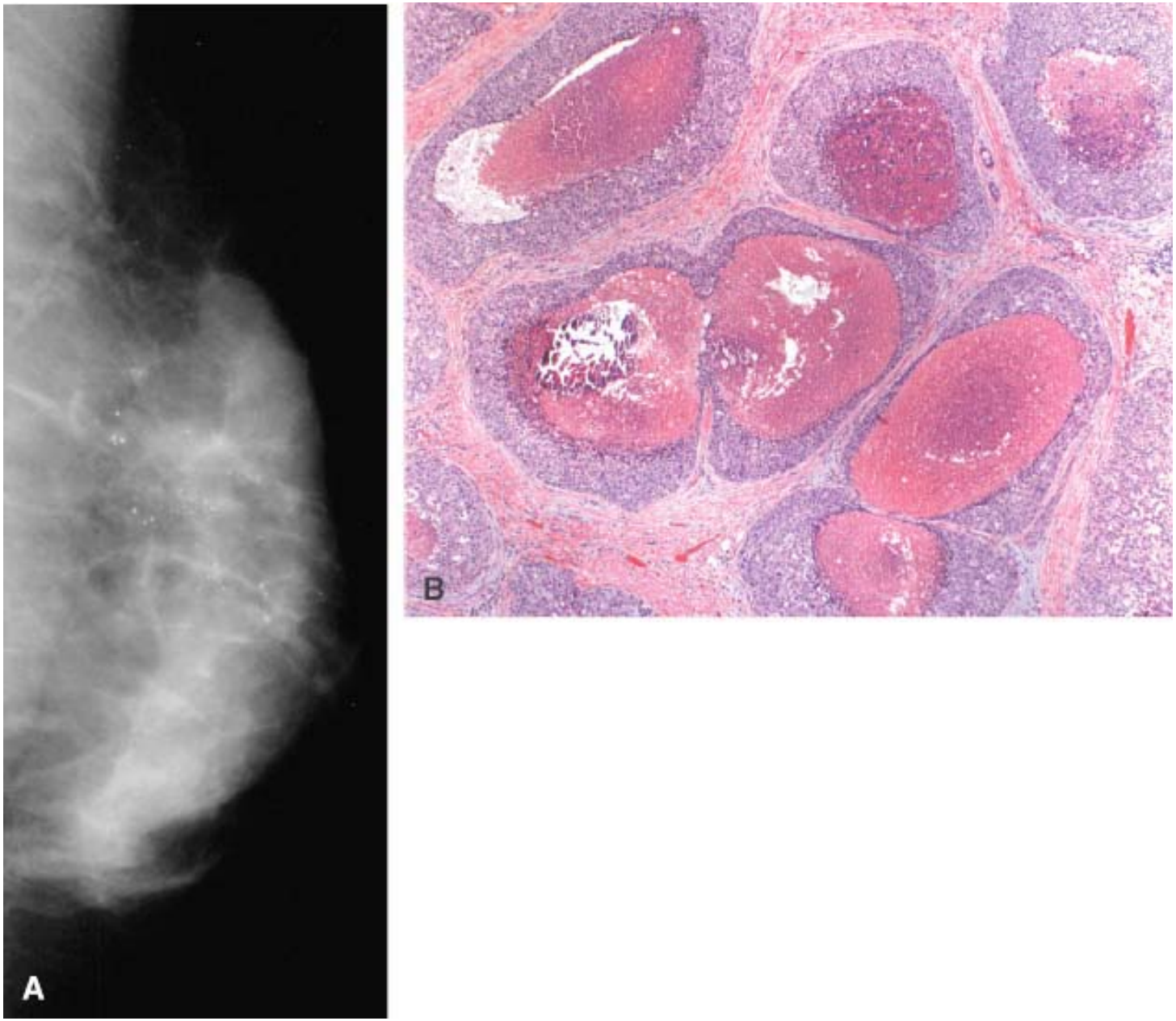


Figure 23-17 Noncomedo DCIS. *A*, Cribriform DCIS comprises cells forming round, regular ("cookie cutter") spaces. The lumens are often filled with calcifying secretory material. *B*, This solid DCIS has almost completely filled and distorted this lobule with only a few remaining luminal cells visible. This type of DCIS is not usually associated with calcifications and may be clinically occult.

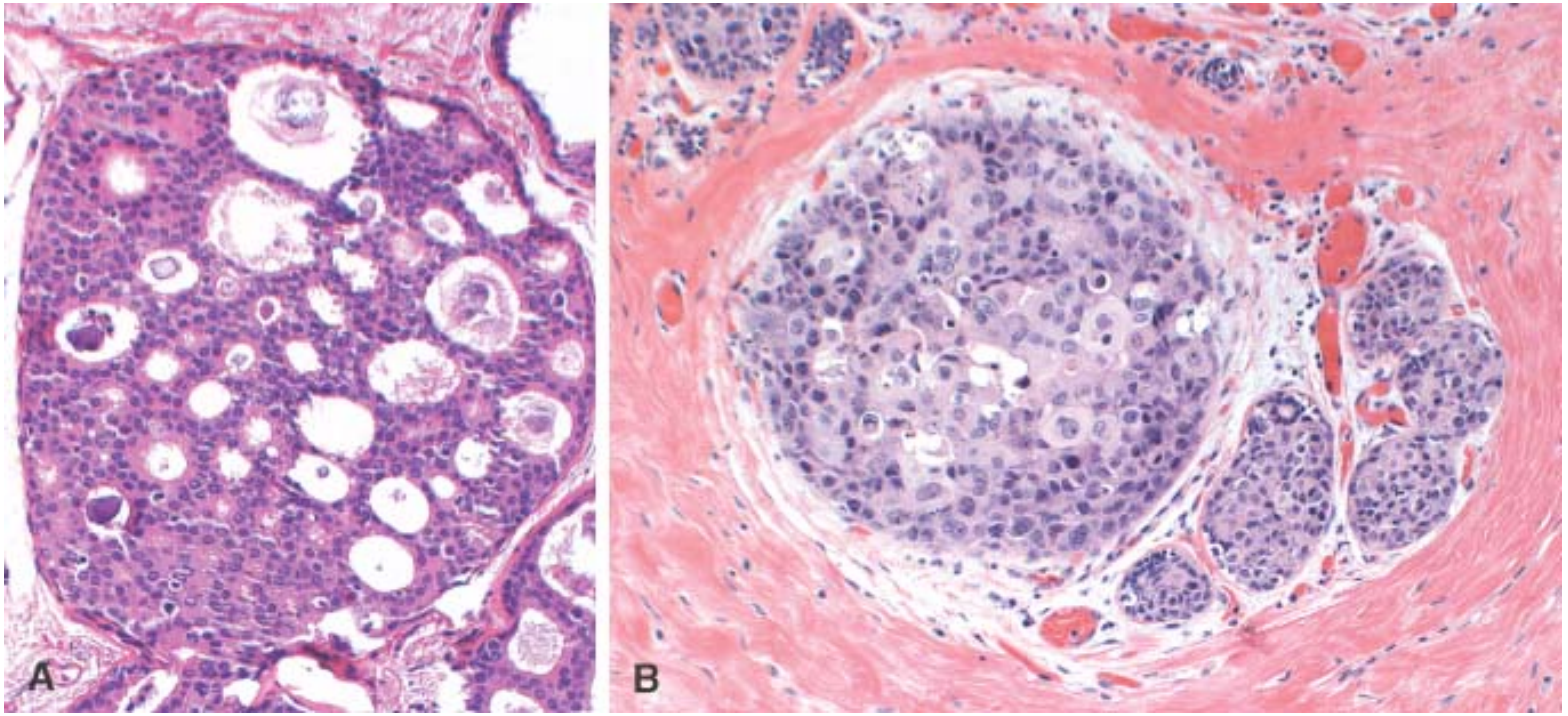


Figure 23-18 Noncomedo DCIS. *A*, Papillary DCIS. Delicate fibrovascular cores extend into a duct and are lined by a monomorphic population of tall columnar cells. Myoepithelial cells are absent. *B*, Micropapillary DCIS. The papillae are connected to the duct wall by a narrow base and often have bulbous or complex outgrowths. The papillae are solid and do not have fibrovascular cores.

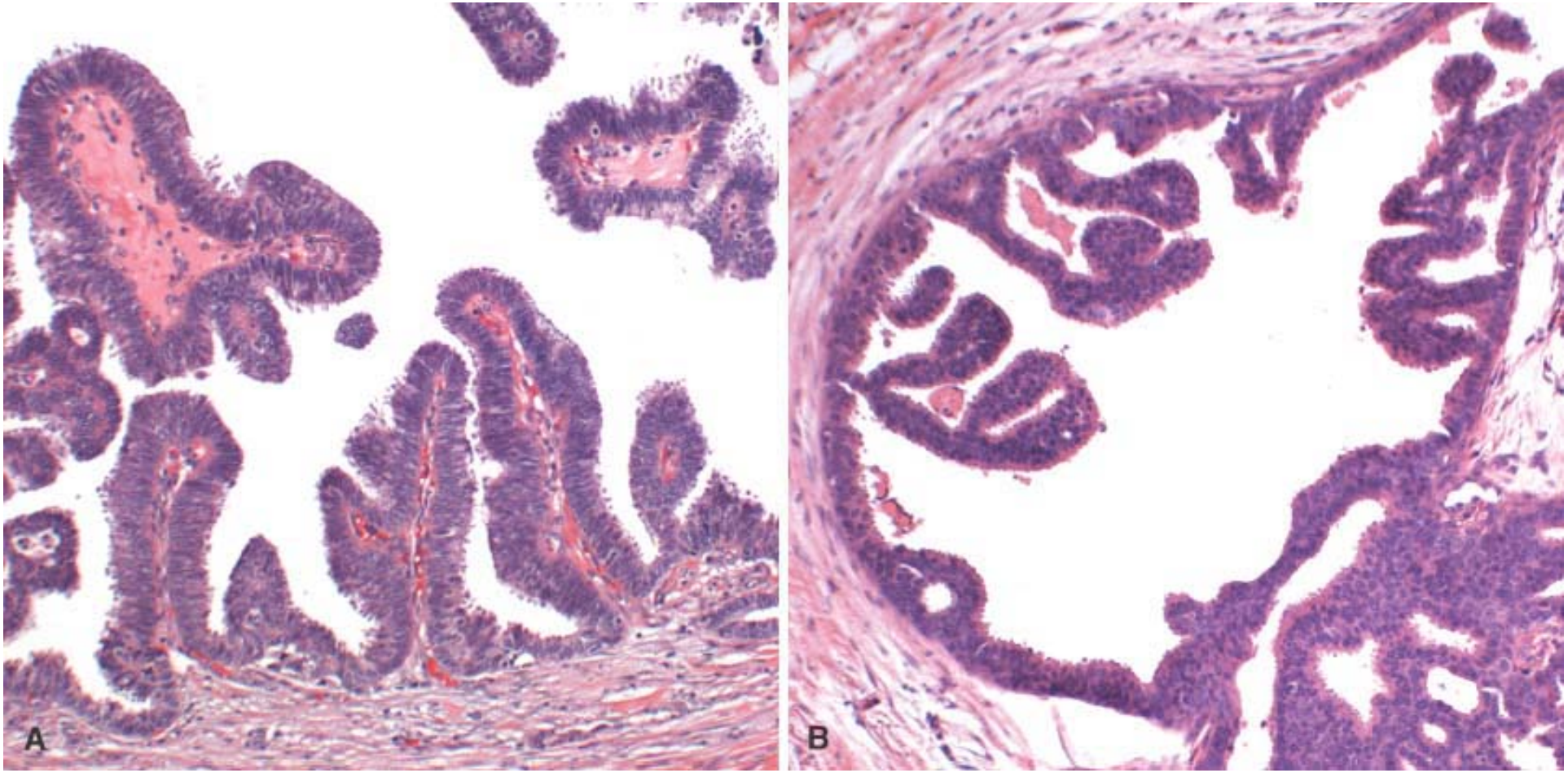


Figure 23-19 Paget disease of the nipple. DCIS arising within the ductal system of the breast can extend up the lactiferous ducts into nipple skin without crossing the basement membrane. The malignant cells disrupt the normally tight squamous epithelial cell barrier, allowing extracellular fluid to seep out and form an oozing scaly crust over the nipple skin.

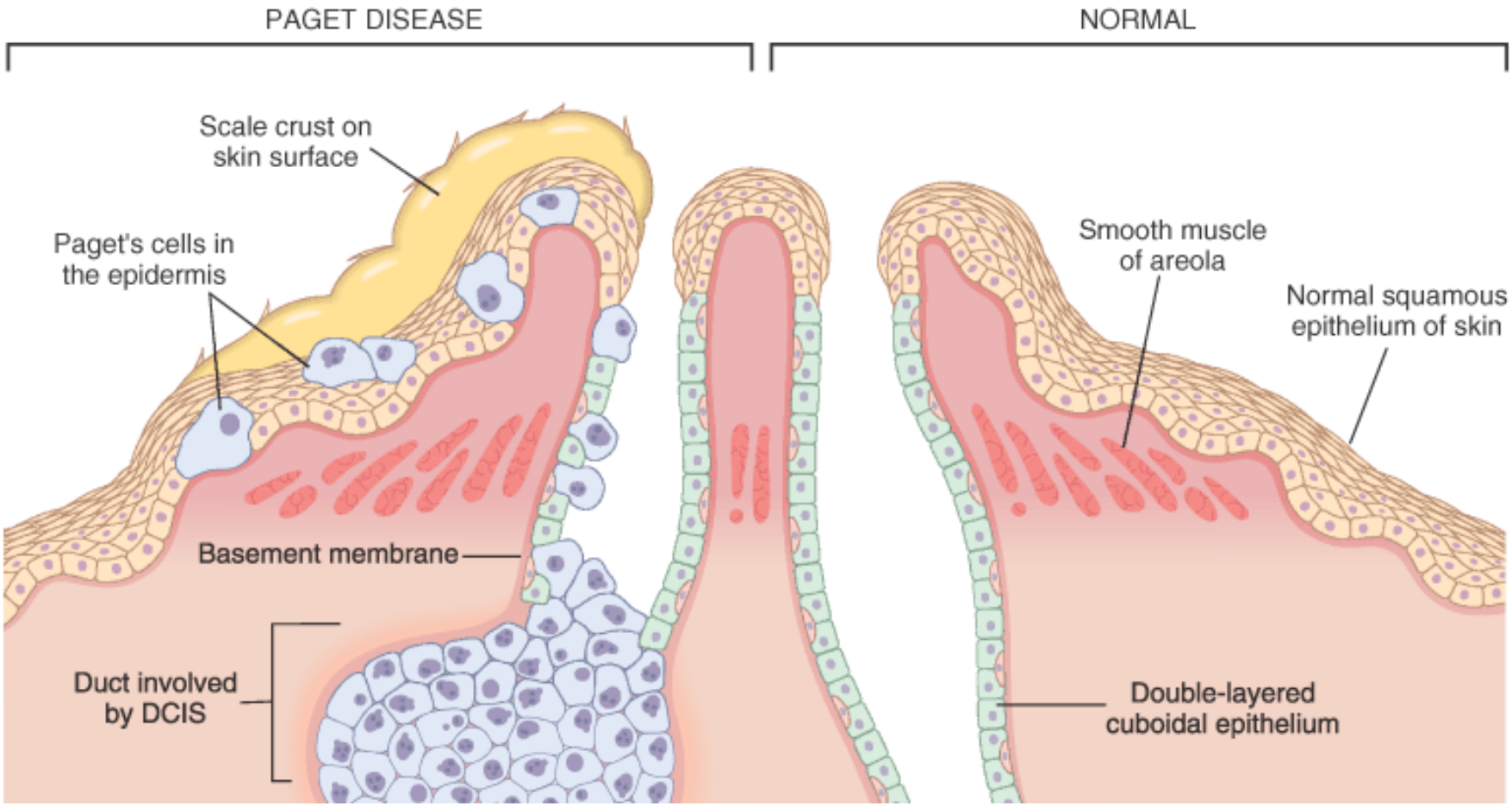


Figure 23-20 Lobular carcinoma in situ. A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture can still be recognized.

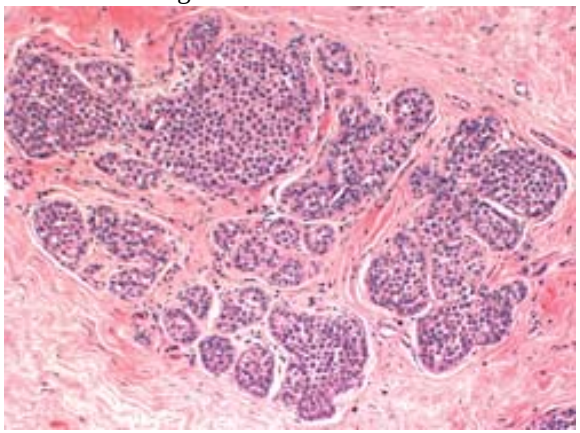
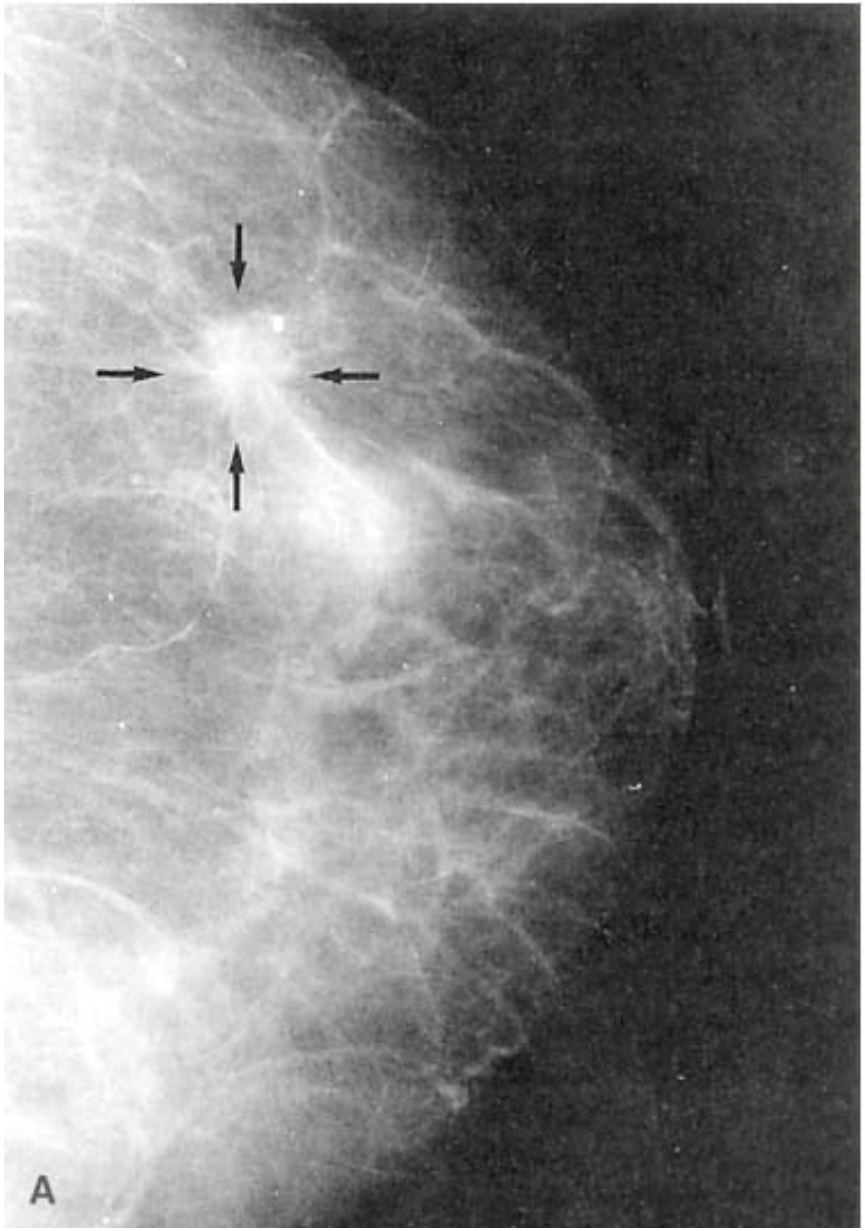


Figure 23-21 Invasive ductal carcinoma. *A*, This mammogram shows a density with an irregular border. There is a small, superimposed, incidental calcification. *(Courtesy of Dr. Jack Meyer, Brigham and Women's Hospital, Boston, MA.)* Over 90% of such masses will prove to be invasive carcinomas. Rarely, complex sclerosing lesions, prior surgical scars, and fibromatosis may present in this fashion. *B*, An irregular dense white mass is present within yellow adipose tissue. The pathologic gross differential diagnosis is the same as the radiologic differential diagnosis.



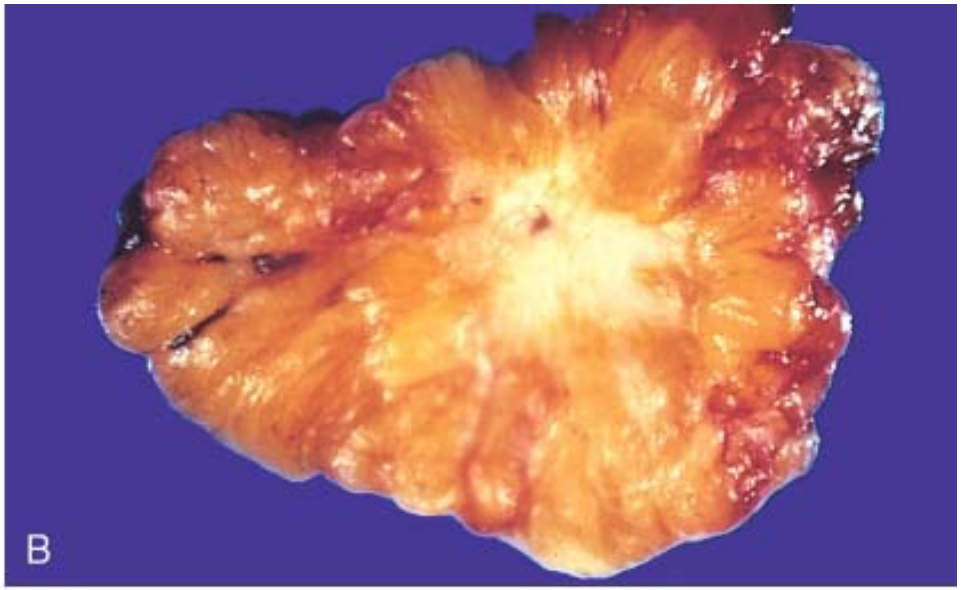


TABLE 23-4 -- Distribution of Histologic Types of Breast Cancer

Total Cancers	Per Cent

In Situ Carcinoma *	***15–30***
Ductal carcinoma in situ	80
Lobular carcinoma in situ	20
Invasive Carcinoma	***70–85***
No special type carcinoma ("ductal")	79
Lobular carcinoma	10
Tubular/cribriform carcinoma	6
Mucinous (colloid) carcinoma	2
Medullary carcinoma	2
Papillary carcinoma	1
Metaplastic carcinoma	<1
The data on invasive carcinomas are modified from Dixon JM, et al: Long-term survivors after breast cancer. Br J Surg 72:445, 1985.	

*The proportion of in situ carcinomas detected depends on the number of women undergoing mammographic screening and ranges from less than 5% in unscreened populations to almost 50% in patients with screen-detected cancers. Current observed numbers are between these two extremes.

typically express hormone receptors and do not overexpress *HER2/neu*. Others are composed of anastomosing sheets of pleomorphic cells (Fig. 23-22*B*) and are less likely to express hormone receptors and more likely to overexpress *HER2/neu*. The majority of invasive ductal carcinomas lie between these two extremes. Most carcinomas induce a marked increase in dense, fibrous desmoplastic stroma, giving the tumor a hard consistency on palpation and replace fat, resulting in a mammographic density (scirrhous carcinoma).

Carcinomas of NST are accompanied by varying amounts of DCIS. The grade of the DCIS usually correlates with the grade of the invasive carcinoma. For example, comedo DCIS is usually associated with poorly differentiated carcinomas, and low-grade DCIS is usually associated with well-differentiated carcinomas. Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences.

Morphologic analysis of this large group of carcinomas has not identified tumor types of significant clinical relevance beyond the specialized types to be described below. Recent studies using microarrays to analyze the transcriptional profile of these cancers have identified additional subgroups. (Box 23-1)[41] [56] [57] The challenge of future studies will be to show the clinical relevance of subtypes identified by gene expression profiling (e.g., with respect to etiology, presentation, prognosis, or response to treatment) and, if found, to determine whether these carcinomas can be recognized by more widely

Figure 23-22 *A*, Well-differentiated invasive carcinoma of no special type. Well-formed tubules and nests of cells with small monomorphic nuclei invade into the stroma with a surrounding desmoplastic response. *B*, Poorly differentiated invasive carcinoma of no special type. Ragged sheets of pleomorphic cells without tubule formation infiltrate into the

adjacent stroma.

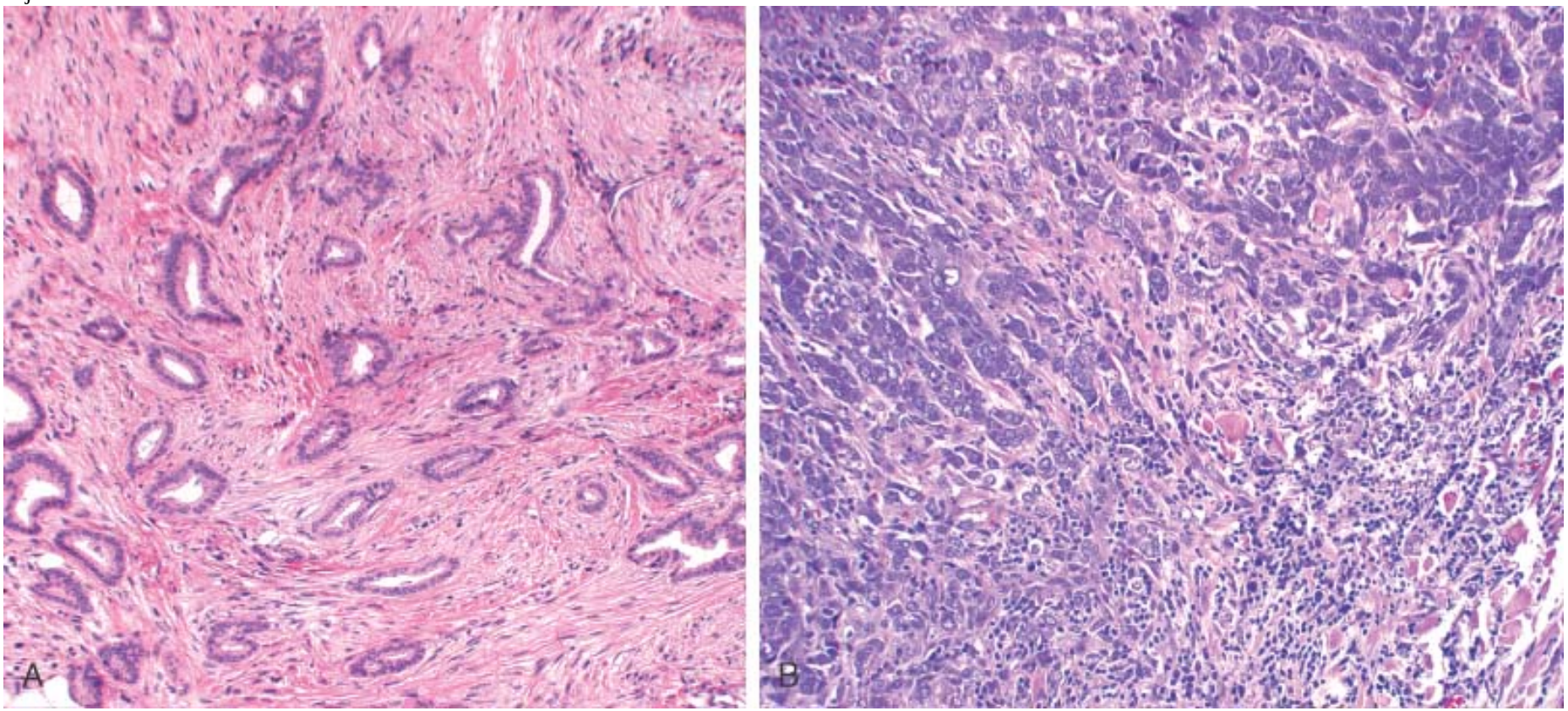


Figure 23-23 Invasive lobular carcinoma. Parallel arrays of small, regular cells with scant cytoplasm infiltrate singly in linear arrays or as small clusters of cells. There is often associated LCIS.

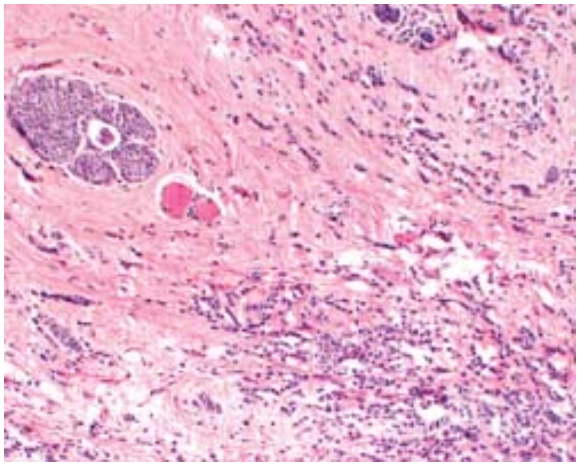


Figure 23-24 Medullary carcinoma. The cells are highly pleomorphic with frequent mitoses and grow as sheets of cohesive cells. A lymphoplasmacytic infiltrate is prominent.

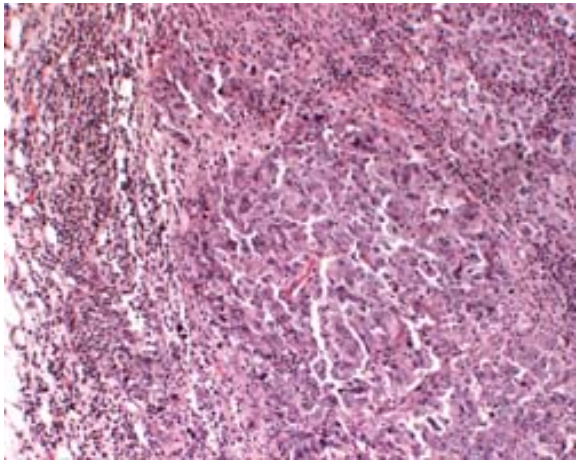


Figure 23-25 Mucinous (colloid) carcinoma. The tumor cells are present as small clusters within large pools of mucin. The borders are typically well circumscribed, and these cancers often mimic benign masses.

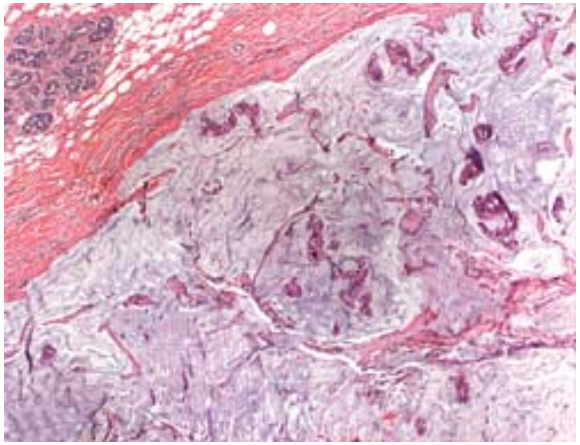
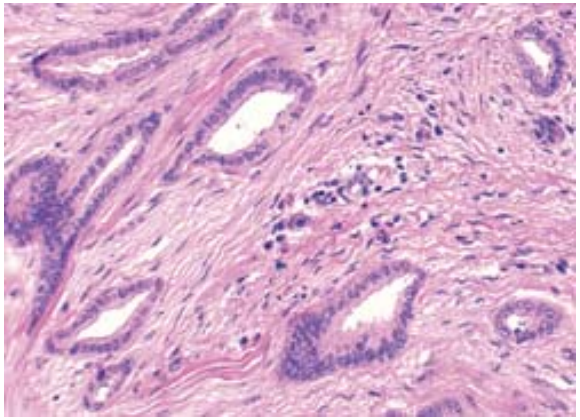


Figure 23-26 Tubular carcinoma. The carcinoma must be completely composed of well-formed tubules lined by a single layer of well-differentiated cells.



With no involvement, the 10-year disease-free survival rate is close to 70% to 80%; the rate falls to 35% to 40%

with one to three positive nodes and 10% to 15% in the presence of more than 10 positive nodes.
Most breast carcinomas drain to one or two *sentinel nodes* that can be identified by radiotracer, colored dye, or both. The sentinel node is highly predictive of the status of the remaining nodes. Sentinel node biopsy can spare women the increased morbidity of a complete axillary dissection. In some women, particularly those with medial tumors, the sentinel node may be an internal mammary node. These nodes are generally not biopsied owing to the morbidity associated with the procedure.
Macrometastases (>0.2 cm) are of proven prognostic importance. Because sentinel nodes often undergo more intense scrutiny with additional sections through the tissue, and immunohistochemistry or reverse transcriptase-polymerase chain reaction (RT-PCR) to detect rare tumor cells, increased numbers of women with minute metastatic deposits in lymph nodes are being identified. The clinical significance of small micrometastases is unclear and is being addressed by current clinical trials.

- **Tumor size.** The size of the carcinoma is the second most important prognostic factor and is independent from lymph node status. However, the risk of axillary lymph node metastases does increase with the size of the carcinoma. Women with node-negative carcinomas under 1 cm in diameter have a prognosis approaching that of women without breast cancer. The 10-year survival rate of such women without treatment is approximately 90%. On the other hand, over half of women with cancers over 2 cm in diameter present with lymph node metastases, and many of these women will eventually succumb to breast cancer.
- **Locally advanced disease.** Tumors invading into skin or skeletal muscle are frequently associated with concurrent or subsequent distant disease. With increased awareness of breast cancer detection, such cases have fortunately decreased in frequency and are now rare at initial presentation.
- **Inflammatory carcinoma.** Women presenting with the clinical appearance of breast swelling and skin thickening have a particularly poor prognosis with a 3-year survival rate of only 3% to 10%.

The major prognostic factors are used by the American Joint Committee on Cancer to divide breast carcinomas into clinical stages as follows:[70]

- Stage 0. DCIS or LCIS (5-year survival rate: 92%).
- Stage I. Invasive carcinoma 2 cm or less in diameter (including carcinoma in situ with microinvasion) without nodal involvement (or only metastases < 0.02 cm diameter) (5-year survival rate: 87%).
- Stage II. Invasive carcinoma 5 cm or less in diameter with up to three involved axillary nodes or invasive carcinoma greater than 5 cm without nodal involvement (5-year survival rate: 75%).
- Stage III. Invasive carcinoma 5 cm or less in diameter with four or more involved axillary nodes; invasive carcinoma greater than 5 cm in diameter with nodal involvement; invasive carcinoma with 10 or more involved axillary nodes; invasive carcinoma with involvement of the ipsilateral internal mammary lymph nodes; or invasive carcinoma with skin involvement (edema, ulceration, or satellite skin nodules), chest wall fixation, or clinical inflammatory carcinoma (5-year survival rate: 46%).
- Stage IV. Any breast cancer with distant metastases (5-year survival rate: 13%).

Minor Prognostic Factors.

Most women with nodal involvement and/or carcinomas over 1 cm in diameter will benefit from some form of systemic therapy. In this group, minor prognostic factors can be used to decide among chemotherapy regimens and/or hormonal therapies. For node-negative women with small carcinomas, minor prognostic factors are used to identify the women most likely to benefit from systemic therapy and those who might not need any additional treatment.[74] Three of these factors—estrogen receptor, progesterone receptor, and *HER2/neu*—are most useful as predictive factors for response to specific therapeutic agents.

1. **Histologic subtypes.** The 30-year survival rate of women with special types of invasive carcinomas (tubular, mucinous, medullary, lobular, and papillary) is greater than 60%, compared with less than 20% for women with cancers of no special type.[75]
2. **Tumor grade.** The most commonly used grading system to assess the degree of tumor differentiation (*Scarff Bloom Richardson*) combines nuclear grade, tubule formation, and mitotic rate. Eighty-five per cent of women with well-differentiated grade I tumors, 60% of women with moderately differentiated grade II tumors, and 15% of women with

poorly differentiated grade III tumors survive for 10 years.

3. **Estrogen and progesterone receptors.** Current assays use immunohistochemistry to detect the receptors in the nucleus (Fig. 23-27*A*). Fifty per cent to 85% of carcinomas express estrogen receptors, and such tumors are more common in postmenopausal women. Women with hormone receptor-positive cancers have a slightly better prognosis than do women with hormone receptor-negative carcinomas. The evaluation of hormone receptors is most valuable to predict response to therapy. Eighty per cent of tumors with estrogen receptors and progesterone receptors respond to hormonal manipulation, whereas only about 40% of those with only one type of receptor respond. Tumors with neither estrogen nor progesterone receptors have a less than 10% likelihood of responding.
4. *HER2/neu. HER2* (human epidermal growth factor receptor 2 or c-*erb B2* or *neu*) is a transmembrane glycoprotein involved in cell growth control.[76] [77] It does not appear to have a specific ligand but acts as a coreceptor for multiple growth factors. *HER2/neu* is overexpressed in 20% to 30% of breast carcinomas. In over 90% of cases, overexpression is associated with amplification of the gene on 17q21, and this can be determined either by evaluating protein content using immunohistochemistry or by determining gene copy number by using FISH (Figs. 23-27*B* and *C*). Although not all studies have come to the same conclusion, many have shown that overexpression of *HER2/neu* is associated with a poor prognosis. In addition, ongoing studies are addressing the possibility that *HER2/neu*-over-expressing tumors respond differently to hormonal or anthracycline chemotherapy regimens. However, evaluation of HER2/neu is most important to determine response to therapy targeted to this protein.

Trastuzumab (Herceptin) is a humanized monoclonal antibody to HER2/neu developed to specifically target tumor cells and, it is hoped, spare normal cells. In clinical trials, the combination of Trastuzumab with chemotherapy improved response in patients with carcinomas overexpressing *HER2/neu*. Unfortunately, cardiac toxicity, due to an unknown mechanism, could limit its usefulness. However, as the first gene-targeted therapeutic agent for a solid tumor, the results have been very promising.

5. **Lymphovascular invasion (LVI).** Tumor cells may be seen within vascular spaces (either lymphatics or small capillaries) surrounding tumors. This finding is strongly associated with the presence of lymph node metastases and is a poor prognostic factor in women without lymph node metastases. The presence of tumor cells in lymphatics of the dermis is strongly associated with the clinical appearance of inflammatory cancer and bodes a very poor prognosis. LVI must be strictly defined to have prognostic significance.
6. **Proliferative rate.** Proliferation can be measured by flow cytometry (as the S-phase fraction), by thymidine labeling index, by mitotic counts, or by immunohistochemical detection of cellular proteins (e.g., cyclins, Ki-67) produced during the cell cycle. Cyclin E content, when both full-length and low-molecular-weight isoforms are detected, is a very strong predictor of survival. [78] Tumors with high proliferation rates have a worse prognosis, but the most reliable method to assess proliferation has not yet been established. Mitotic counts are included as part of the standard grading system.
7. **DNA content.** The amount of DNA per tumor cell can be determined by flow cytometric analysis or by image analysis of tissue sections. Tumors with a DNA index of 1 have the same total amount of DNA as normal diploid cells, although marked karyotypic changes may be present. Aneuploid tumors are those with abnormal DNA indices and have a slightly worse prognosis.

Figure 23-27 Predictive markers. *A*, Estrogen receptor is detected in the nucleus by immunohistochemical studies. Progesterone receptor has the same appearance. *B, HER2/neu* overexpression is detected on the cell membrane by immunohistochemistry. *C,* Amplification of the *HER2/neu* gene can be detected by FISH analysis with a fluorescent probe for the gene. A normal cell has two copies of the gene. These tumor cells have over 25 signals, indicating amplification of the gene for *HER2/neu*. *(Courtesy of Dr. Jonathan Fletcher, Brigham and Women's Hospital, Boston, MA.)*

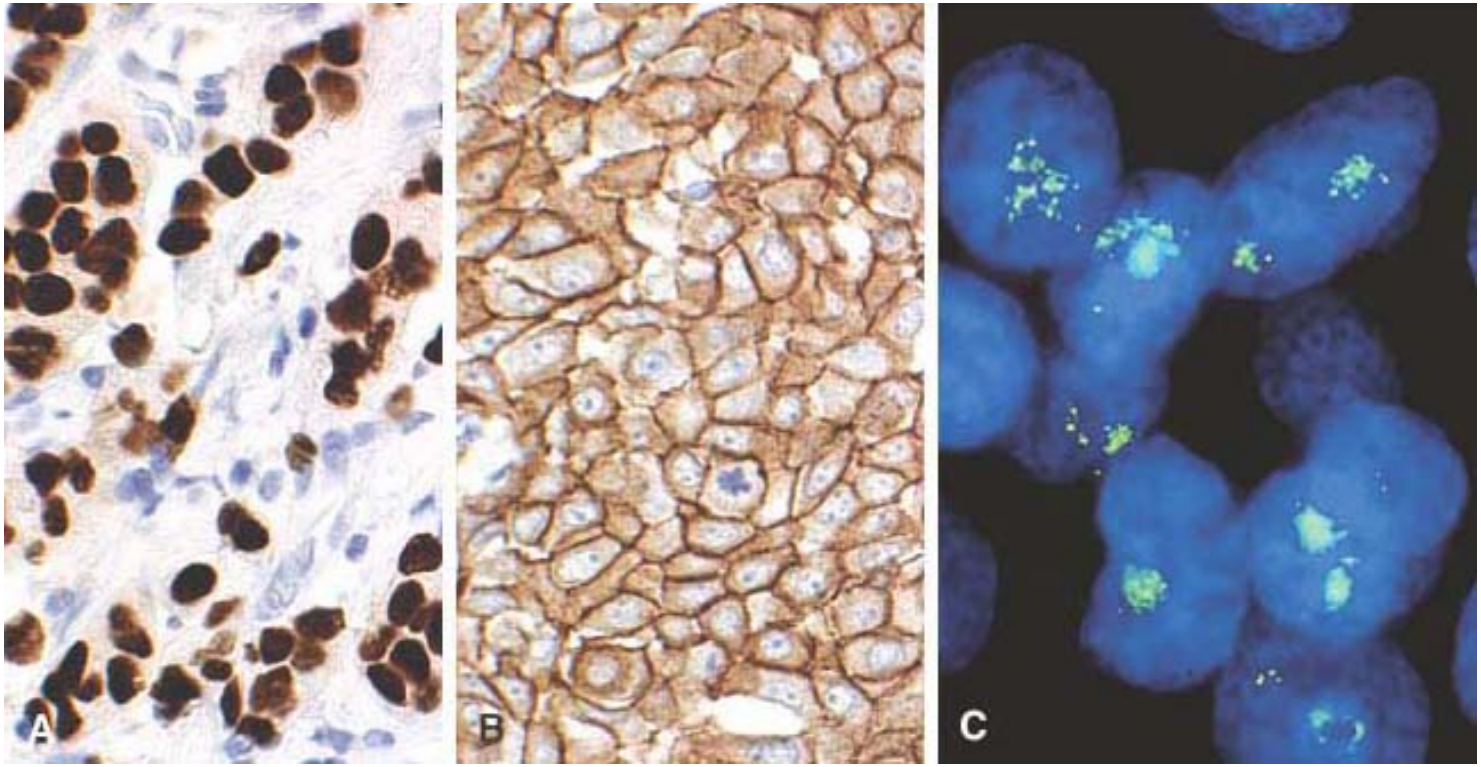


Figure 23-28 *A,* This mammogram shows a well-circumscribed mass. *(Courtesy of Dr. Jack Meyer, Brigham and Women's Hospital, Boston, MA.)* Although the most common lesion would be a fibroadenoma, other benign (e.g., fibrous lesions or PASH) and malignant (e.g., medullary or mucinous carcinomas) lesions can also have this appearance. *B,* Fibroadenoma. A rubbery, white, well-circumscribed mass is clearly demarcated from the surrounding yellow adipose tissue. The fibroadenoma does not contain adipose tissue and therefore appears denser than the surrounding normal tissue on mammogram.

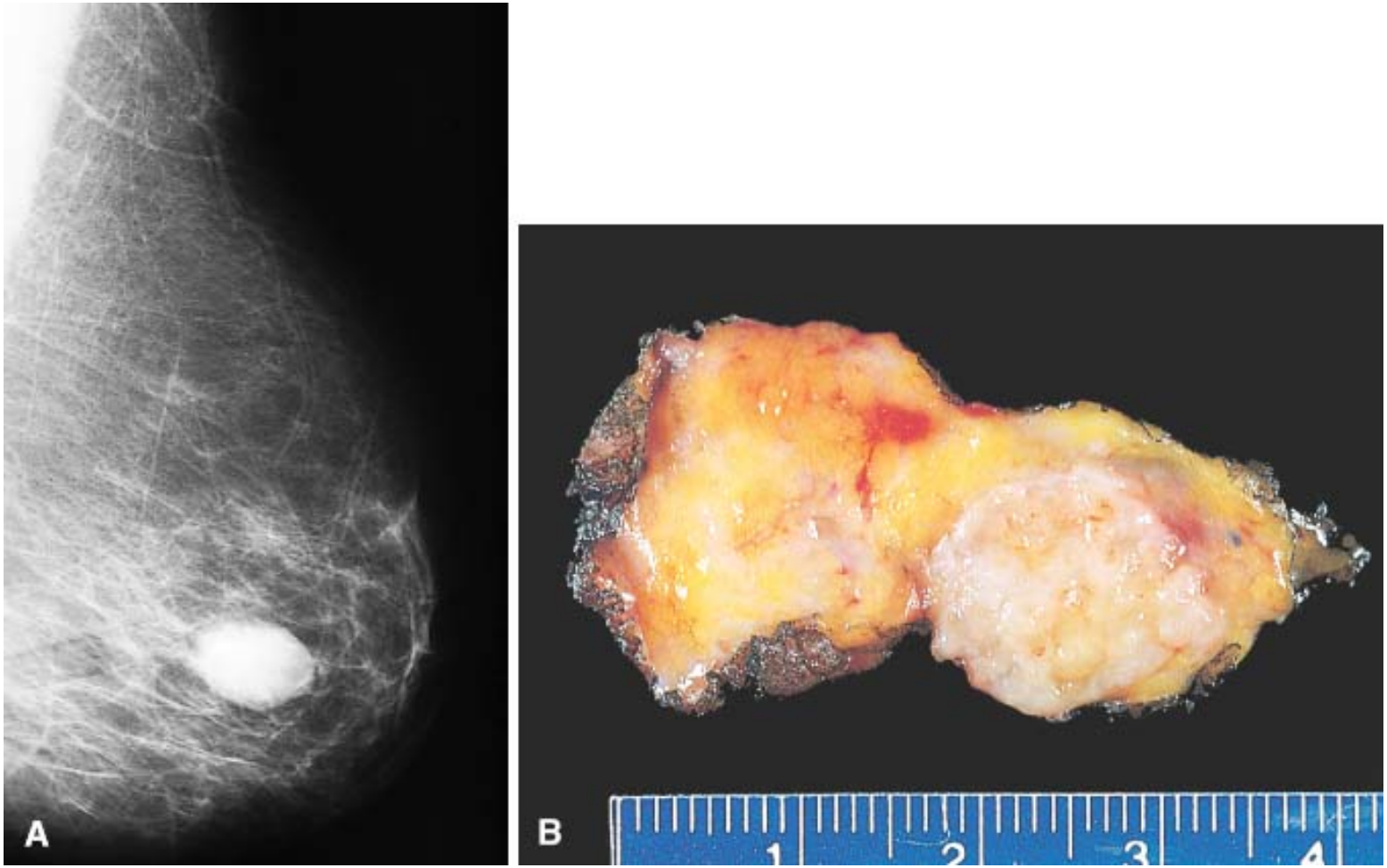


Figure 23-29 Fibroadenoma. The lesion consists of a proliferation of intralobular stroma surrounding and often pushing and distorting the associated epithelium. The border is sharply delimited from the surrounding tissue.

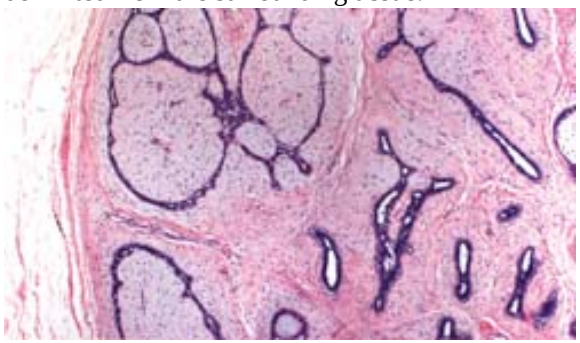


Figure 23-30 Phyllodes tumor. Compared to a fibroadenoma, there is increased stromal cellularity, cytologic atypia, and stromal overgrowth, giving rise to the typical leaflike architecture.

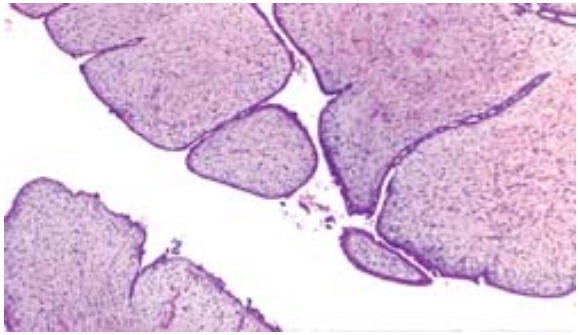
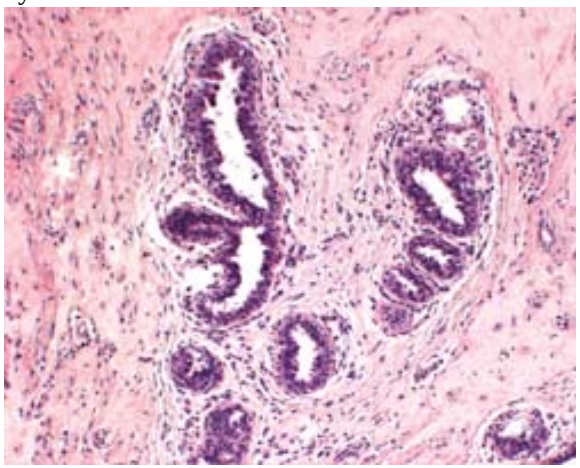


Figure 23-31 Gynecomastia. Terminal ducts (without lobule formation) are lined by a multilayered epithelium with small papillary tufts. There is typically surrounding periductal hyalinization and fibrosis.



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Chapter 24 - The Endocrine System

Anirban Maitra MBBS
Abul K. Abbas MBBS

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

Hormones can be classified into several broad categories on the basis of the nature of their receptors. Cellular receptors and signaling pathways were discussed in Chapter 3 , and only a few comments about signaling by hormone receptors follow:

- *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 signaling molecules, termed *second messengers*, such as cyclic adenosine monophosphate (cAMP); production of mediators from membrane phospholipids, such as inositol 1,4,5-trisphosphate or IP_3 ; and shifts in the intracellular levels of ionized calcium. The elevated levels of one or more of these can control 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 diffuse across the plasma membrane and interact with receptors in the cytosol or the nucleus. The resulting hormone-receptor complexes bind specifically to recognition elements in DNA, thereby affecting the expression of specific target genes. Hormones of this type include the steroids (e.g., estrogen, progesterone, and glucocorticoids), and thyroxine.

A number of processes can 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. Endocrine diseases can be generally classified as (1) diseases of *underproduction or overproduction* of hormones and their resulting biochemical and clinical consequences and (2) diseases associated with the development of *mass lesions*. Such lesions might be nonfunctional, or they might be associated with overproduction or underproduction of hormones. The study of endocrine diseases requires integration of morphologic findings with biochemical measurements of the levels of hormones, their regulators, and other metabolites.

Pituitary Gland

Normal

The pituitary is a small bean-shaped organ that measures about 1 cm in greatest diameter and weighs about 0.5 gm, although it enlarges during pregnancy. Its small size belies its great functional significance. It is located at the base of the brain, where it lies nestled within the confines of the sella turcica in close proximity to the optic chiasm and the cavernous sinuses. The pituitary is attached to the hypothalamus by the pituitary stalk, which passes out of the sella through an opening in the dura mater surrounding the brain. Along with the hypothalamus, the pituitary gland plays a critical role in

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Figure 24-1 Hormones released by the anterior pituitary. The adenohypophysis (anterior pituitary) releases five hormones that are in turn under the control of various stimulatory and inhibitory hypothalamic releasing factors. TSH, thyroid-stimulating hormone (thyrotropin); PRL, prolactin; ACTH, adrenocorticotrophic hormone (corticotropin); GH, growth hormone (somatotropin); FSH, follicle-stimulating hormone; LH, luteinizing hormone. The stimulatory releasing factors are TRH (thyrotropin-releasing factor), CRH (corticotropin-releasing factor), GHRH (growth hormone-releasing factor), GnRH (gonadotropin-releasing factor). The inhibitory hypothalamic influences are comprised of PIF (prolactin inhibitory factor or dopamine) and growth hormone inhibitory factor (GIH or somatostatin).

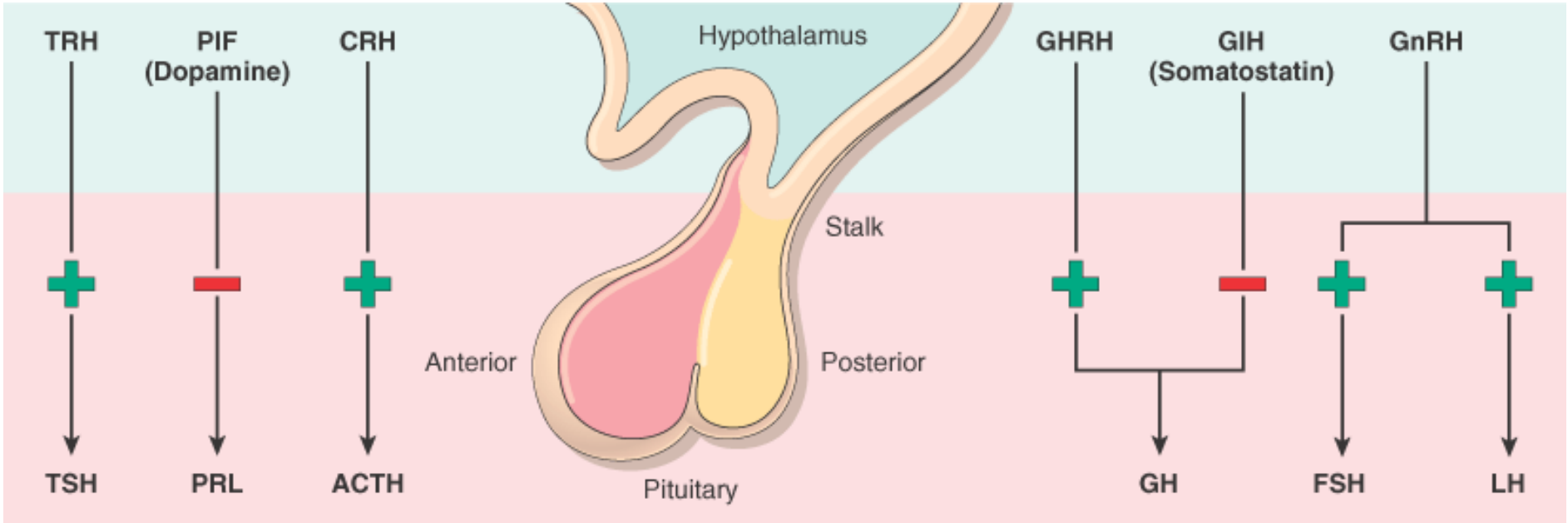

Figure 24-2 *A*, Photomicrograph of normal pituitary. The gland is populated by several distinct cell populations containing a variety of stimulating (trophic) hormones. *B*, Each of the hormones has different staining characteristics, resulting in a mixture of cell types in routine histologic preparations. Immunostain for human growth hormone.

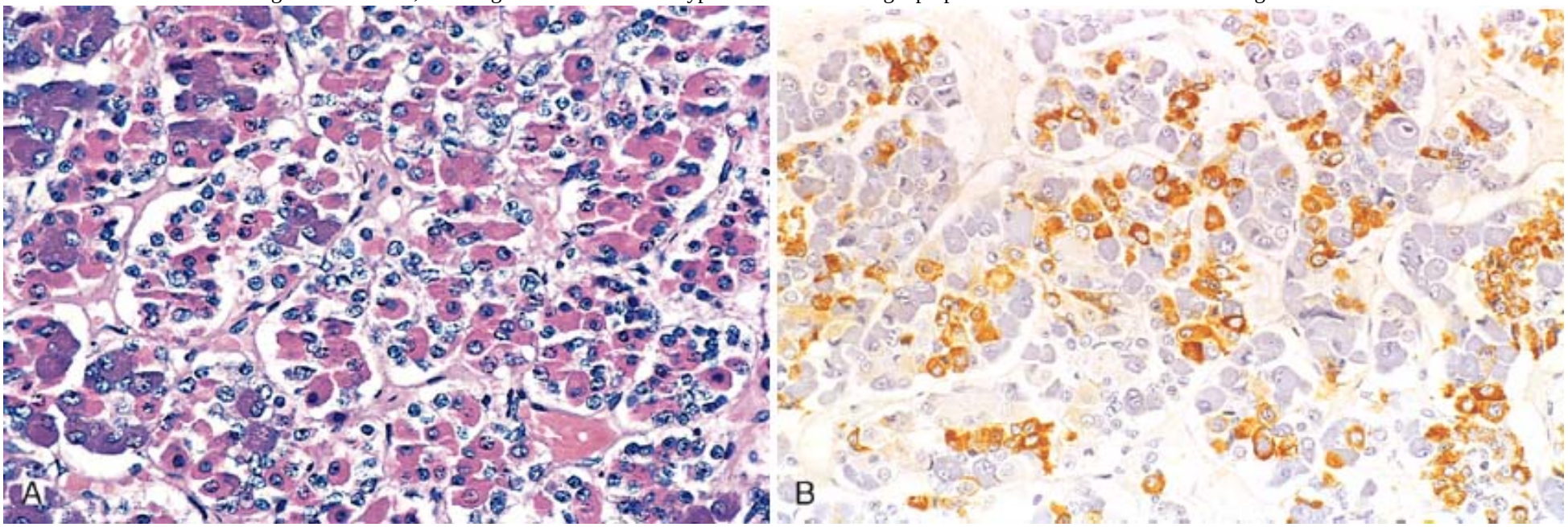

TABLE 24-1 -- Classification of Pituitary Adenomas

Prolactin cell (lactotroph) adenoma
Growth hormone cell (somatotroph) adenoma
••Densely granulated GH cell adenoma
••Sparsely granulated GH cell adenoma with fibrous bodies
Thyroid-stimulating hormone cell (thyrotroph) adenomas
ACTH cell (corticotroph) adenomas
Gonadotroph cell adenomas
••Silent gonadotroph adenomas include most so-called null cell and oncocytic adenomas
Mixed growth hormone-prolactin cell (mammosomatotroph) adenomas
Other plurihormonal adenomas
Hormone-negative adenomas

ACTH, adrenocorticotropic hormone.

demonstration of lineage-specific differentiation. Both silent and hormone-negative pituitary adenomas may cause hypopituitarism as they encroach on and destroy adjacent anterior pituitary parenchyma.

Clinically diagnosed pituitary adenomas are responsible for about 10% of intracranial neoplasms; they are discovered incidentally in up to 25% of routine autopsies. In fact, using high-resolution computed tomography or magnetic resonance imaging suggest that approximately 20% of "normal" adult pituitary glands harbor an incidental lesion measuring 3 mm or more in diameter, usually a silent adenoma. [1] Pituitary adenomas are usually found in adults, with a peak incidence from the thirties to the fifties. Most pituitary adenomas occur as isolated lesions. In about 3% of cases, however, adenomas are associated with *multiple endocrine neoplasia (MEN) type 1* (discussed later). Pituitary adenomas are designated, somewhat arbitrarily, *microadenomas* if they are less than 1 cm in diameter and *macroadenomas* if they exceed 1 cm in diameter. Silent and hormone-negative adenomas are likely to come to clinical attention at a later stage than those associated with endocrine abnormalities and are therefore more likely to be macroadenomas.

With recent advances in molecular techniques, substantial insight has been gained into *the genetic abnormalities associated with pituitary adenomas*:[2]

- The great majority of pituitary adenomas are monoclonal in origin, even those that are plurihormonal, suggesting that most arise from a single somatic cell. Some plurihormonal tumors may arise from clonal expansion of primitive stem cells, which then differentiate in several directions simultaneously.
- G-protein mutations are possibly the best-characterized molecular abnormalities in pituitary adenomas. G-proteins are described in Chapter 3 ; here we will review their function in the context of endocrine neoplasms. G-proteins play a critical role in signal transduction, transmitting signals from *cell-surface receptors* (e.g., GHRH receptor) to *intracellular effectors* (e.g., adenyl cyclase), which then generate *second messengers* (e.g., cyclic AMP, cAMP). These are heterotrimeric proteins, composed of a specific α-subunit that binds guanine nucleotide and interacts with both cell surface receptors and intracellular effectors (Fig. 24-3); the β- and γ-subunits are noncovalently bound to the specific α-subunit. G_s is a stimulatory G-protein that has a pivotal role in signal transduction in several endocrine organs, including the pituitary. The α-subunit of G_s (G_s α) is encoded by the *GNAS1* gene, located on chromosome 20q13. In the basal state, G_s exists as an inactive protein, with GDP bound to the guanine nucleotide-binding site of the α-subunit of G_s . On interaction with the ligand-bound cell-surface receptor, GDP dissociates, and GTP binds to G_s α, activating the G-protein. The activation of G_s α results in the generation of cAMP, which acts as a potent mitogenic stimulus for a variety of endocrine cell types (such as pituitary somatotrophs and corticotrophs, thyroid follicular cells, parathyroid cells), promoting cellular proliferation and hormone synthesis and secretion. The activation of G_s α, and 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 will therefore result in constitutive activation of G_s α, persistent generation of cAMP, and unchecked cellular proliferation* (Fig. 24-3). Approximately 40% of somatotroph cell adenomas bear *GNAS1* mutations that abrogate the GTPase activity of G_s α. The mutant form of *GNAS1* is also known as the *gsp oncogene* because of its effects on tumorigenesis. In addition, *GNAS1* mutations have also been described in a minority of corticotroph adenomas; in contrast, *GNAS1* mutations are absent in thyrotroph, lactotroph, and gonadotroph adenomas, since their respective hypothalamic release hormones do not mediate their action via cAMP-dependent pathways.
- Multiple endocrine neoplasia (MEN) syndrome (discussed in detail below) is a familial disorder associated with tumors and hyperplasias of multiple endocrine organs, including the pituitary. A subtype of MEN syndrome, known as MEN-1, is caused by germ line mutations of the gene *MEN1*, on chromosome 11q13. While *MEN1* mutations are, by definition, present in pituitary adenomas arising in context of the MEN-1 syndrome, they are uncommon in sporadic pituitary adenomas.
- Additional molecular abnormalities present in *aggressive or advanced pituitary adenomas* include activating mutations of the *RAS* oncogene and overexpression of the *c-MYC* oncogene, suggesting that these genetic events are linked to disease progression.[3]

Figure 24-3 The mechanism of G-protein mutations in endocrine neoplasia. Mutations in the G-protein-signaling pathway are seen in a variety of endocrine neoplasms, including pituitary, thyroid, and parathyroid adenomas. G-proteins play a critical role in signal transduction, transmitting signals from cell-surface receptors (GHRH, TSH, or PTH receptor) to intracellular effectors (e.g., adenyl cyclase), which then generate second messengers (cAMP).

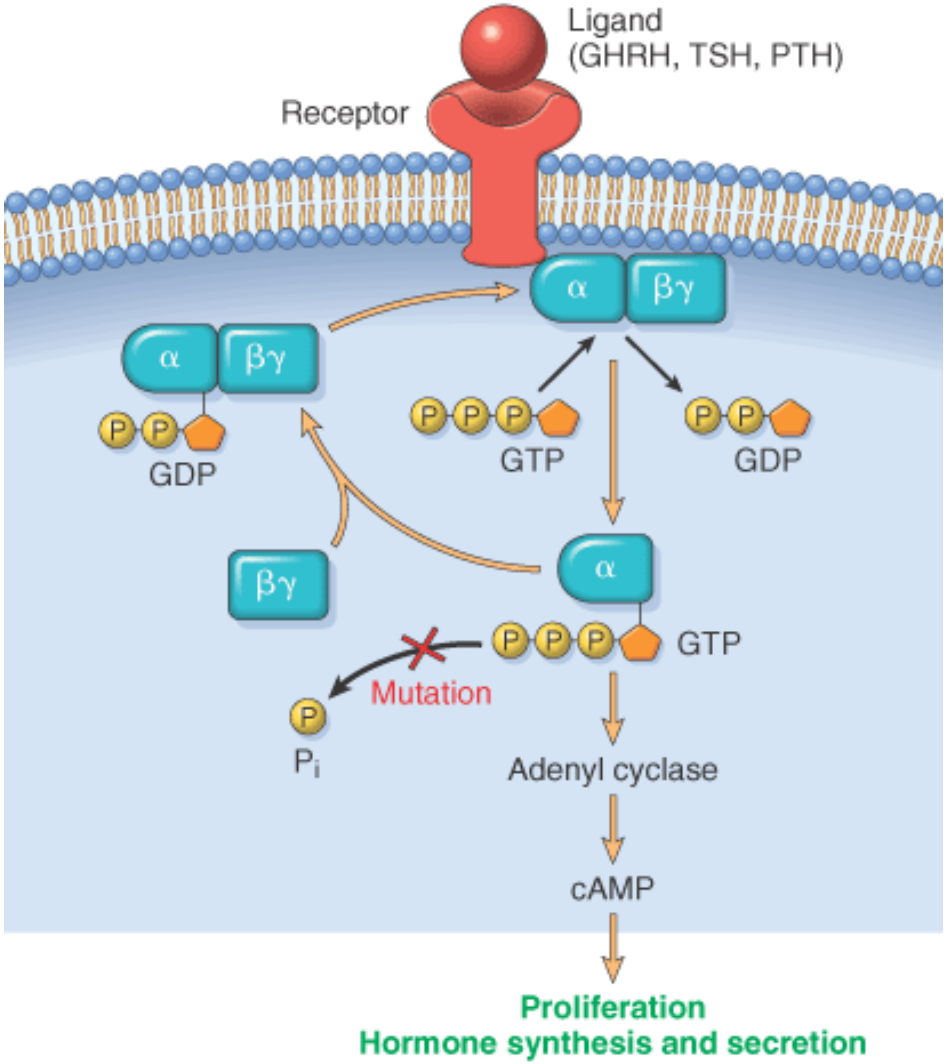

Figure 24-4 Pituitary adenoma. This massive, nonfunctional adenoma has grown far beyond the confines of the sella turcica and has distorted the overlying brain. Nonfunctional adenomas tend to be larger at the time of diagnosis than those that secrete a hormone.

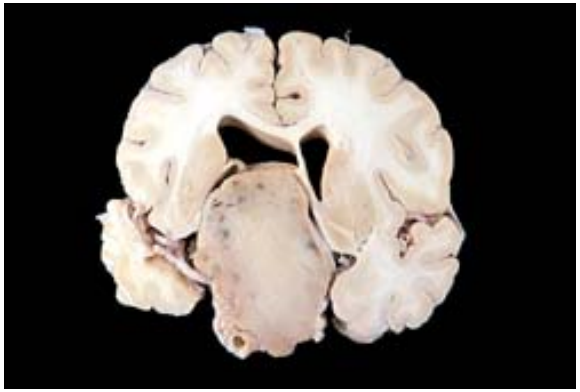

Figure 24-5 Pituitary adenoma. The monomorphism of these cells contrasts markedly with the mixture of cells seen in the normal anterior pituitary. Note also the absence of reticulin network.

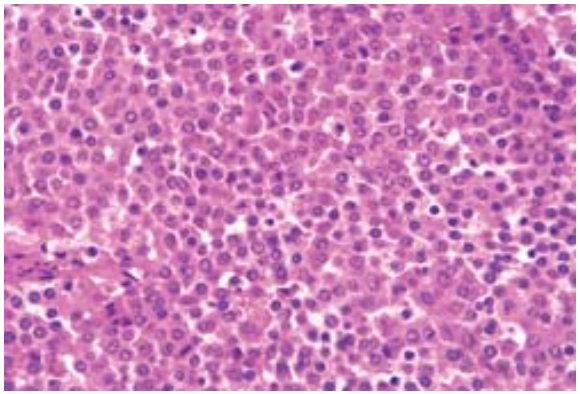

Figure 24-6 Ultrastructural features of prolactinomas. *A,* Electron micrograph of a sparsely granulated prolactinoma. The tumor cells contain abundant granular endoplasmic reticulum (indicative of active protein synthesis) and small numbers of secretory granules (6000X). *B,* Electron micrograph of densely granulated growth hormone-secreting adenoma. The tumor cells are filled with large, membrane-bound secretory granules (6000X). *(Courtesy of Dr. Eva Horvath, St. Michael's Hospital, Toronto, Ontario, Canada.)*

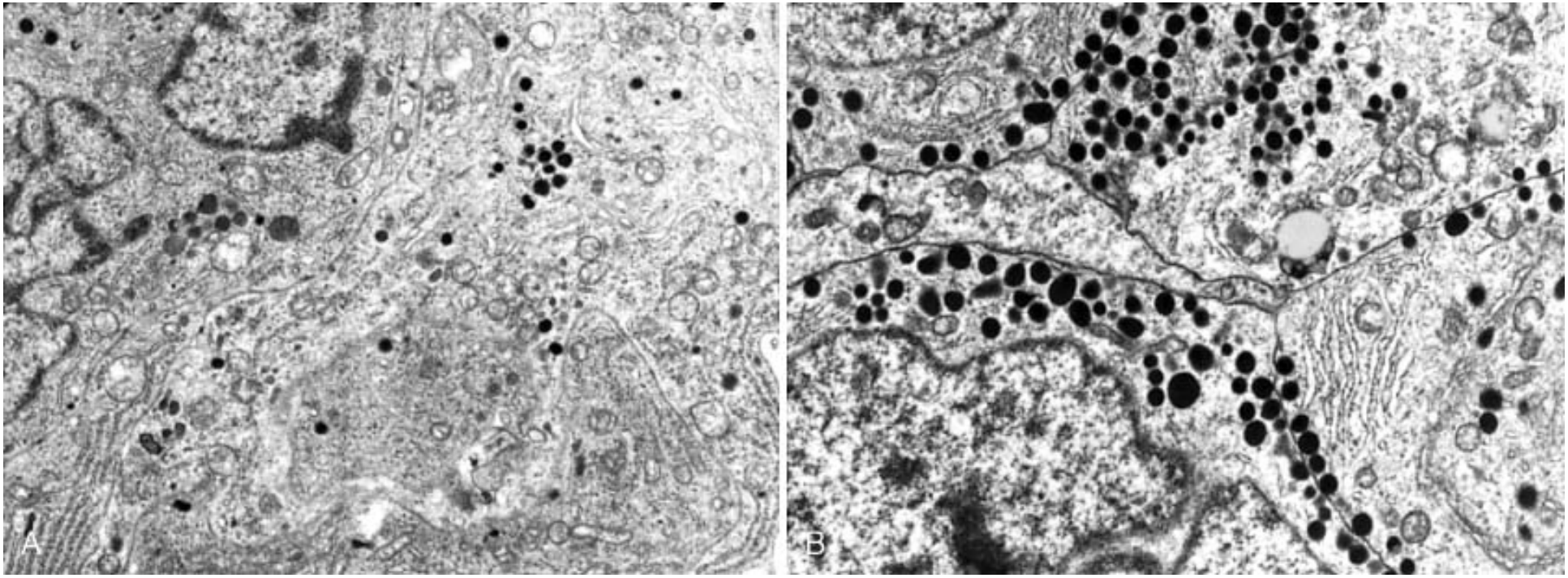

Figure 24-7 Homeostasis in the hypothalamus-pituitary-thyroid axis and mechanism of action of thyroid hormones. Secretion of thyroid hormones (T_3 and T_4) is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary. Decreased levels of T_3 and T_4 stimulate the release 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, and cyclic AMP (cAMP)-mediated synthesis and release of thyroid hormones (T3 and T4). In the periphery, T_3 and T_4 interact with the thyroid hormone receptor (TR) to form a hormone-receptor complex that translocates to the nucleus and binds to so-called thyroid response elements (TREs) on target genes initiating transcription.

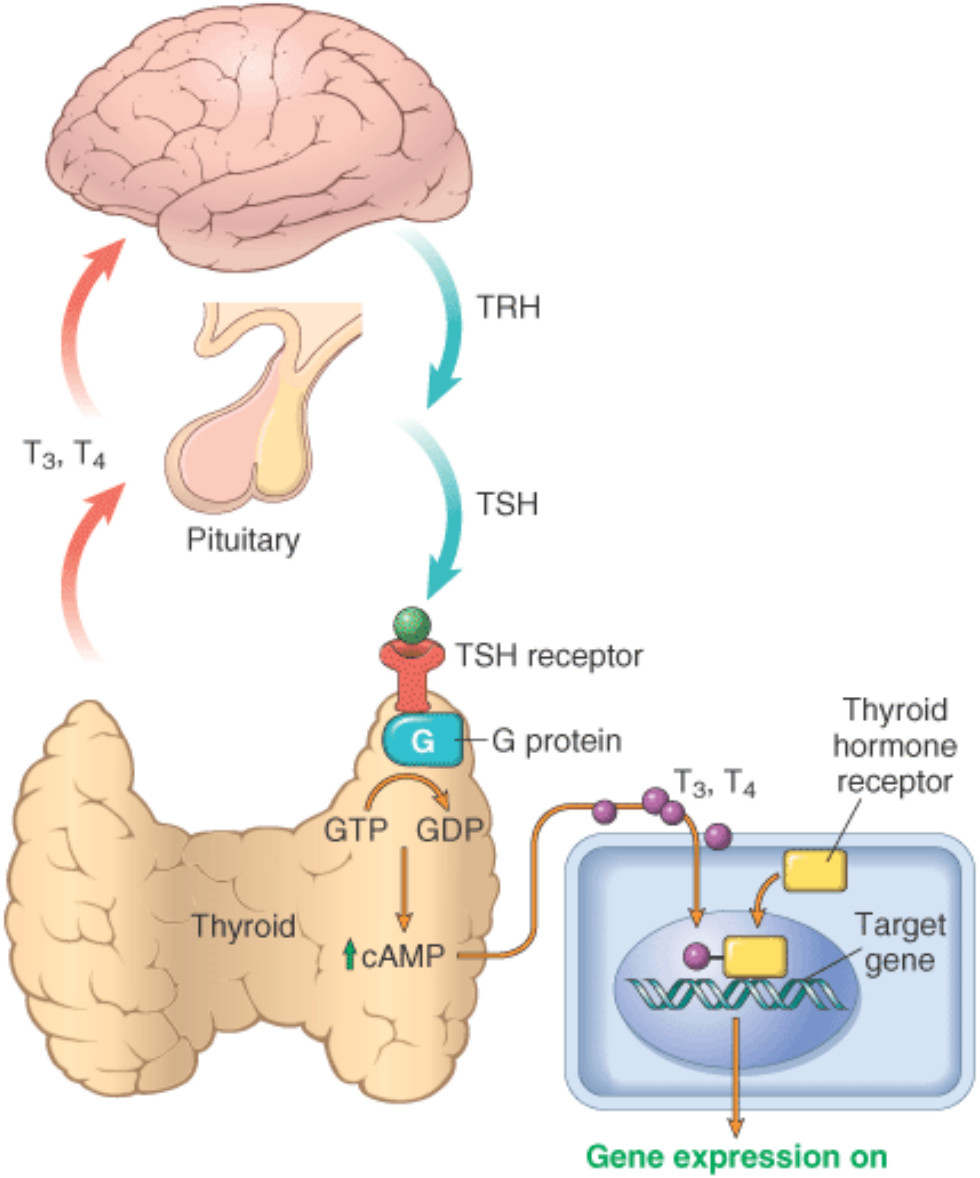

TABLE 24-2 -- Disorders Associated with Thyrotoxicosis

Associated with Hyperthyroidism
Primary
••Diffuse toxic hyperplasia (Graves disease)
••Hyperfunctioning ("toxic") multinodular goiter

••Hyperfunctioning ("toxic") adenoma
••Hyperfunctioning thyroid carcinoma
••Iodine-induced hyperthyroidism
••Neonatal thyrotoxicosis associated with maternal Graves disease
Secondary
••TSH-secreting pituitary adenoma (rare) *
Not Associated with Hyperthyroidism
Subacute granulomatous thyroiditis (*painful*)
Subacute lymphocytic thyroiditis (*painless*)
Struma ovarii (ovarian teratoma with ectopic thyroid)
Factitious thyrotoxicosis (exogenous thyroxine intake)

*Associated with increased TSH; all other causes of thyrotoxicosis associated with decreased TSH.

one (albeit the most common) cause of thyrotoxicosis. The terms *primary* and *secondary hyperthyroidism* are sometimes used to designate hyperthyroidism arising from an intrinsic thyroid abnormality and that arising from processes outside of the thyroid, such as a TSH-secreting pituitary tumor. With this disclaimer, we will follow the common practice of using the terms *thyrotoxicosis* and *hyperthyroidism* interchangeably. The three most common causes of thyrotoxicosis are also associated with hyperfunction of the gland and include the following:

- *Diffuse hyperplasia* of the thyroid associated with Graves disease (accounts for 85% of cases)
- Hyperfunctional *multinodular goiter*
- Hyperfunctional *adenoma* of the thyroid

Clinical Course.

The clinical manifestations of hyperthyroidism are protean and include changes referable to the *hypermetabolic state* induced by excess thyroid hormone as well as those related to overactivity of the *sympathetic nervous system* (i.e., an increase in the β-adrenergic "tone").

Excessive levels of thyroid hormone result in *an increase in the basal metabolic rate*. The *skin* of thyrotoxic patients tends to be soft, warm, and flushed because of increased blood flow and peripheral vasodilation to increase heat loss. *Heat intolerance* is common. Sweating is increased because of higher levels of calorigenesis. Increased basal metabolic rate also results in characteristic *weight loss despite increased appetite*.

Cardiac manifestations are among the earliest and most consistent features of hyperthyroidism. Patients with hyperthyroidism can have an increase in cardiac output, owing to both increased cardiac contractility and increased peripheral oxygen requirements. Tachycardia, palpitations, and cardiomegaly are common. Arrhythmias, particularly atrial fibrillation, occur frequently and are more common in older patients. Congestive heart failure may develop, particularly in elderly patients with pre-existing cardiac disease. Myocardial changes, such as foci of lymphocytic and eosinophilic infiltration, mild fibrosis in the interstitium, fatty changes in myofibers, and an increase in size and number of mitochondria, have been described. Some patients with thyrotoxicosis develop a reversible *diastolic dysfunction* and a "low-output" failure, so-called *thyrotoxic dilated cardiomyopathy*.

In the *neuromuscular system*, overactivity of the sympathetic nervous system produces tremor, hyperactivity, emotional lability, anxiety, inability to concentrate, and insomnia. Proximal muscle weakness is common with decreased muscle mass (*thyroid myopathy*).

Ocular changes often call attention to hyperthyroidism. A wide, staring gaze and lid lag are present because of sympathetic overstimulation of the levator palpebrae superioris (Fig. 24-8). However, true *thyroid ophthalmopathy* associated with proptosis is a feature seen only in Graves disease (see below).

In the *gastrointestinal system*, sympathetic hyperstimulation of the gut results in hypermotility, malabsorption, and diarrhea.

The *skeletal system* is also affected in hyperthyroidism. Thyroid hormone stimulates bone resorption, resulting in increased porosity of cortical bone and reduced volume of trabecular bone. The net effect is osteoporosis and an increased risk of fractures in patients with chronic hyperthyroidism.

Figure 24-8 A patient with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system, is one of the features of this disorder. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue behind the eyeballs also adds to the protuberant appearance of the eyes.

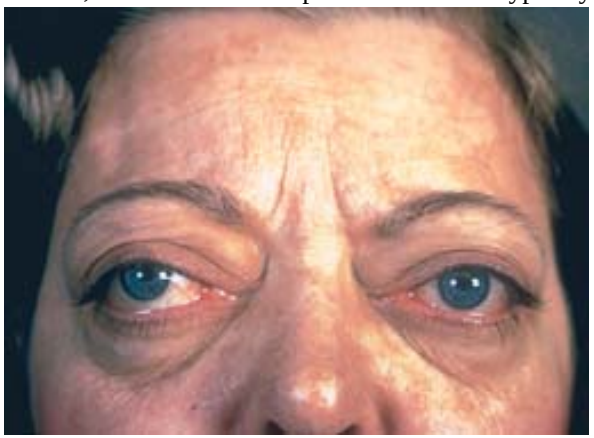

TABLE 24-3 -- Causes of Hypothyroidism

Primary
Developmental (thyroid dysgenesis: *PAX-8, TTF-2, TSH-receptor* mutations)
Thyroid hormone resistance syndrome (TRβ mutations)
Postablative
••Surgery, radioiodine therapy, or external radiation
Autoimmune hypothyroidism

••Hashimoto thyroiditis *
Iodine deficiency *
Drugs (lithium, iodides, *p*-aminosalicylic acid) *
Congenital biosynthetic defect (dyshormonogenetic goiter) *
Secondary
Pituitary failure
Tertiary
Hypothalamic failure (rare)

*Associated with enlargement of thyroid ("goitrous hypothyroidism"). Hashimoto thyroiditis and postablative hypothroidism account for the majority of cases.

exogenous irradiation, such as external radiation therapy to the neck.

Autoimmune hypothyroidism is the most common cause of goitrous hypothyroidism in iodine-sufficient areas of the world. The vast majority of cases of autoimmune hypothyroidism are due to Hashimoto thyroiditis. Circulating autoantibodies, including *anti-TSH receptor autoantibodies*, are commonly found in Hashimoto thyroiditis. Some patients with hypothyroidism have circulating anti-TSH antibodies, but they usually do not have the goitrous enlargement or lymphocytic infiltrate characteristic of Hashimoto thyroiditis. In the past, many of these patients were classified as having primary "idiopathic" hypothyroidism, but the disease is now recognized as a type of autoimmune disorder of the thyroid, occurring either in isolation or in conjunction with other autoimmune endocrine manifestations.

Drugs given intentionally to decrease thyroid secretion (e.g., methimazole and propylthiouracil) can cause hypothyroidism, as can agents used to treat nonthyroid conditions (e.g., lithium, *p*-aminosalicylic acid).

Inborn errors of thyroid metabolism are an uncommon cause of goitrous hypothyroidism (*dyshormonogenetic goiter*). Any one of the multiple steps leading to thyroid hormone synthesis may be deficient: (1) iodide transport defect, (2) organification defect, (3) dehalogenase defect, and (4) iodotyrosine coupling defect. Organification of iodine involves binding of oxidized iodide with tyrosyl residues in thyroglobulin, and this process is deficient in patients with *Pendred syndrome*, wherein goitrous hypothyroidism is accompanied by sensorineural deafness.

Thyroid hormone resistance syndrome is a rare autosomal-dominant disorder caused by inherited mutations in the thyroid hormone receptor (TR), which abolish the ability of the receptor to bind thyroid hormones.[11] Patients demonstrate a generalized resistance to thyroid hormone, despite high circulating levels of T_3 and T_4 . Since the pituitary is also resistant to feedback from thyroid hormones, TSH levels tend to be high as well. In rare instances, there may be complete absence of thyroid parenchyma (*thyroid agenesis*), or the gland may be greatly reduced in size (*thyroid hypoplasia*). Mutations in the *TSH receptor* are a newly recognized cause of congenital hypothyroidism associated with a hypoplastic thyroid gland.[12] Recently, mutations in two transcription factors that are expressed in the developing thyroid and regulate follicular differentiation—*thyroid transcription factor-2* (*TTF-2*)[13] and *Paired*

Homeobox-8 (*PAX-8*) [14] —have been reported in patients with thyroid agenesis. Thyroid agenesis caused by TTF-2 mutations is usually associated with a cleft palate.

Secondary hypothyroidism is caused by TSH deficiency, and tertiary (central) hypothyroidism is caused by TRH deficiency. Secondary hypothyroidism can result from any of the causes of hypopituitarism. Frequently, the cause is a pituitary tumor; other causes include postpartum pituitary necrosis, trauma, and nonpituitary tumors, as was previously discussed. *Tertiary* (central) hypothyroidism can be caused by any disorder that damages the hypothalamus or interferes with hypothalamic-pituitary portal blood flow, thereby preventing delivery of TRH to the pituitary. This can result from hypothalamic damage from tumors, trauma, radiation therapy, or infiltrative diseases. Classic clinical manifestations of hypothyroidism include cretinism and myxedema.

CRETINISM

Cretinism refers to hypothyroidism that develops in infancy or early childhood. The term *cretin* was derived from the French *chrétien*, meaning Christian or Christlike, and was applied to these unfortunates because they were considered to be so mentally retarded as to be incapable of sinning. In the past, this disorder occurred fairly commonly in areas of the world where dietary iodine deficiency is endemic, such as the Himalayas, inland China, Africa, and other mountainous areas. It has become much less frequent in recent years, owing to the widespread supplementation of foods with iodine. On rare occasions, cretinism may also result from inborn errors in metabolism (e.g., enzyme deficiencies) that interfere with the biosynthesis of normal levels of thyroid hormone (*sporadic* cretinism).

Clinical features of cretinism include impaired development of the skeletal system and central nervous system, manifested by severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia. The severity of the mental impairment in cretinism appears to be related to the time at which thyroid deficiency occurs in utero. Normally, maternal hormones, including T_3 and T_4 , cross the placenta and are critical to fetal brain development. If there is maternal thyroid deficiency before the development of the fetal thyroid gland, mental retardation is severe. In contrast, reduction in maternal thyroid hormones later in pregnancy, after the fetal thyroid has developed, allows normal brain development.

MYXEDEMA

The term *myxedema* is applied to hypothyroidism developing in the older child or adult. 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. The clinical manifestations vary with the age of onset of the deficiency. The older child shows signs and symptoms intermediate between those of the cretin and those of the adult with hypothyroidism. In the adult, the condition appears insidiously and may take years to reach the level of clinical suspicion.

Clinical features of myxedema are characterized by a slowing of physical and mental activity. The initial symptoms include generalized fatigue, apathy, and mental sluggishness, which may mimic depression in the early stages of the disease. Speech and intellectual functions become slowed. Patients with myxedema are listless, cold-intolerant, and frequently overweight. Reduced cardiac output probably contributes to shortness of breath and decreased exercise capacity, two frequent complaints in patients with hypothyroidism. Decreased sympathetic activity results in constipation and decreased sweating. The skin in these patients is cool and pale because of decreased blood flow. Histologically, there is an accumulation of matrix substances, such as glycosaminoglycans and hyaluronic acid, in skin, subcutaneous tissue, and a number of visceral sites. This results in edema, a broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice.

Laboratory evaluation plays a vital role in the diagnosis of suspected hypothyroidism because of the nonspecific nature

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of symptoms. *Measurement of the serum TSH level is the most sensitive screening test for this disorder.* The TSH level is increased in primary hypothyroidism due to a loss of feedback

inhibition of TRH and TSH production by the hypothalamus and pituitary, respectively. The TSH level is not increased in patients with hypothyroidism due to primary hypothalamic or pituitary disease. *T_4 levels are 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, subacute granulomatous thyroiditis) and disorders in which there is relatively little inflammation and the illness is manifested primarily by thyroid dysfunction (subacute lymphocytic thyroiditis and fibrous [Reidel] thyroiditis).

Infectious thyroiditis may be either acute or chronic. Acute infections can reach the thyroid via hematogenous spread or through direct seeding of the gland, such as via a fistula from the piriform sinus adjacent to the larynx. Other infections of the thyroid, including mycobacterial, fungal, and *Pneumocystis* infections, are more chronic and frequently occur in immunocompromised patients. Whatever the cause, the inflammatory involvement may cause sudden onset of neck pain and tenderness in the area of the gland and is accompanied by fever, chills, and other signs of infection. Infectious thyroiditis can be self-limited or can be controlled with appropriate therapy. Thyroid function is usually not significantly affected, and there are few residual effects except for possible small foci of scarring. This section focuses on the more common and clinically significant types of thyroiditis: (1) Hashimoto thyroiditis (or chronic lymphocytic thyroiditis), (2) subacute granulomatous thyroiditis, and (3) subacute lymphocytic thyroiditis.

HASHIMOTO THYROIDITIS

Hashimoto thyroiditis (or chronic lymphocytic 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 because of autoimmune destruction of the thyroid gland. The name *Hashimoto thyroiditis* is derived from the 1912 report by Hashimoto describing patients with goiter and intense lymphocytic infiltration of the thyroid (*struma lymphomatosa*). This disorder is most prevalent between 45 and 65 years of age and is more common in women than in men, with a female predominance 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.

Epidemiologic studies have demonstrated a significant *genetic component* to Hashimoto thyroiditis, although, as in most other autoimmune disorders, the pattern of inheritance is non-Mendelian and likely to be influenced by subtle variations in the functions of multiple genes. The concordance rate in monozygotic twins is 30% to 60%, and up to 50% of asymptomatic first-degree relatives of Hashimoto patients demonstrate circulating antithyroid antibodies.[15] Several chromosomal abnormalities have been associated with thyroid autoimmunity. For example, adults with Turner syndrome (see Chapter 5) have a high prevalence of circulating antithyroid antibodies, and a substantial minority (~20%) develops subclinical or clinical hypothyroidism that is indistinguishable from Hashimoto thyroiditis. Similarly, adults with trisomy 21 (Down syndrome, see Chapter 5) are also at an increased risk for developing Hashimoto thyroiditis and hypothyroidism. There are reports that polymorphisms in the HLA locus, specifically the HLA-DR3 and HLA-DR5 alleles, are linked to Hashimoto thyroiditis, but the association is weak. Finally, genomewide linkage analyses in families with Hashimoto thyroiditis have provided evidence for several susceptibility loci, such as on chromosomes 6p and 12q, that may harbor genes predisposing to this disorder.[16]

Pathogenesis.

Hashimoto thyroiditis is an autoimmune disease in which the immune system reacts against a variety of thyroid antigens. The overriding feature of Hashimoto thyroiditis is progressive depletion of thyroid epithelial cells (thyrocytes), which are gradually replaced by mononuclear cell infiltration and fibrosis. Multiple immunologic mechanisms may contribute to the death of thyrocytes (Fig. 24-9).[17] [18] Sensitization of autoreactive CD4+ T-helper cells to thyroid antigens appears to be the initiating event. The effector mechanisms for thyrocyte death include the following:

- *CD8+ cytotoxic T cell-mediated cell death:* CD8+ cytotoxic T cells may cause thyrocyte destruction by one of two pathways: exocytosis of perforin/granzyme granules or engagement of death receptors, specifically CD95 (also known as Fas) on the target cell (Chapter 6).
- *Cytokine-mediated cell death:* CD4+ T cells produce inflammatory cytokines such as IFN-γ in the immediate thyrocyte milieu, with resultant recruitment and activation of

macrophages and damage to follicles.
• Binding of antithyroid antibodies (anti-TSH receptor antibodies, antithyroglobulin, and antithyroid peroxidase antibodies) followed by antibody-dependent cell-mediated cytotoxicity (ADCC) (Chapter 6).

Morphology.

The thyroid is often diffusely enlarged, although more localized enlargement may be seen in some cases. The capsule is intact, and the gland is well demarcated from adjacent structures. The cut surface is pale, yellow-tan, firm, and somewhat nodular. Microscopic examination reveals extensive infiltration of the parenchyma by a **mononuclear inflammatory infiltrate** containing small lymphocytes, plasma cells, and well-developed **germinal centers** (Fig. 24-10). 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** cells. This is a metaplastic response of the normally low cuboidal follicular epithelium to ongoing injury. In fine-needle aspiration biopsies, the presence of Hürthle cells in conjunction with a heterogeneous population of lymphocytes is characteristic of Hashimoto thyroiditis. In "classic" Hashimoto thyroiditis, interstitial connective tissue is increased and may be abundant. A **fibrous variant** is

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Figure 24-9 Pathogenesis of Hashimoto thyroiditis. Three proposed models for mechanism of thyrocyte destruction in Hashimoto disease. Sensitization of autoreactive CD4+ T cells to thyroid antigens appears to be the initiating event for all three mechanisms of thyroid cell death. See the text for details.

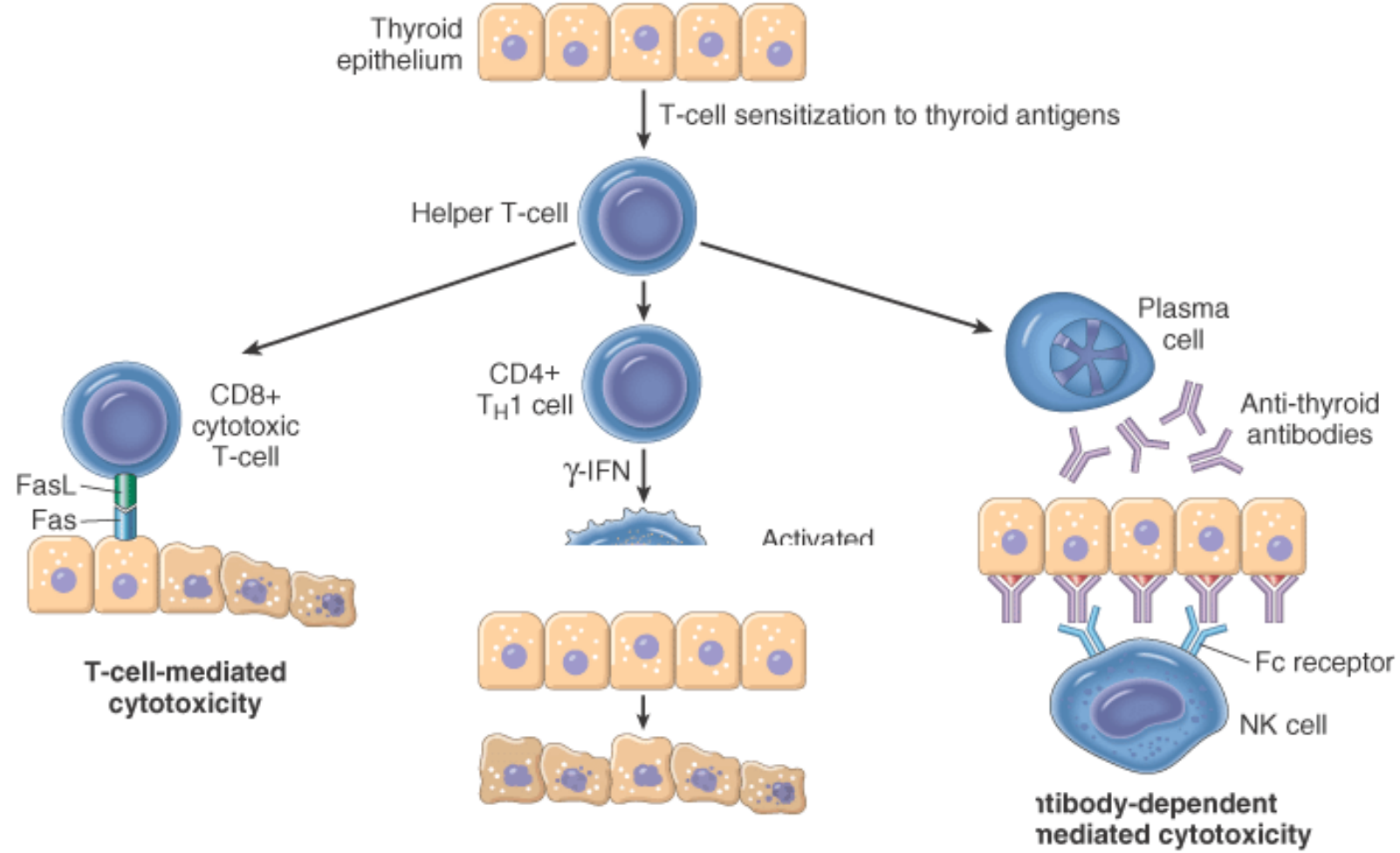


Figure 24-10 Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells are also seen.

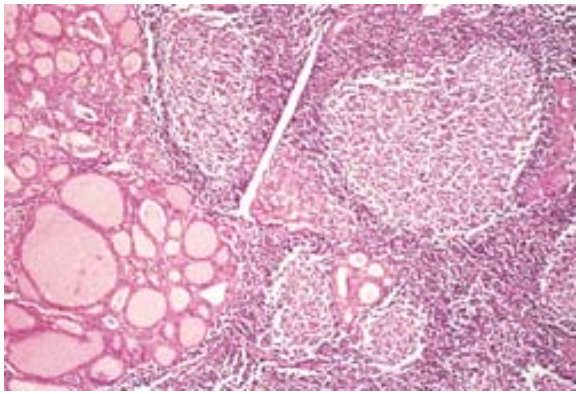


Figure 24-11 Subacute thyroiditis. The thyroid parenchyma contains a chronic inflammatory infiltrate with a multinucleate giant cell (*above left*) and a colloid follicle (*bottom right*).

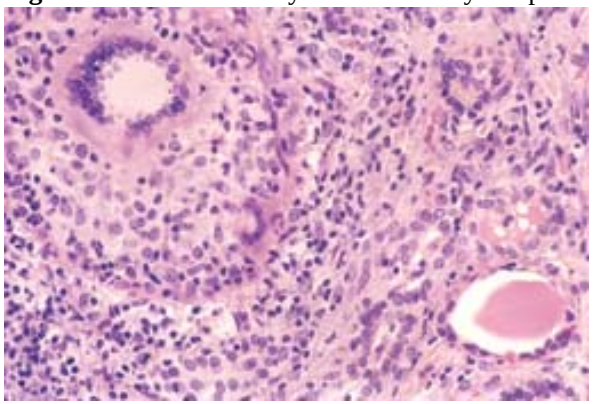


Figure 24-12 Diffusely hyperplastic thyroid in a case of Graves disease. The follicles are lined by tall, columnar epithelium. The crowded, enlarged epithelial cells project into the lumens of the follicles. These cells actively resorb the colloid in the centers of the follicles, resulting in the scalloped appearance of the edges of the colloid.

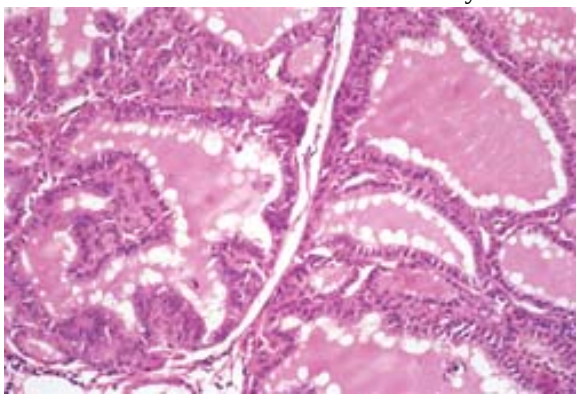


Figure 24-13 Nodular goiter. The gland is coarsely nodular and contains areas of fibrosis and cystic change.

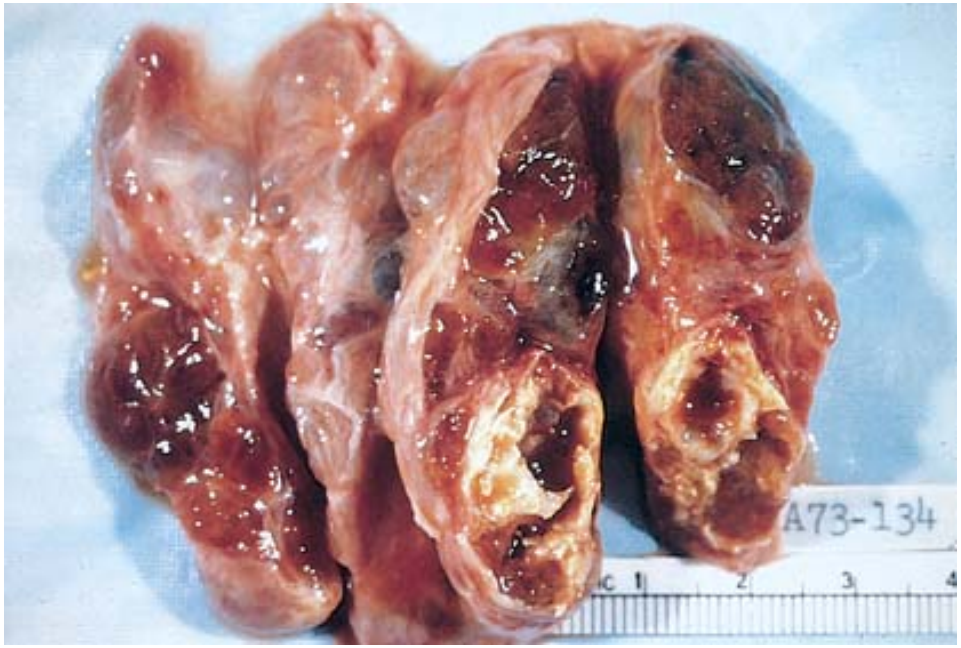


Figure 24-14 Follicular adenoma of the thyroid. A solitary, well-circumscribed nodule is seen.

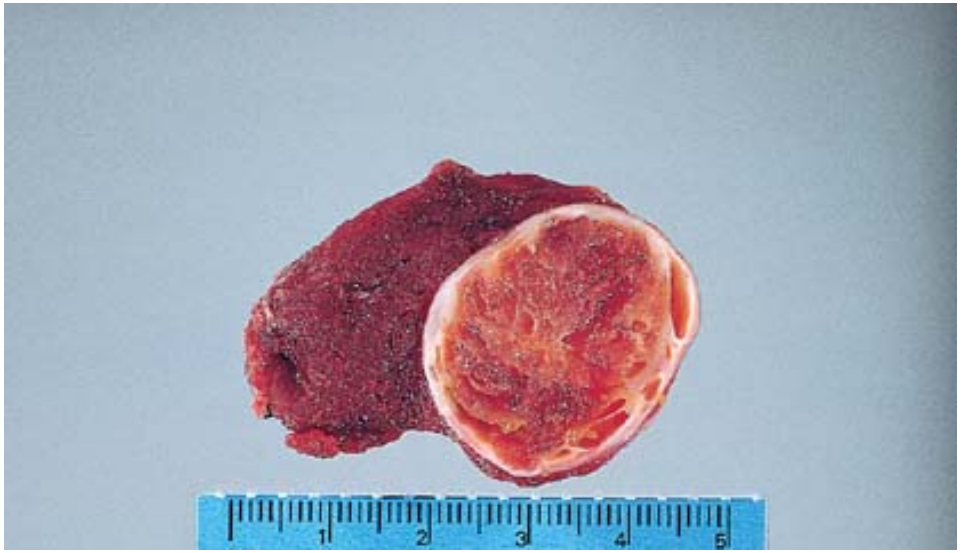


Figure 24-15 Follicular adenoma. The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.

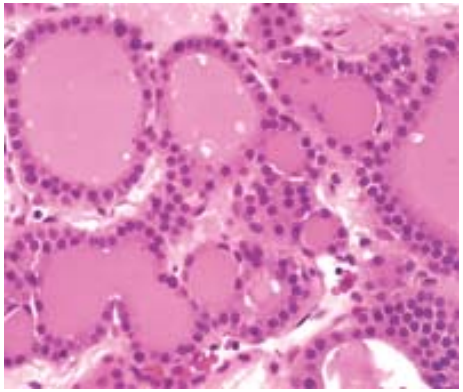


Figure 24-16 Hürthle cell tumor. A high-power view showing that the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei. *(Courtesy of Dr. Mary Sunday, Brigham and Women's Hospital, Boston, MA.)*

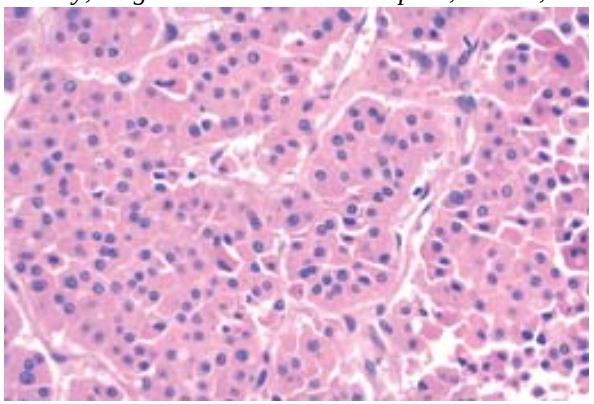
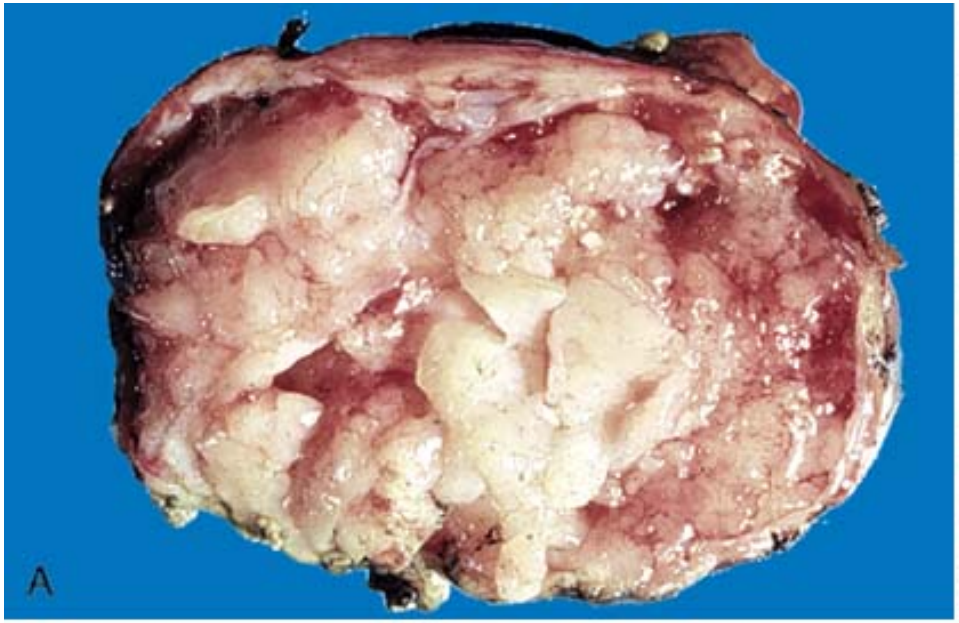
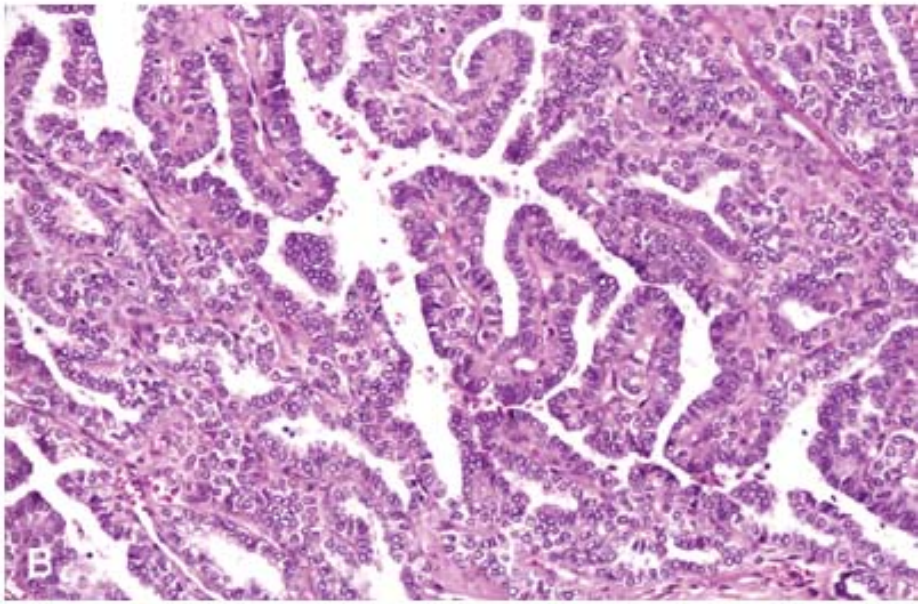
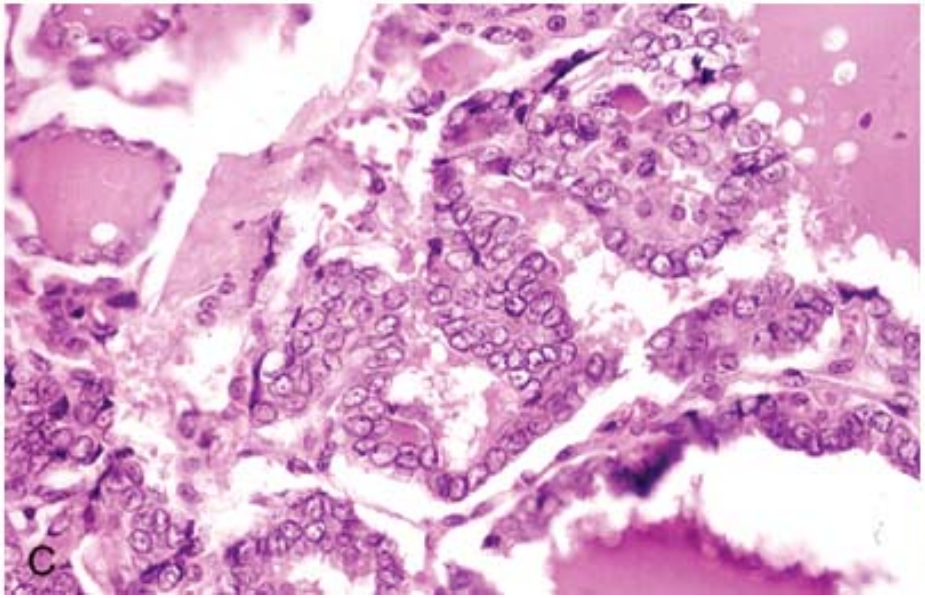


Figure 24-17 Papillary carcinoma of the thyroid. *A*, The macroscopic appearance of a papillary carcinoma with grossly discernible papillary structures. This particular example contains well-formed papillae (*B*), lined by cells with characteristic empty-appearing nuclei, sometimes termed "Orphan Annie 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.







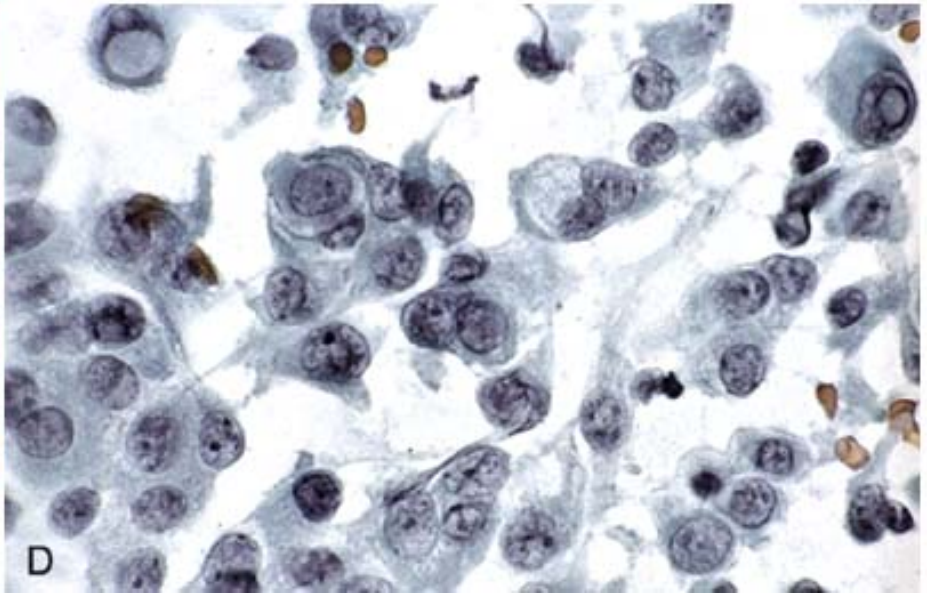


TABLE 24-4 -- Thyroid Lesions with a Follicular Architecture

Non-Neoplastic
Hyperplastic nodule in goiter
Neoplastic
Follicular adenoma *

Follicular carcinoma *
Follicular variant of papillary carcinoma †

*Differentiating follicular carcinoma from follicular adenoma requires histologic evidence of *capsular or blood vessel invasion*, or *documented metastasis*.
†The diagnosis of papillary carcinoma is rendered on the presence of *characteristic nuclear features*, irrespective of the presence or absence of papillae.

potential than the *ret/PTC* observed in usual papillary thyroid cancers. The presence of this genetic abnormality might result in more aggressive behavior.[42] [43]

An unusual **diffuse sclerosing variant** of papillary carcinoma occurs in younger individuals, including children. These tumors do not present with a mass, but rather with a bilateral goiter. There is a characteristic "gritty" sensation to the cut surface of the lesion due to the presence of abundant psammoma bodies. The tumor demonstrates a prominent papillary growth pattern, intermixed with solid areas containing nests of squamous cells (squamous morules). The neoplastic cells exhibit classic nuclear features of a papillary neoplasm. As the name suggests, there is extensive, diffuse fibrosis throughout the thyroid gland, often associated with a prominent lymphocytic infiltrate, simulating Hashimoto thyroiditis. The neoplastic cells have a peculiar propensity to invade intrathyroidal lymphatic channels; hence, nodal metastases are present in almost all cases.

Hyalinizing trabecular tumors, a group that includes both adenomas and carcinomas, have recently been reconsidered as a variant of papillary carcinomas, based on the presence of *ret/PTC* gene rearrangements in 30% to 60% of these tumors.[44] They are characterized by an "organoid" growth pattern, with nests and trabeculae of elongated tumor cells within a fibrovascular stroma; at first glance, the tumor may resemble an extra-adrenal paraganglioma (see below). Both intracellular and extracellular hyalinization are prominent and confer a pink hue on the tumor on low-power microscopic examination. The nuclear features resemble those seen in classic papillary carcinomas, and psammoma bodies may be present. Hyalinizing trabecular adenomas are well encapsulated, while carcinomas demonstrate capsular and/or vascular invasion.

Clinical Course.

Most papillary carcinomas present as asymptomatic thyroid nodules, but the first manifestation may be a mass in a cervical lymph node. Interestingly, the presence of isolated cervical nodal metastases does not appear to have a significant influence on the generally good prognosis of these lesions. The carcinoma, which is usually a single nodule, moves freely during swallowing and is not distinguishable from a benign nodule. Hoarseness, dysphagia, cough, or dyspnea suggests advanced disease. In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly in the lung.

A variety of diagnostic tests have been employed to help separate benign from malignant thyroid nodules, including radionuclide scanning and fine-needle aspiration. Most papillary lesions are *cold* masses on scintiscans. Improvements in cytologic analysis have made fine-needle aspiration cytology a reliable test for distinguishing between benign and malignant nodules. The nuclear features are often nicely demonstrable in aspirated specimens.

Papillary thyroid cancers have an excellent prognosis, with a 10-year survival rate in excess of 95%. Five per cent to 20% of patients have local or regional recurrences, and 10% to 15% have distant metastases. The prognosis of a patient with papillary thyroid cancers 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 are the second most common form of thyroid cancer, accounting for 10% to 20% of all thyroid cancers. They tend to present in women, and at an older age than do papillary carcinomas, with a peak incidence in the forties and fifties. The incidence of follicular carcinoma is increased in areas of dietary iodine deficiency, suggesting that in some cases, nodular goiter may predispose to the development of the neoplasm. The high frequency of *RAS* mutations in follicular adenomas and carcinomas suggests that the two may be related tumors.

Morphology.

Follicular carcinomas are single nodules that may be well circumscribed or widely infiltrative (Fig. 24-18). Sharply demarcated lesions may be exceedingly difficult to distinguish from follicular adenomas by gross examination. Larger lesions may penetrate the capsule and infiltrate well beyond the thyroid capsule into the adjacent neck. They are gray to tan to pink on cut section and, on occasion, are somewhat translucent when large, colloid-filled follicles are present. Degenerative changes, such as central fibrosis and foci of calcification, are sometimes present.

Microscopically, most follicular carcinomas are composed of fairly uniform cells forming small follicles containing colloid, quite reminiscent of normal thyroid (Fig. 24-19). In other cases, follicular differentiation may be less apparent, and there may be nests

Figure 24-18 Follicular carcinoma. Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage.

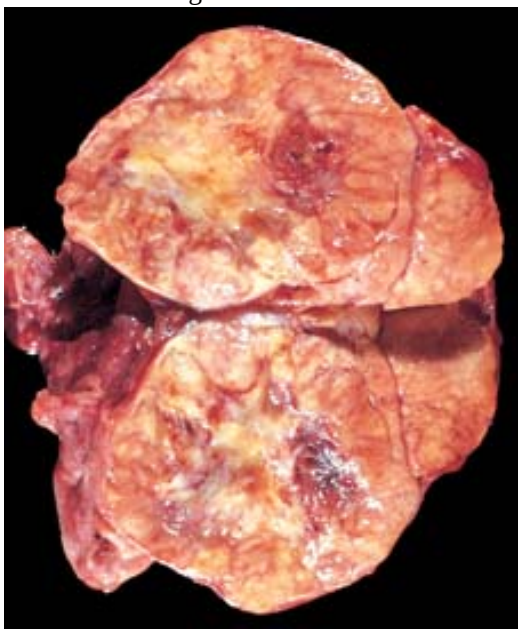


Figure 24-19 Follicular carcinoma of the thyroid. A few of the glandular lumens contain recognizable colloid.

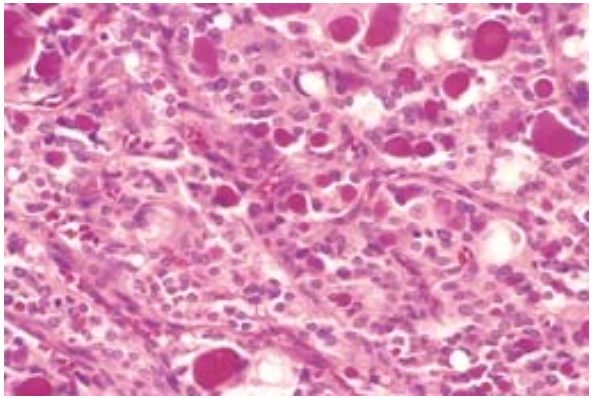


Figure 24-20 Capsular integrity in follicular neoplasms. Evaluating the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas. In adenomas (*A*), a fibrous capsule, usually thin but occasionally more prominent, circumferentially surrounds the neoplastic follicles and no capsular invasion is seen (*arrowheads*); compressed normal thyroid parenchyma is usually present external to the capsule (*top of the panel*). In contrast, follicular carcinomas demonstrate capsular invasion (*B, arrow-heads*) that may be minimal, as in this case, or widespread with extension into local structures of the neck. The presence of vascular invasion is another feature of follicular carcinomas.

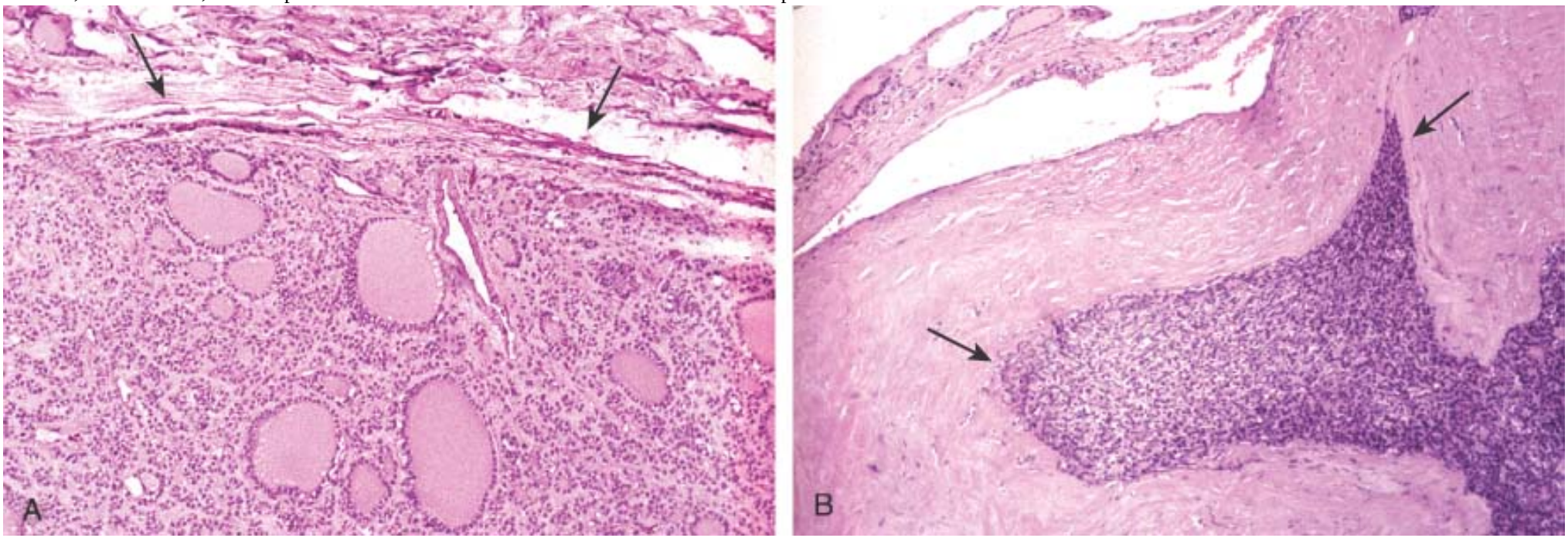


Figure 24-21 Medullary carcinoma of thyroid. These tumors typically show a solid pattern of growth and do not have connective tissue capsules. *(Courtesy of Dr. Joseph Corson, Brigham and Women's Hospital, Boston, MA.)*

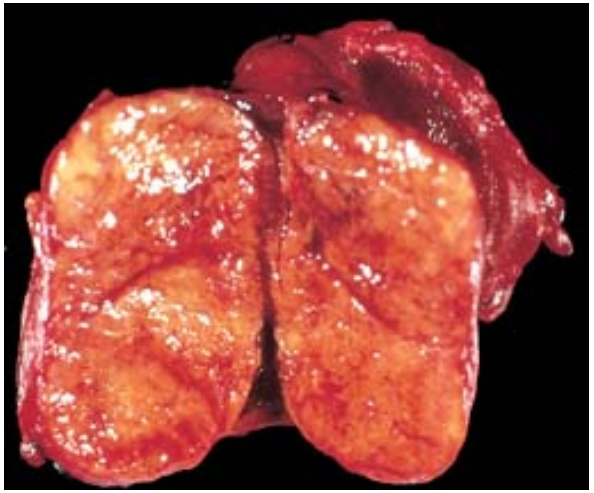


Figure 24-22 Medullary carcinoma of the thyroid. These tumors typically contain amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells.

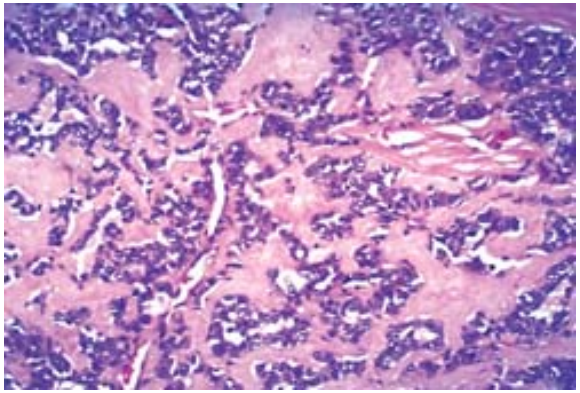


Figure 24-23 Electron micrograph of medullary thyroid carcinoma. These cells contain membrane-bound secretory granules that are the sites of storage of calcitonin and other peptides (30,000X).

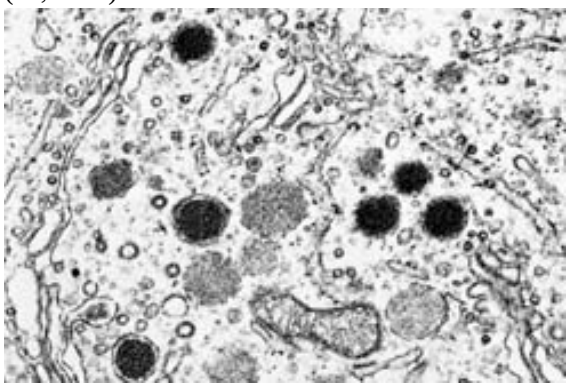


Figure 24-24 Parathyroid adenomas are almost always solitary lesions. Technetium-99m-sestamibi radionuclide scan demonstrates an area of increased uptake corresponding to the left

inferior parathyroid gland *(arrow)*. This patient had a parathyroid adenoma. Preoperative scintigraphy is useful in localizing and distinguishing adenomas from parathyroid hyperplasia, where more than one gland would demonstrate increased uptake.

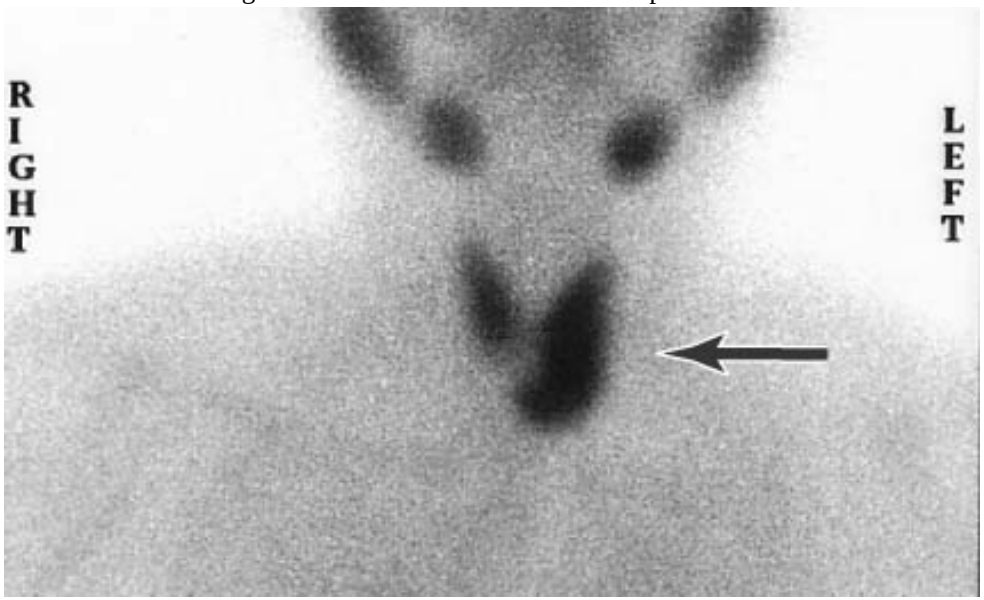


Figure 24-25 Parathyroid adenoma. *A*, Solitary chief cell parathyroid adenoma (low-power photomicrograph) revealing clear delineation from the residual gland below. *B*, High-power detail of a chief cell parathyroid adenoma. There is some slight variation in nuclear size but no anaplasia and some slight tendency to follicular formation.

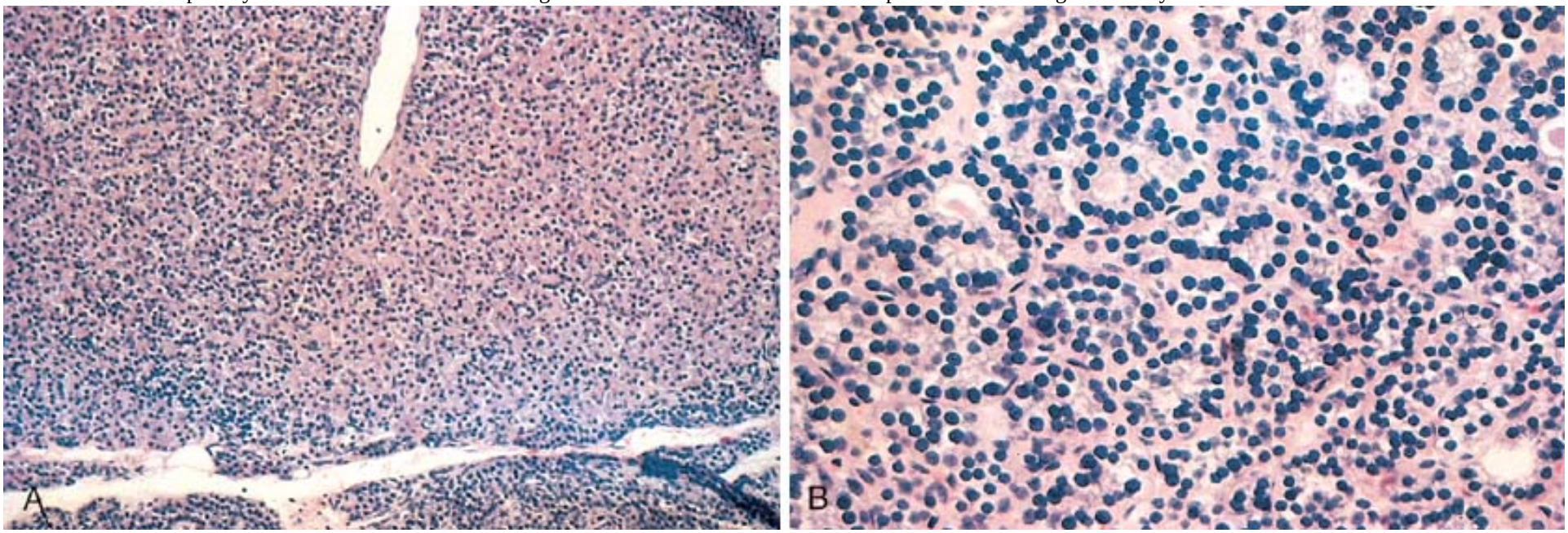


TABLE 24-5 -- Causes of Hypercalcemia

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

PTH-rP, Parathyroid hormone-related protein. RANKL, Receptor activator of nuclear factor κB ligand.

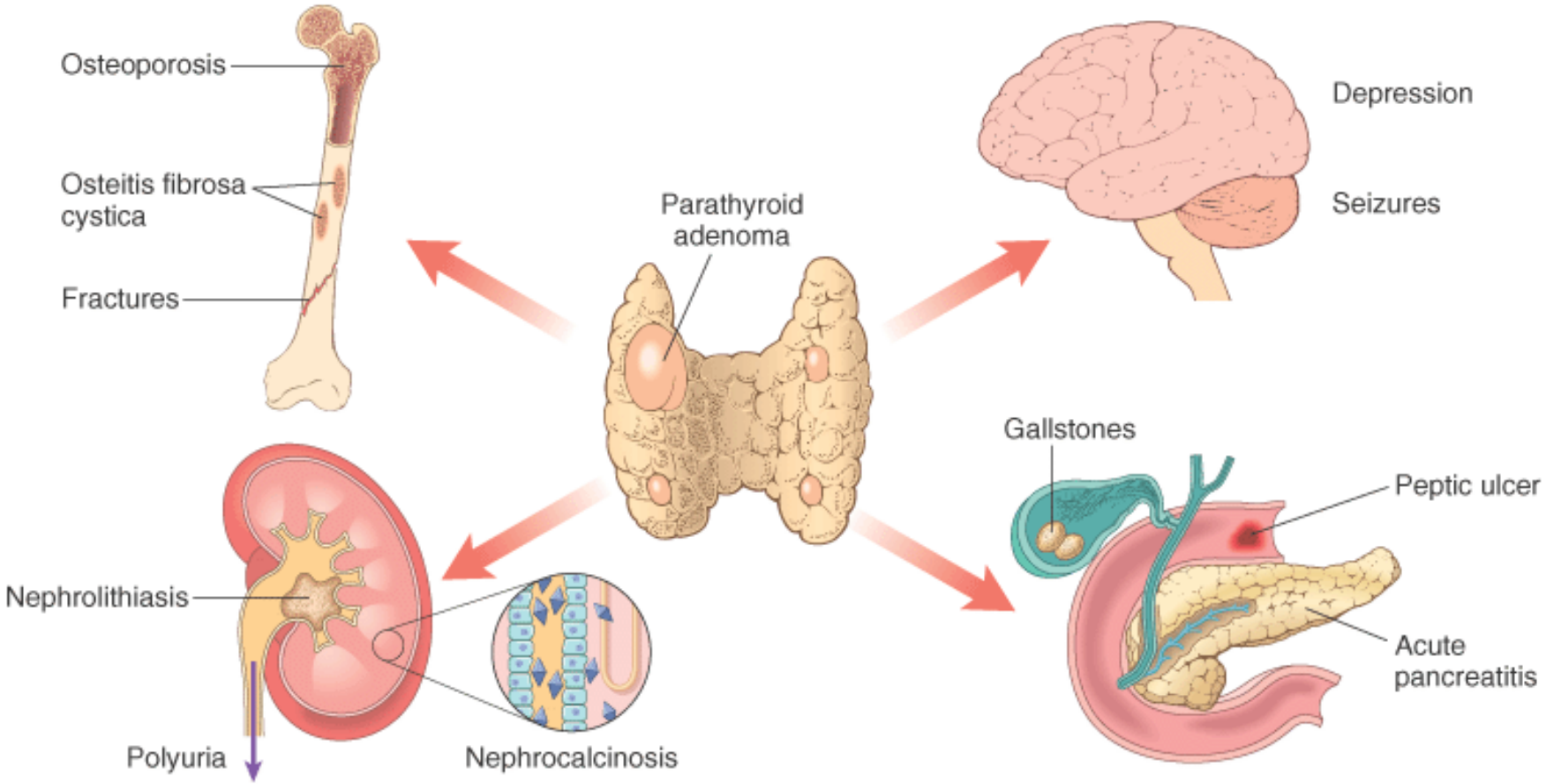
*Primary hyperparathyroidism is the most common cause of hypercalcemia overall. Malignancy is the most common cause of *symptomatic* hypercalcemia. Primary hyperparathyroidism and malignancy account for nearly 90% of cases of hypercalcemia.
†Secondary and tertiary hyperparathyroidism are most commonly associated with progressive renal failure.

In patients with primary hyperparathyroidism, serum PTH levels are inappropriately elevated for the level of serum calcium, whereas PTH levels are low to undetectable in hypercalcemia because of nonparathyroid disease (see Table 24-5). In patients with hypercalcemia caused by secretion of PTHrP by certain nonparathyroid tumors, radioimmunoassays specific for PTH and PTHrP can distinguish between the two molecules. Other laboratory alterations referable to PTH excess include hypophosphatemia and increased urinary excretion of both calcium and phosphate. Secondary renal disease may lead to phosphate retention with normalization of serum phosphates.

Symptomatic Primary Hyperparathyroidism.

The signs and symptoms of hyperparathyroidism reflect the combined effects of increased PTH secretion and hypercalcemia. Primary hyperparathyroidism has been traditionally associated

Figure 24-26 Cardinal features of hyperparathyroidism. With routine evaluation of calcium levels in most patients, primary hyperparathyroidism is often detected at a clinically silent stage. Hypercalcemia from any other cause can also give rise to the same symptoms.



Type 2 diabetes is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β-cells ("relative insulin deficiency"). Approximately 80% to 90% of patients have type 2 diabetes.

A variety of monogenic and secondary causes are responsible for the remaining cases, and these will be discussed later. It should be stressed that while the major types of diabetes have different pathogenic mechanisms, *the long-term complications*

TABLE 24-6 -- Classification of Diabetes Mellitus

•**1. Type 1 diabetes** (β-cell destruction, leads to absolute insulin deficiency)
••••••Immune-mediated
••••••Idiopathic
•**2. Type 2 diabetes** (insulin resistance with relative insulin deficiency)
•**3. Genetic defects of β-cell function**
••••••Maturity-onset diabetes of the young (MODY), caused by mutations in:

•••••••Hepatocyte nuclear factor 4α [HNF-4α] (MODY1)
•••••••Glucokinase (MODY2)
•••••••Hepatocyte nuclear factor 1α [HNF-1α] (MODY3)
•••••••Insulin promoter factor [IPF-1] (MODY4)
•••••••Hepatocyte nuclear factor 1β [HNF-1β] (MODY5)
•••••••Neurogenic differentiation factor 1 [Neuro D1] (MODY6)
••••••Mitochondrial DNA mutations
•4. Genetic defects in insulin processing or insulin action
••••••Defects in proinsulin conversion
••••••Insulin gene mutations
••••••Insulin receptor mutations
•5. Exocrine pancreatic defects
••••••Chronic pancreatitis
••••••Pancreatectomy
••••••Neoplasia
••••••Cystic fibrosis
••••••Hemachromatosis
••••••Fibrocalculous pancreatopathy
•6. Endocrinopathies
••••••Acromegaly
••••••Cushing syndrome
••••••Hyperthyroidism
••••••Pheochromocytoma
••••••Glucagonoma
•7. Infections
••••••Cytomegalovirus
••••••Coxsackie virus B
•8. Drugs
••••••Glucocorticoids

••••••Thyroid hormone
••••••α-interferon
••••••Protease inhibitors
••••••β-adrenergic agonists
••••••Thiazides
••••••Nicotinic acid
••••••Phenytoin
•9. Genetic syndromes associated with diabetes
••••••Down syndrome
••••••Kleinfelter syndrome
••••••Turner syndrome
10. Gestational diabetes mellitus
Data from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetic Care 25 (suppl. 1):S5–S20, 2002.

in kidneys, eyes, nerves, and blood vessels are the same, as are the principal causes of morbidity and death. The pathogenesis of the two major types is discussed separately, but first we briefly review normal insulin secretion and the mechanism of insulin signaling, since these aspects are critical to understanding the pathogenesis of diabetes.

NORMAL INSULIN PHYSIOLOGY

Normal glucose homeostasis is tightly regulated by three interrelated processes: glucose production in the liver; glucose uptake and utilization by peripheral tissues, chiefly skeletal

---

muscle; and actions of insulin and counter-regulatory hormones, including glucagon, on glucose.

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. Following a meal, insulin levels rise and glucagon levels fall in response to the large glucose load. Insulin promotes glucose uptake and utilization in tissues (discussed later). The skeletal muscle is the major insulin-responsive site for postprandial glucose utilization, and is critical for preventing hyperglycemia and maintaining glucose homeostasis.

Regulation of Insulin Release

The insulin gene is expressed in the β cells of the pancreatic islets (Fig. 24-27). Preproinsulin is synthesized in the rough endoplasmic reticulum from insulin mRNA and delivered to the Golgi apparatus. There, a series of proteolytic cleavage steps generate the mature insulin and a cleavage peptide, C-peptide. Both insulin and C-peptide are then stored in secretory granules and secreted in equimolar quantities after physiologic stimulation; increasingly, C-peptide

Figure 24-27 Hormone production in pancreatic islet cells. Immunoperoxidase staining shows a dark reaction product for insulin in β cells (*A*), glucagon in α cells (*B*), and somatostatin in δ cells (*C*). *D*, Electron micrograph of a β cell shows the characteristic membrane-bound granules, each containing a dense, often rectangular core and distinct halo. *E*, Portions of an α cell (*left*) and a δ cell (*right*) also exhibit granules, but with closely apportioned membranes. The α-cell granule exhibits a dense, round center. *(Electron micrographs courtesy of Dr. A. Like, University of Massachusetts Medical School, Worcester, MA.)*

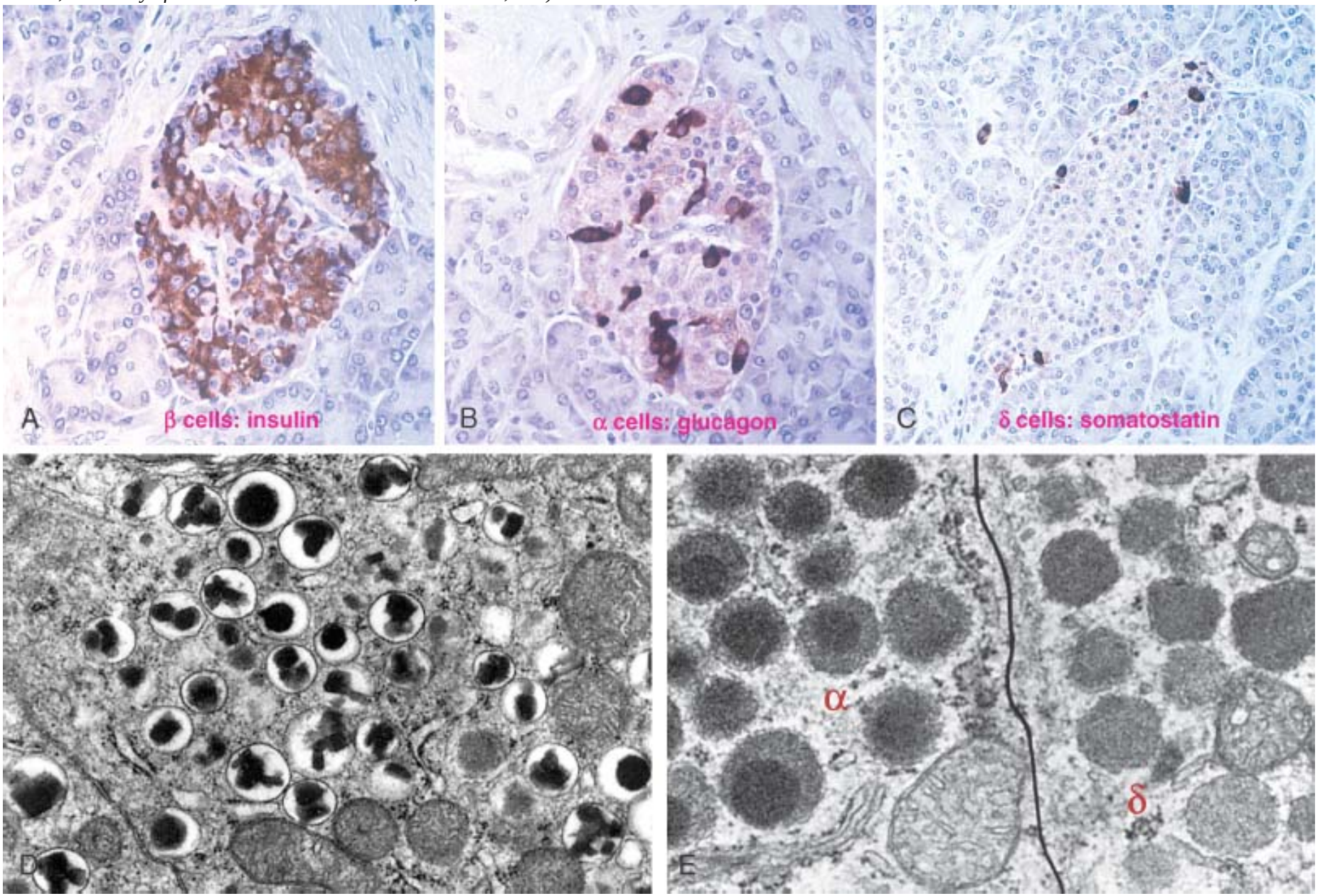


Figure 24-28 Insulin synthesis and secretion. Intracellular transport of glucose is mediated by GLUT-2, an insulin-independent glucose transporter in β cells. Glucose undergoes

oxidative metabolism in the β cell to yield ATP. ATP inhibits an inward rectifying potassium channel receptor on the β-cell surface; the receptor itself is a dimeric complex of the sulfonylurea receptor and a K^+ -channel protein. Inhibition of this receptor leads to membrane depolarization, influx of Ca^{2+} ions, and release of stored insulin from β cells.

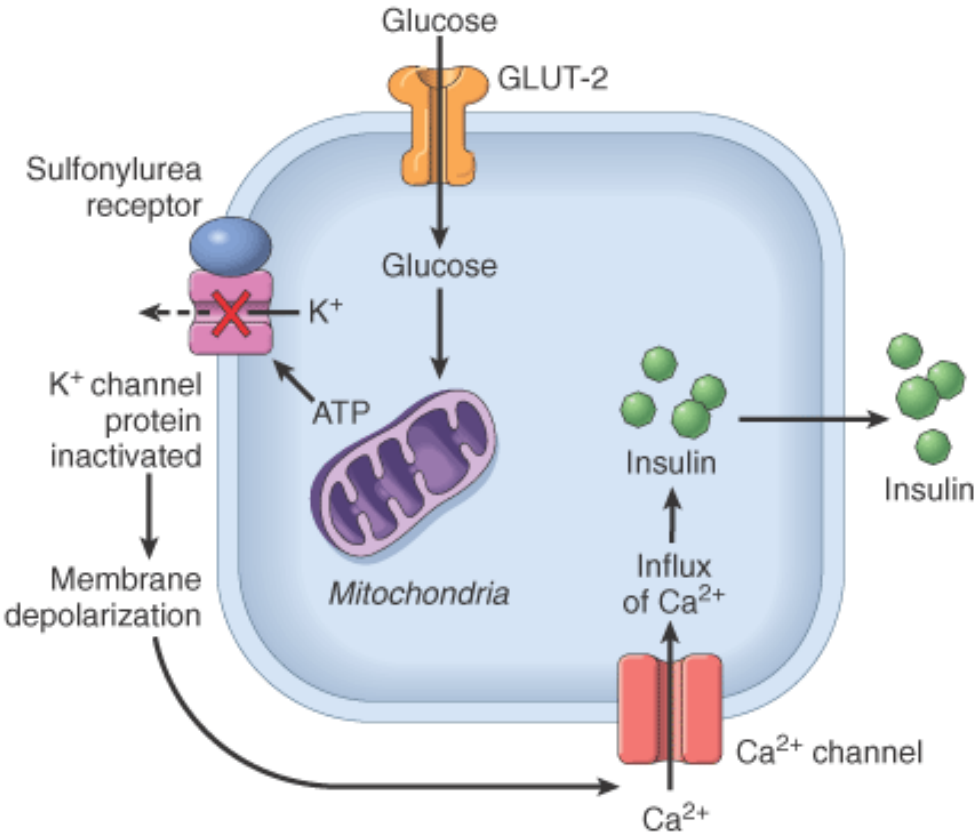


Figure 24-29 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

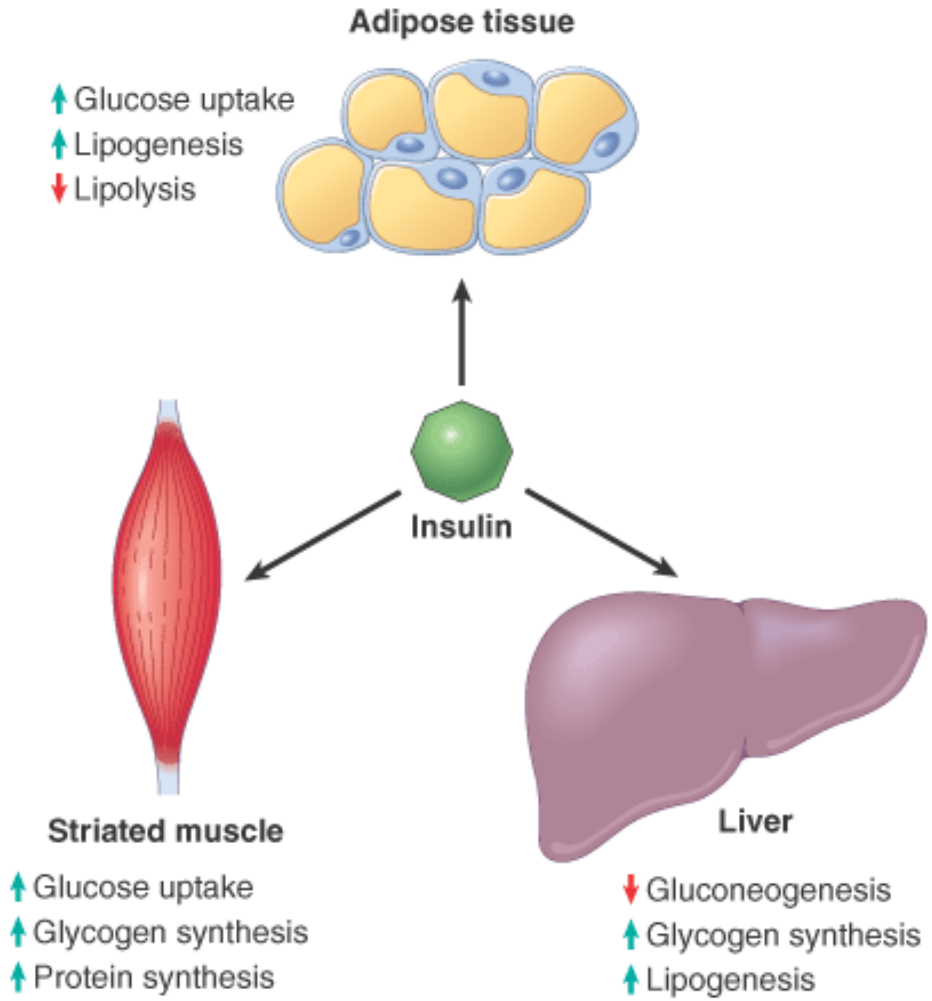


Figure 24-30 Insulin action on a target cell. Insulin binds to the α subunit of insulin receptor, leading to activation of the kinase activity in the β-subunit, and sets in motion a phosphorylation (i.e., activation) cascade of multiple downstream target proteins. The mitogenic functions of insulin (and the related insulin-like growth factors) are mediated via the mitogen-activated protein kinase (MAP kinase) pathway. The metabolic actions of insulin are mediated primarily by activation of the phosphatidylinositol-3-kinase (PI-3K) pathway. The PI-3K-signaling pathway is responsible for a variety of effects on target cells, including translocation of GLUT-4 containing vesicles to the surface; increasing GLUT-4 density on the membrane and rate of glucose influx; promoting glycogen synthesis via activation of glycogen synthase; and promoting protein synthesis and lipogenesis, while inhibiting lipolysis. The PI-3K pathway also promotes cell survival and proliferation.

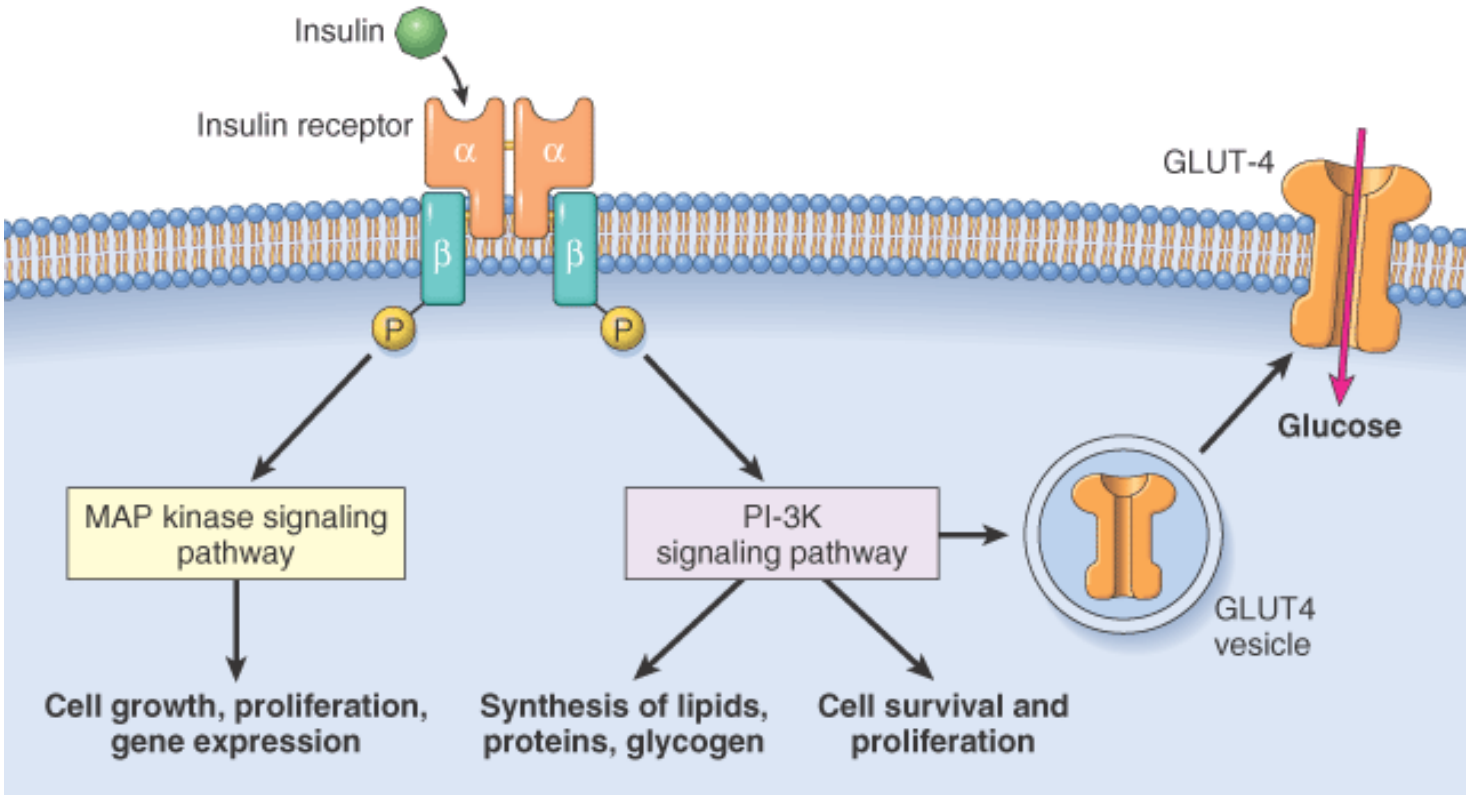


Figure 24-31 Stages in the development of type 1 diabetes mellitus. The stages are listed from left to right, and hypothetical β-cell mass is plotted against age. *(From Eisenbarth GE: Type 1 diabetes: a chronic autoimmune disease. N Engl J Med 314:1360, 1986. Copyright © 1986, Massachusetts Medical Society. All rights reserved.)*

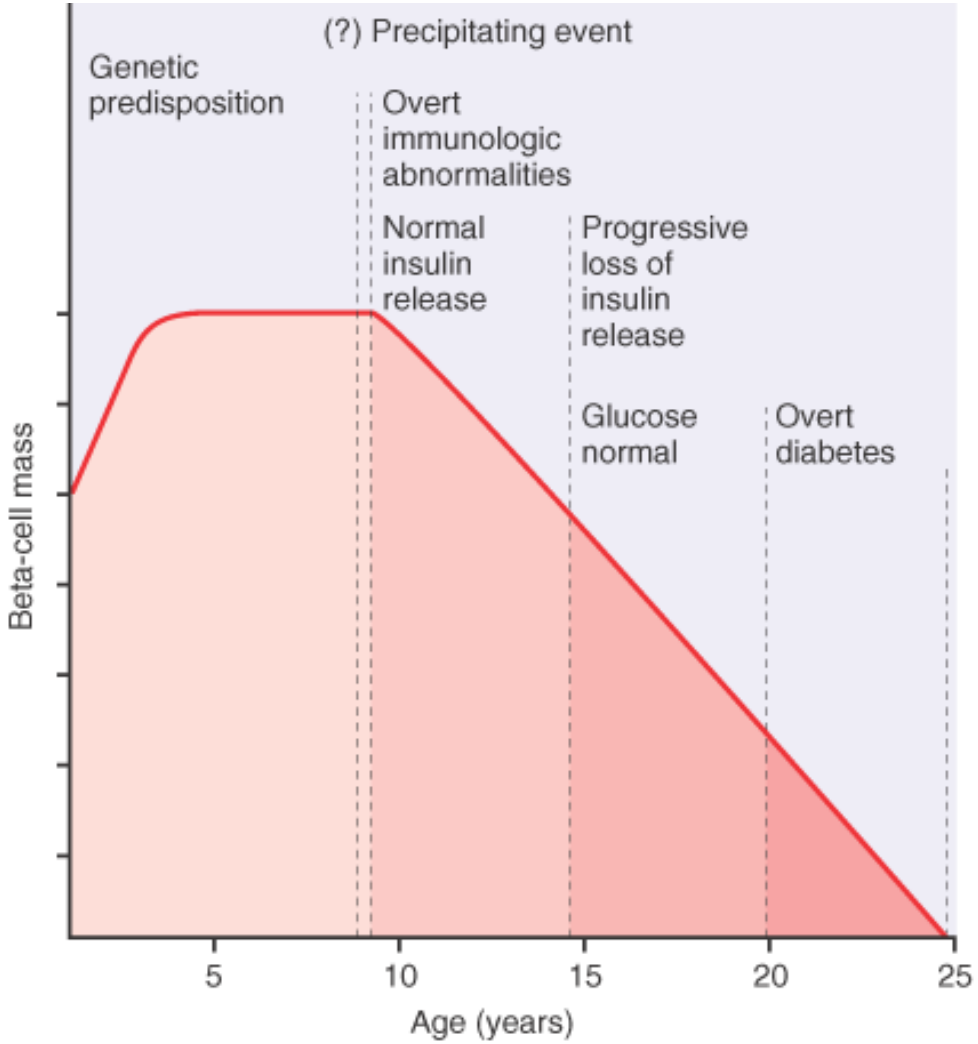


Figure 24-33 Obesity and insulin resistance: the missing links? Adipocytes release a variety of factors (free fatty acids and adipokines) that may play a role in modulating insulin resistance in peripheral tissues (illustrated here is striated muscle). Excess free fatty acids (FFAs) and resistin are associated with insulin resistance; in contrast, adiponectin, whose levels are decreased in obesity, is an insulin-sensitizing adipokine. Leptin is also an insulin-sensitizing agent, but it acts via central receptors (in the hypothalamus). The peroxisome proliferator-activated receptor gamma (PPARγ) is an adipocyte nuclear receptor that is activated by a class of insulin-sensitizing drugs called thiazolidinediones (TZDs). The mechanism of action of TZDs may eventually be mediated through modulation of adipokine and FFA levels that favor a state of insulin sensitivity.

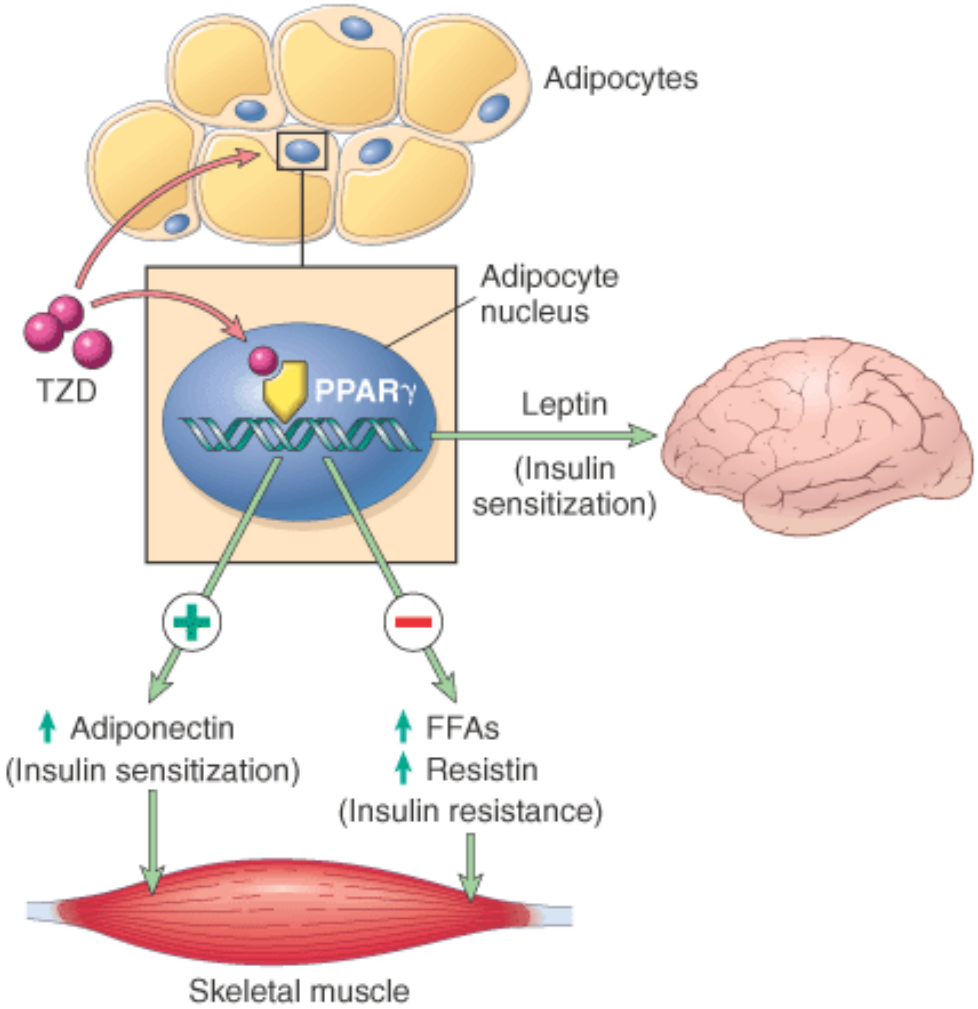


TABLE 24-7 -- Effects of Advanced Glycation End Products (AGEs)

Extracellular Matrix Components
Abnormal matrix-matrix and matrix-cell interactions
Corss-linking of polypeptides of same protein (e.g., collagen)
Trapping of nonglycated proteins (e.g., LDL, albumin)
Resistance to proteolytic digestion
Intracellular and Plasma Proteins
AGE receptor ligation leads to generation of reactive oxygen species and NF-κB activation
Target cells (endothelium, mesangial cells, macrophages) respond by:

••Cytokines and growth factor secretion
••Induction of procoagulant activity
Increased vascular permeability
••Enhanced ECM production
ECM, extracellular matrix; LDL, low-density lipoprotein.

You will recall from the discussion of atherosclerosis (Chapter 11) that *endothelial dysfunction*, particularly endothelial activation, is a critical process in vascular injury and atherogenesis. AGEs, by virtue of their ability to modify extracellular matrix components, as well as to activate NF-κB and its downstream targets in the vascular endothelium, are postulated to play a central role in the accelerated atherogenesis characteristic of diabetes. In addition to large vessel disease, AGEs also contribute to microvascular injury in diabetes. The AGE inhibitor aminoguanidine has recently been shown to retard the progression of nephropathy in type 1 diabetics.

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 the following: [97]

- Production of the proangiogenic molecule vascular endothelial growth factor (VEGF), implicated in the neovascularization characterizing diabetic retinopathy (Chapter 29)
- Increased activity of the vasoconstrictor endothelin-1 and decreased activity of the vasodilator endothelial nitric oxide synthase (eNOS)
- Production of profibrogenic molecules like transforming growth factor-β (TGF-β), leading to increased deposition of extracellular matrix and basement membrane material
- Production of the procoagulant molecule plasminogen activator inhibitor-1 (PAI-1), leading to reduced fibrinolysis and possible vascular occlusive episodes
- Production of pro-inflammatory cytokines by the vascular endothelium.

It should be evident that some effects of AGEs and activated PKCs (e.g., activation of NF-κB) are overlapping. Not surprisingly, therefore, therapeutic inhibition of PKC can retard the progression of diabetic retinopathy. [98]

Intracellular Hyperglycemia with Disturbances in Polyol Pathways.

In some tissues that do not require insulin for glucose transport (e.g., nerves, lenses, 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 this process, intracellular NADPH is used as a cofactor. NADPH is also required as a cofactor by the enzyme glutathione reductase for regenerating reduced glutathione (GSH). You will recall that GSH is one of the important antioxidant mechanisms in the cell (Chapter 1), and a reduction in GSH levels increases cellular susceptibility to oxidative stress. [99] In the face of sustained hyperglycemia, progressive depletion of intracellular NADPH by aldol reductase leads to a compromise of

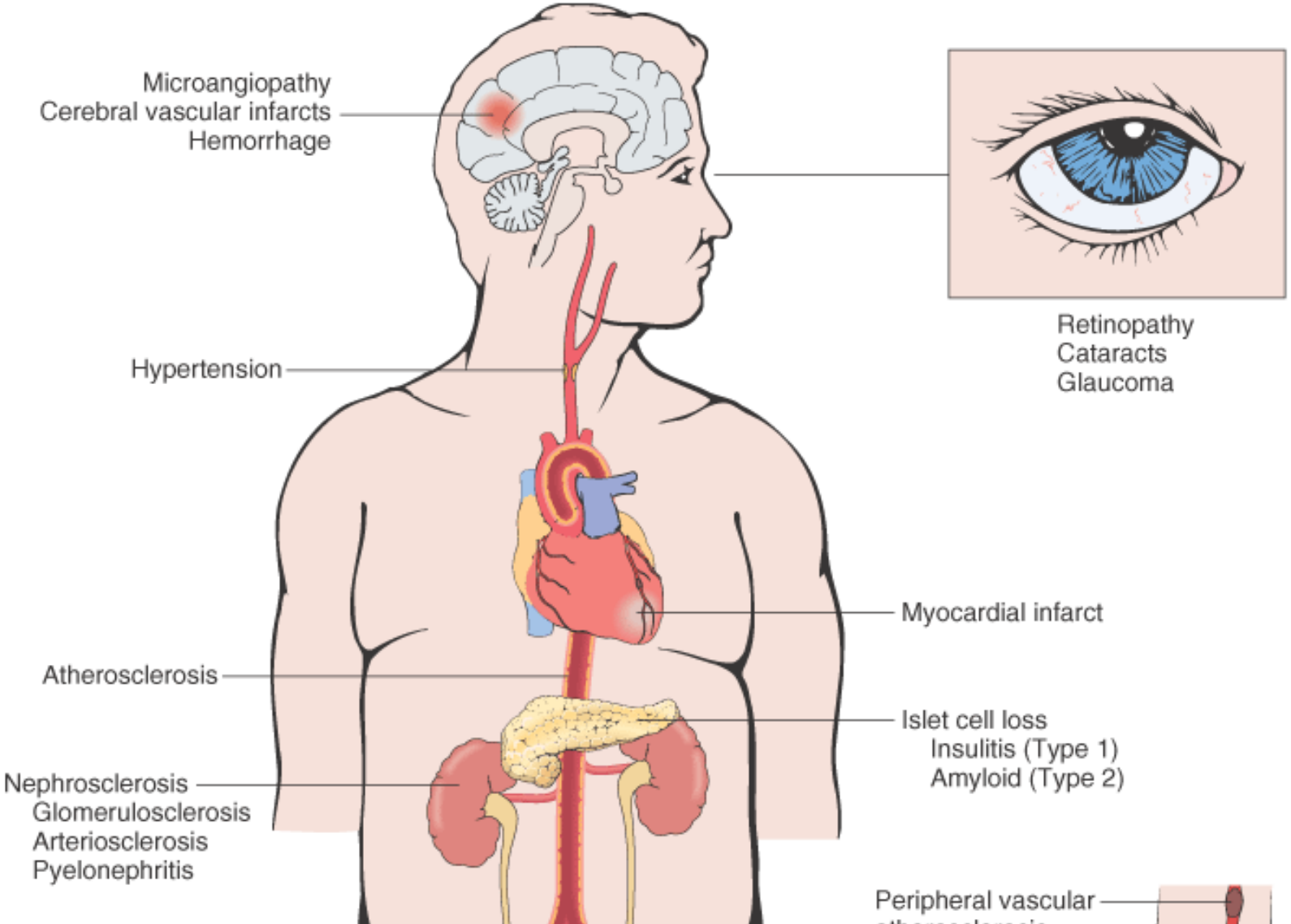
GSH regeneration. Thus, the deleterious consequences of the aldose reductase pathway arise primarily by increasing cellular susceptibility to oxidative stress. The importance of this

pathway in human diabetes was best exemplified in clinical trials using an aldose reductase inhibitor, which significantly ameliorated the development of diabetic neuropathy. Unfortunately, the effects of these inhibitors on other long-term complications have been less promising.

MORPHOLOGY OF DIABETES AND ITS LATE COMPLICATIONS

Pathologic findings in the pancreas are variable and not necessarily dramatic. The important morphologic changes are related to the many late systemic complications of diabetes. There is extreme variability among patients in the time of onset of these complications, their severity, and the particular organ or organs involved. In individuals with tight control of diabetes, the onset might be delayed. In most patients, however, 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

Figure 24-34 Long-term complications of diabetes.



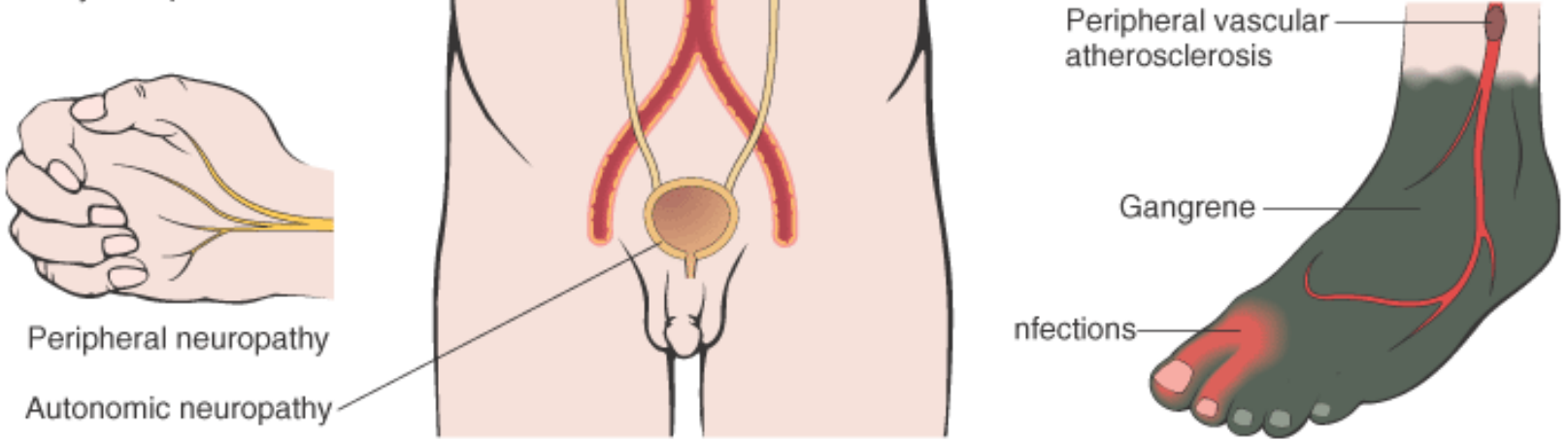


Figure 24-35 *A,* Insulitis, shown here from a rat (BB) model of autoimmune diabetes, also seen in type 1 human diabetes. *(Courtesy of Dr. Arthur Like, University of Massachusetts, Worchester, MA.) B,* Amyloidosis of a pancreatic islet in type 2 diabetes.

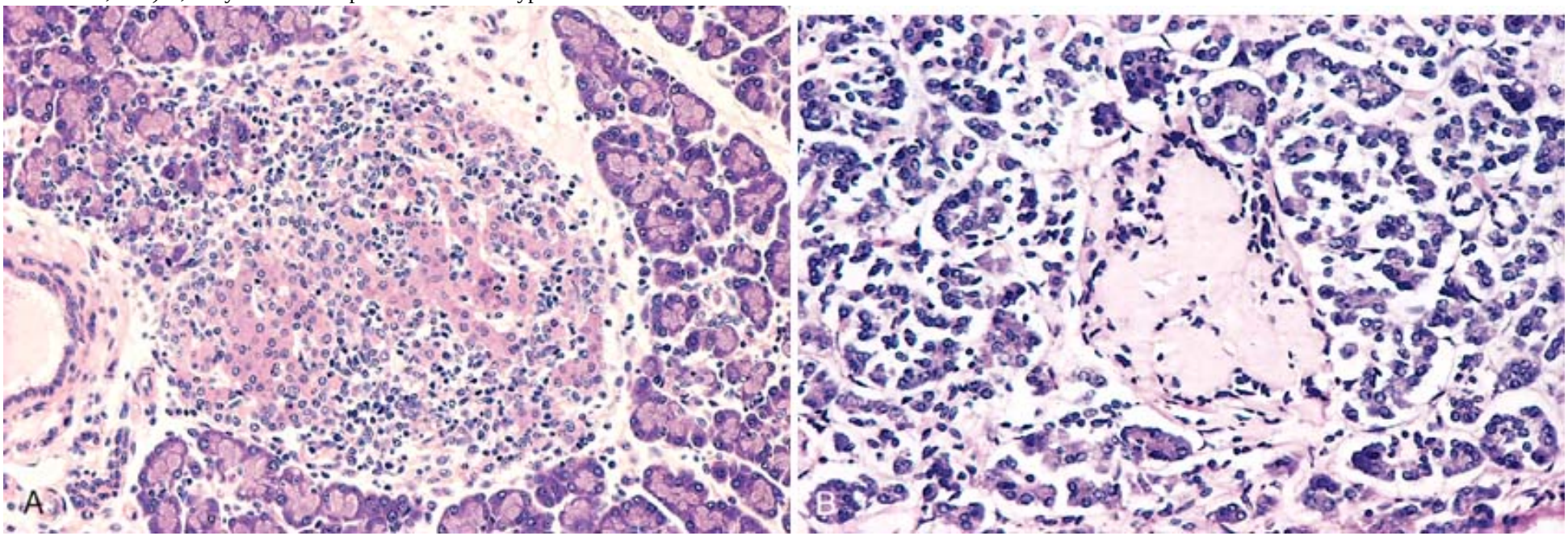


Figure 24-36 Severe renal hyaline arteriolosclerosis. Note a markedly thickened, tortuous afferent arteriole. The amorphous nature of the thickened vascular wall is evident. *(Periodic acid-Schiff [PAS] stain; courtesy of M.A. Venkatachalam, MD, Department of Pathology, University of Texas Health Science Center at San Antonio, TX.)*

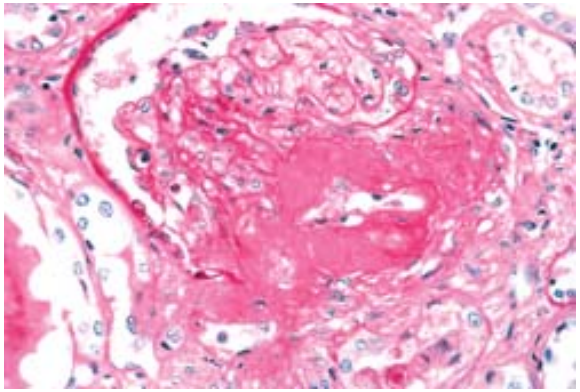


Figure 24-37 Renal cortex showing thickening of tubular basement membranes in a diabetic patient (PAS stain).

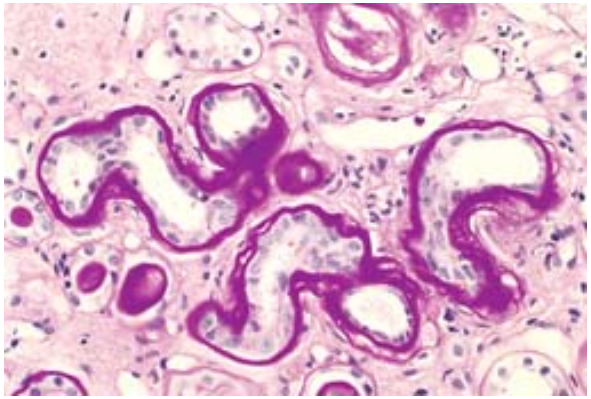


Figure 24-38 Electron micrograph of a renal glomerulus showing markedly thickened glomerular basement membrane (B) in a diabetic. L, glomerular capillary lumen; U, urinary space. *(Courtesy of Dr. Michael Kashgarian, Department of Pathology, Yale University School of Medicine, New Haven, CT.)*

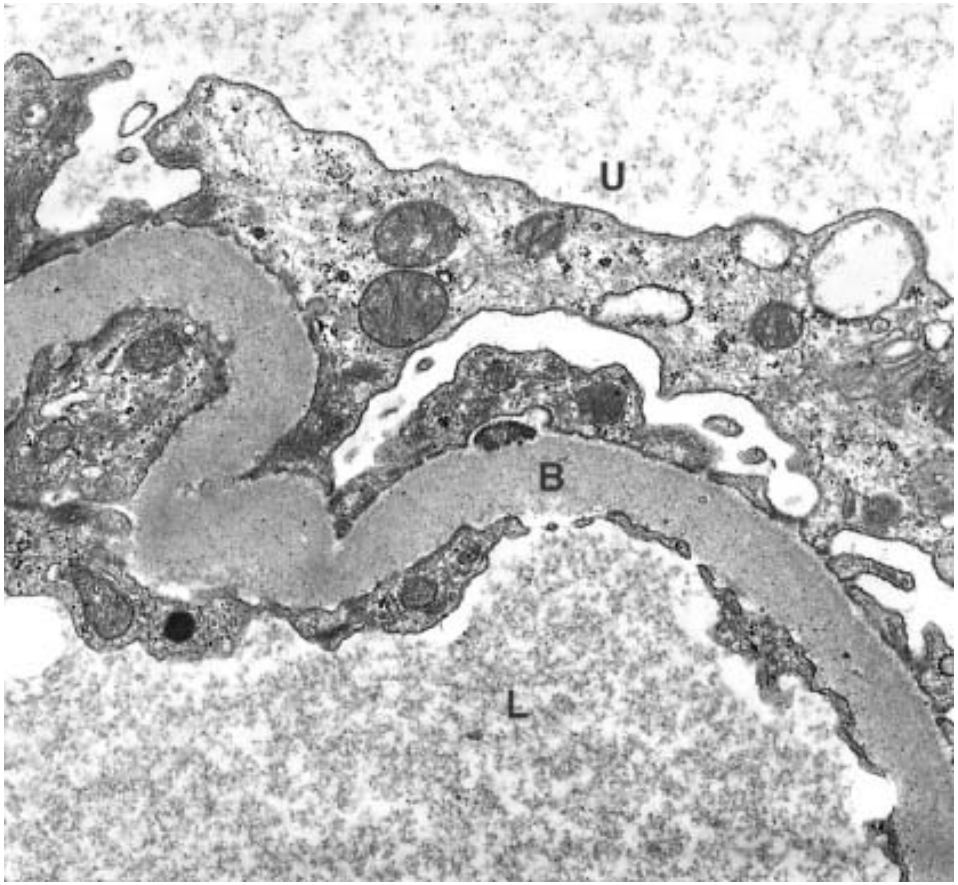


Figure 24-39 Nephrosclerosis in a patient with long-standing diabetes. The kidney has been bisected to demonstrate both diffuse granular transformation of the surface *(left)* and marked thinning of the cortical tissue *(right)*. Additional features include some irregular depressions, the result of pyelonephritis, and an incidental cortical cyst *(far right)*.

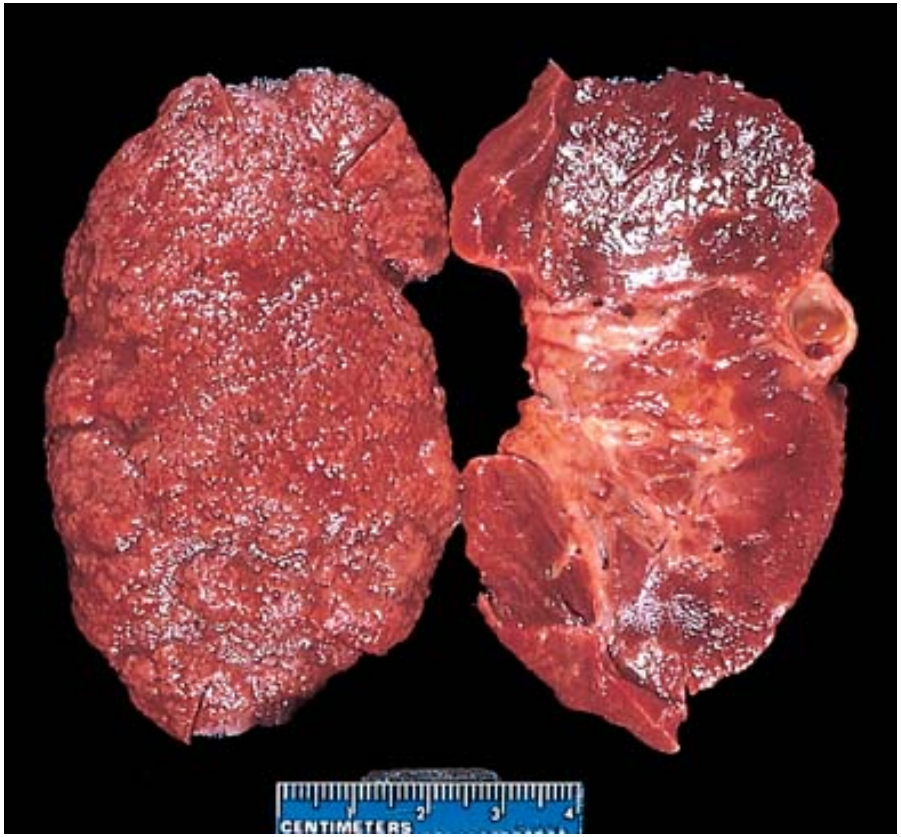
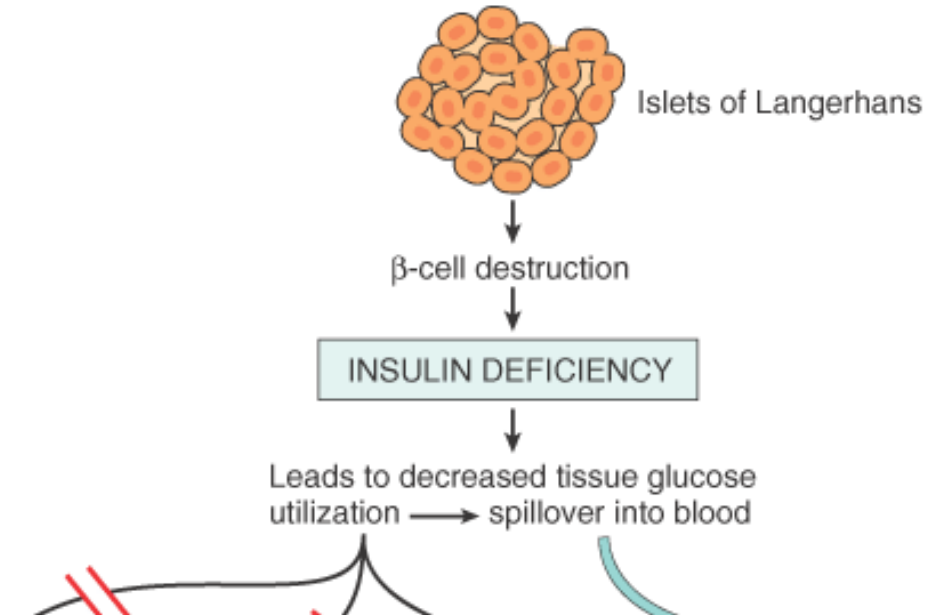
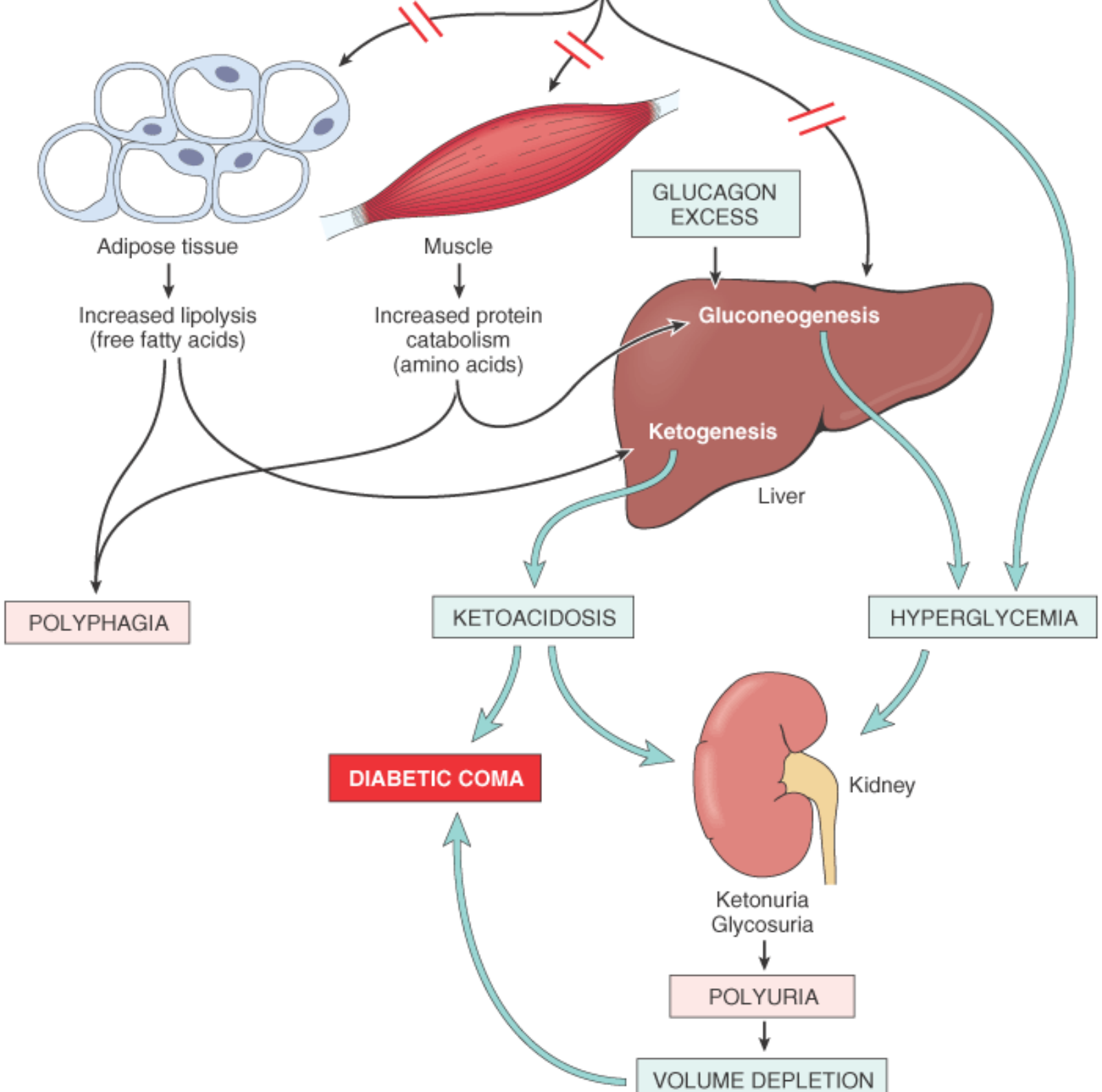


Figure 24-40 Sequence of metabolic derangements leading to diabetic coma in type 1 diabetes mellitus. An absolute insulin deficiency leads to a catabolic state, eventuating in ketoacidosis and severe volume depletion. These cause sufficient central nervous system compromise to lead to coma and eventual death if left untreated.




Adipose tissue
Muscle
GLUCAGON EXCESS
Increased lipolysis (free fatty acids)
Increased protein catabolism (amino acids)
Gluconeogenesis
Ketogenesis
Liver
POLYPHAGIA
KETOACIDOSIS
HYPERGLYCEMIA
DIABETIC COMA
Kidney
Ketonuria
Glycosuria
POLYURIA
VOLUME DEPLETION

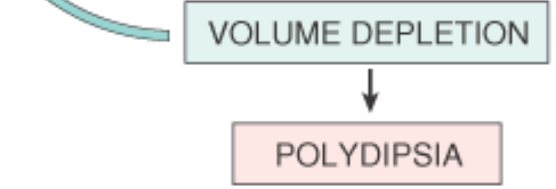


TABLE 24-8 -- Type 1 Versus Type 2 Diabetes Mellitus (DM)

	Type 1 DM	Type 2 DM
Clinical	Onset: <20 years	Onset: >30 years
	Normal weight	Obese
	Markedly decreased blood insulin	Increased blood insulin (early);normal to moderate decreased insulin (late)
	Anti-islet cell antibodies	No anti-islet cell antibodies
	Ketoacidosis common	Ketoacidosis rare; nonketotic hyperosmolar coma
Genetics	30–70% concordance in twins	50–90% concordance in twins
	Linkage to MHC Class II HLA genes	No HLA linkage
		Linkage to candidate diabetogenic genes (PPARγ, calpain 10)
Pathogenesis	Autoimmune destruction of β-cells mediated by T cells and humoral mediators (TNF, IL-1, NO)	Insulin resistance in skeletal muscle, adipose tissue and liver
		β-cell dysfunction and relative insulin deficiency
	Absolute insulin deficiency	
Islet cells	Insulitis early	No insulitis
	Marked atrophy and fibrosis	Focal atrophy and amyloid deposition
	β-cell depletion	Mild β-cell depletion

pertinent clinical, genetic, and histopathologic features that distinguish type 1 and type 2 diabetes.

In both forms, it is the long-term effects of diabetes, more than the acute metabolic complications, that are responsible for the overwhelming proportion of morbidity and mortality. In most instances, these complications appear approximately 15 to 20 years after the onset of hyperglycemia. *Cardiovascular events such as myocardial infarction, renal vascular insufficiency, and cerebrovascular accidents are the most common causes of mortality in long-standing diabetics.* The impact of cardiovascular disease can be gauged from the fact that it accounts for up to 80% of deaths in type 2 diabetes; in fact, diabetics have a 3 to 7.5 times greater incidence of death from cardiovascular causes compared to the nondiabetic population[100] (Fig. 24-41). The hallmark of cardiovascular disease is *accelerated atherosclerosis* of the large and medium-sized arteries (i.e., macrovascular disease). *The pathogenesis of accelerated atherosclerosis involves multiple factors.* We have previously

Figure 24-41 Incidence of death from cardiovascular causes in diabetic and nondiabetic individuals after a 7-year follow up. MI, myocardial infarction. *(Reproduced with permission from Haffner et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. N Engl J Med 339:229,*

1998.)

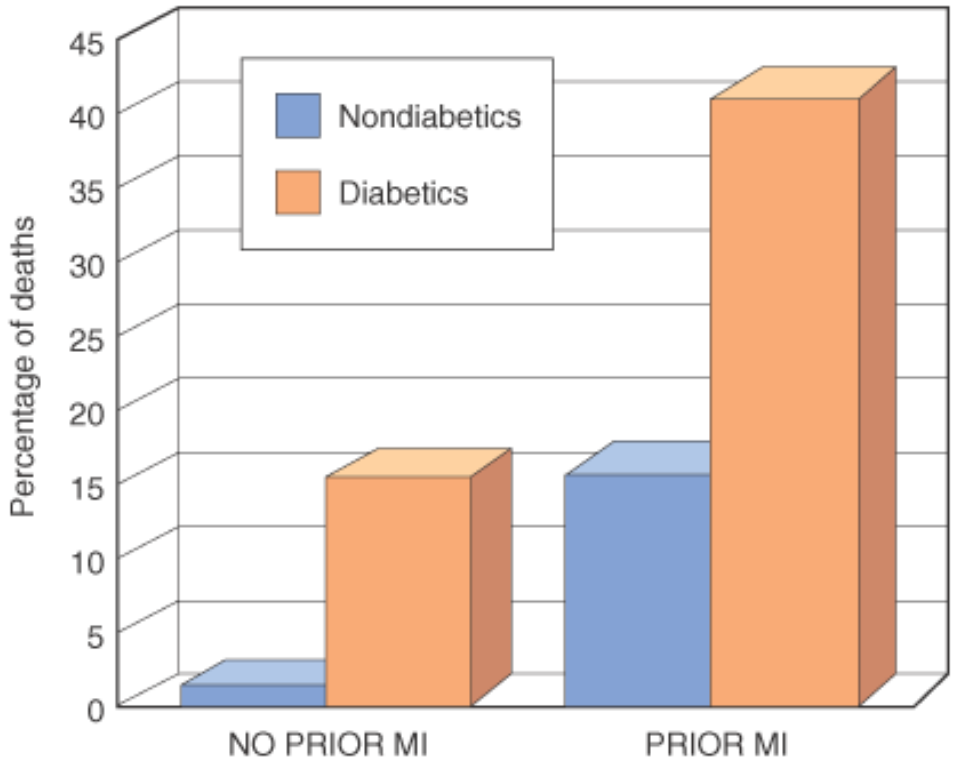


Figure 24-42 Pancreatic endocrine tumor ("islet cell tumor"). *A*, The neoplastic cells are monotonous and demonstrate minimal pleomorphism or mitotic activity (H & E stain). *B*, Immunoreactivity for insulin confirms the neoplasm is an insulinoma. Clinically, the patient had episodic hypoglycemia.

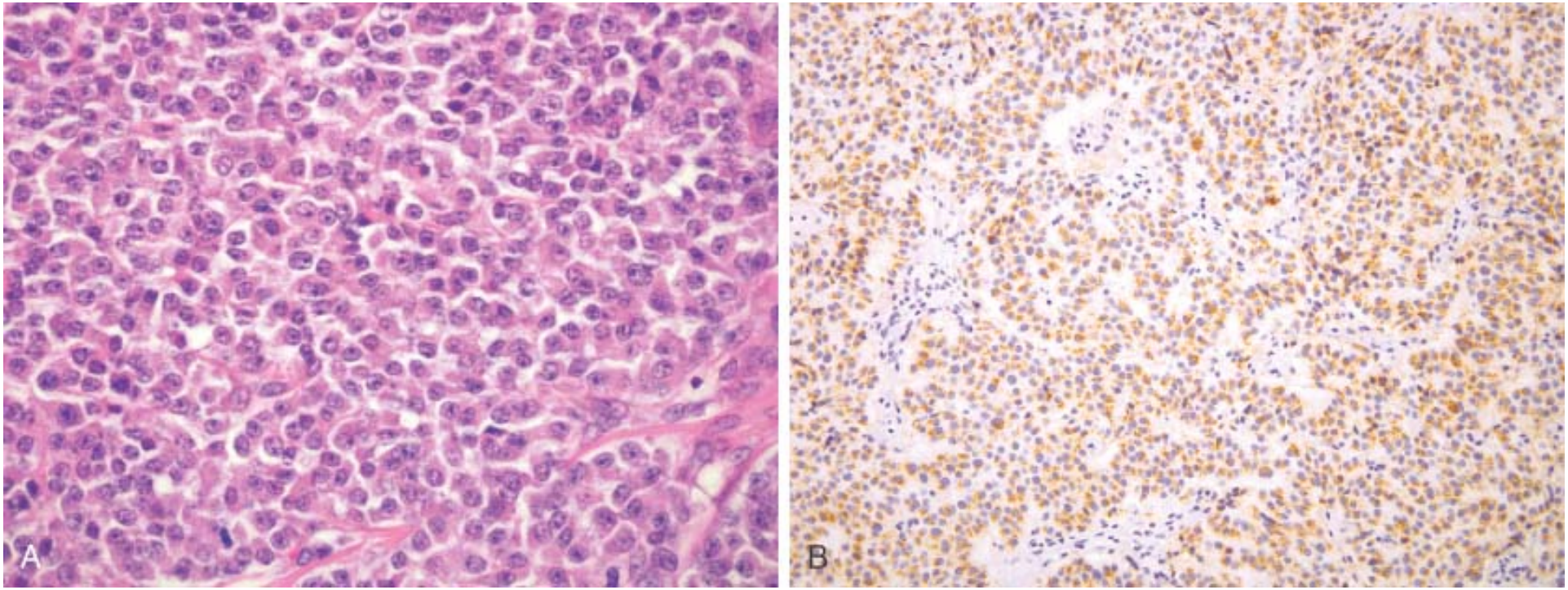


Figure 24-43 A schematic representation of the various forms of Cushing syndrome, illustrating the three endogenous forms as well as the more common exogenous (iatrogenic) form. ACTH, adrenocorticotropic hormone.

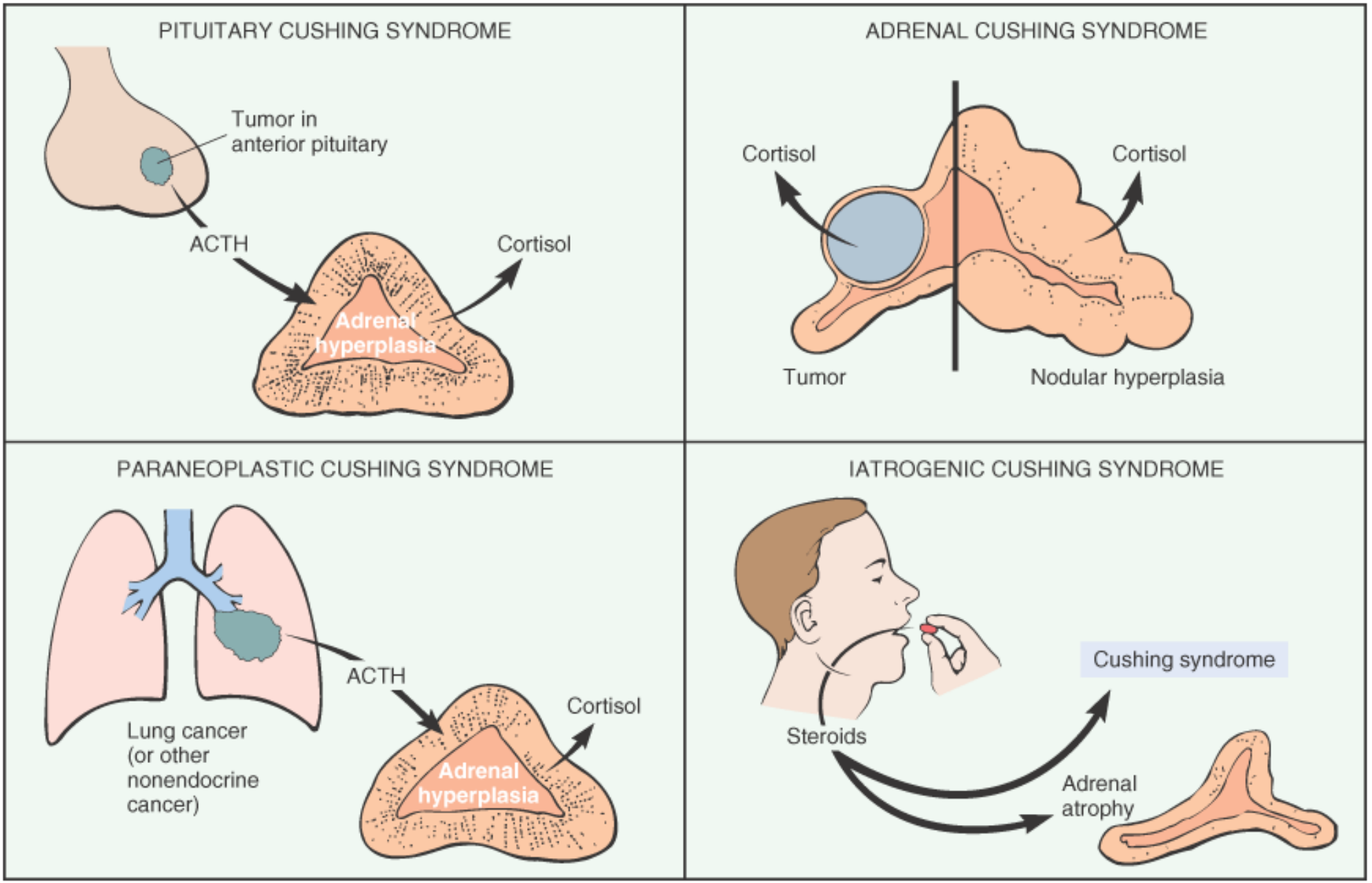


TABLE 24-9 -- Major Features of Cushing Syndrome with Approximate Frequency

Clinical Features	Percentages
Central obesity (about trunk and upper back)	85–90%

Moon facies	85%
Weakness and fatigability	85%
Hirsutism	75%
Hypertension	75%
Plethora	75%
Glucose intolerance/diabetes	75/20%
Osteoporosis	75%
Neuropsychiatric abnormalities	75–80%
Menstrual abnormalities	70%
Skin striae (sides of lower abdomen)	50%

because glucocorticoids suppress the immune response. Additional manifestations include a number of *mental disturbances*, including mood swings, depression, and frank psychosis, as well as *hirsutism* and *menstrual abnormalities*.

Cushing syndrome is diagnosed in the laboratory with the following: (1) the 24-hour urine free cortisol level, which is increased, and (2) loss of normal diurnal pattern of cortisol secretion. Determining the cause of Cushing syndrome depends on the level of serum ACTH and measurement of urinary steroid excretion after administration of dexamethasone. Three general patterns can be obtained:[111]

1. In pituitary Cushing syndrome, the most common form, ACTH levels are elevated and cannot be suppressed by the administration of a low dose of dexamethasone. Hence, there is no reduction in urinary excretion of 17-hydroxy-corticosteroids. After higher doses of injected dexamethasone, however, the pituitary responds by reducing ACTH secretion, which is reflected by suppression of urinary steroid secretion.
2. Ectopic ACTH secretion results in an elevated level of ACTH, but its secretion is completely insensitive to low or high doses of exogenous dexamethasone.
3. When Cushing syndrome is caused by an adrenal tumor, the ACTH level is quite low because of feedback inhibition of the pituitary. As with ectopic ACTH secretion, both low-dose and high-dose dexamethasone fail to suppress cortisol excretion.

Primary Hyperaldosteronism

Hyperaldosteronism is the generic term for a small group of closely related, uncommon syndromes, all characterized by chronic excess aldosterone secretion. *Excessive levels of aldosterone cause sodium retention and potassium excretion, with resultant hypertension and hypokalemia.* Hyperaldosteronism may be primary, or it may be a secondary event resulting from an extra-adrenal cause.

Primary hyperaldosteronism indicates an autonomous overproduction of aldosterone, with resultant suppression of the renin-angiotensin system and decreased plasma renin activity. Primary hyperaldosteronism is caused by one of three mechanisms[115] (Fig. 24-44):

• *Adrenocortical neoplasm*, either an aldosterone-producing adrenocortical adenoma (the most common cause) or, rarely, an adrenocortical carcinoma. In approximately 80% of cases, primary hyperaldosteronism is caused by a solitary aldosterone-secreting adenoma, a condition referred to as *Conn syndrome*. This syndrome occurs most frequently in adult middle life and is more common in women than in men (2:1). Multiple adenomas may be present in an occasional patient.
• *Primary adrenocortical hyperplasia (idiopathic hyperaldosteronism)*, characterized by bilateral nodular hyperplasia of the adrenal glands, highly reminiscent of those found in the nodular hyperplasia of Cushing syndrome. The genetic basis of idiopathic hyperaldosteronism is not clear, although it is possibly caused by an overactivity of the aldosterone synthase gene, *CYP11B2*. [116]
• *Glucocorticoid-remediable hyperaldosteronism* is an uncommon cause of primary hyperaldosteronism that is familial and genetic. In some families, it is caused by a chimeric gene resulting from fusion between *CYP11B1* (the 11β-hydroxylase gene) and *CYP11B2* (the aldosterone synthase gene).[117] This leads to a sustained production of hybrid steroids in addition to both cortisol and aldosterone. The activation of aldosterone secretion is under the influence of ACTH and hence is suppressible by exogenous administration of dexamethasone.

In *secondary hyperaldosteronism*, in contrast, aldosterone release occurs in response to activation of the renin-angiotensin system (Chapter 4). It is characterized by increased levels of plasma renin and is encountered in conditions such as the following:

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

Morphology.

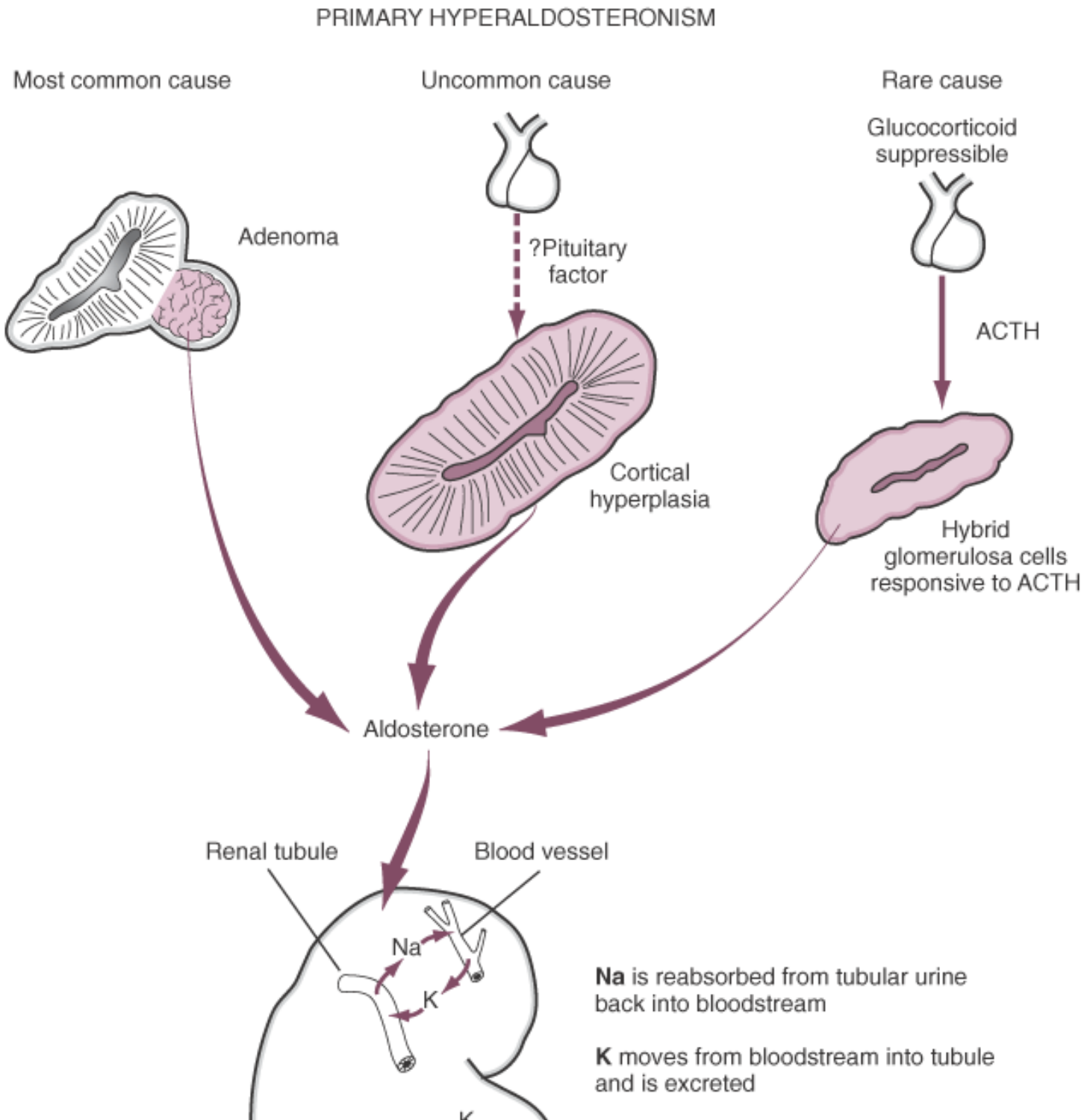
Aldosterone-producing adenomas are almost always solitary, small (<2 cm in diameter), well-circumscribed lesions, more often found on the left than on the right. They tend to occur in the thirties and forties, and in women more often than in men. These lesions are often buried within the gland and do not produce visible enlargement, a point to be remembered in interpreting sonographic or scanning images. They are bright yellow on cut section (Fig. 24-45) and, surprisingly, are composed of lipid-laden cortical cells that more closely resemble fasciculata cells than glomerulosa cells (the normal source of aldosterone). In general, the cells tend to be uniform in size and shape and resemble mature cortical cells; occasionally, there is some nuclear and cellular pleomorphism but no evidence of anaplasia (Fig. 24-46). A characteristic feature of aldesterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions, known as **spironolactone bodies**, found after treatment with the anti-hypertensive drug spironolactone. In contrast to 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 (Fig. 24-47) is marked by diffuse and focal hyperplasia of cells resembling those of the normal zona glomerulosa. The hyperplasia is often wedge-shaped, extending from the periphery toward the center of the gland. Bilateral enlargement can be subtle in idiopathic hyperplasia, and as a rule, an adrenocortical adenoma should be carefully excluded as the cause for hyperaldosteronism.

Clinical Course.

The clinical manifestations of primary hyperaldosteronism are hypertension and hypokalemia. Serum renin, as was mentioned previously, is low. Hypokalemia results from renal potassium wasting and can cause a variety of neuromuscular manifestations, including weakness, paresthesias, visual disturbances, and occasionally frank tetany. Sodium retention increases the total body sodium and

Figure 24-44 The major causes of primary hyperaldosteronism and its principal effects on the kidney.



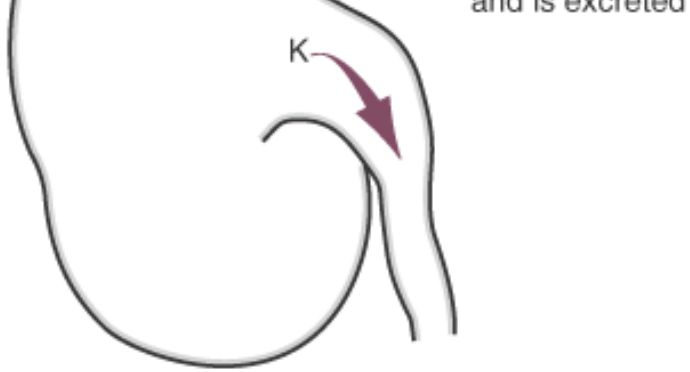


Figure 24-45 Adrenal cortical adenoma. The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature. The functional status of an adrenal cortical adenoma cannot be predicted from its gross or microscopic appearance.

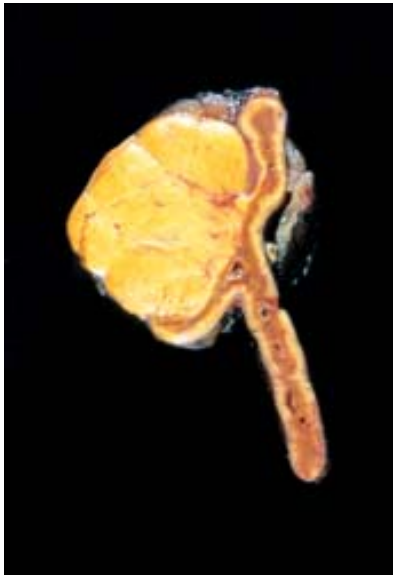


Figure 24-46 Histologic features of an adrenal cortical adenoma. The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid. There is mild nuclear pleomorphism. Mitotic activity and necrosis are not seen.

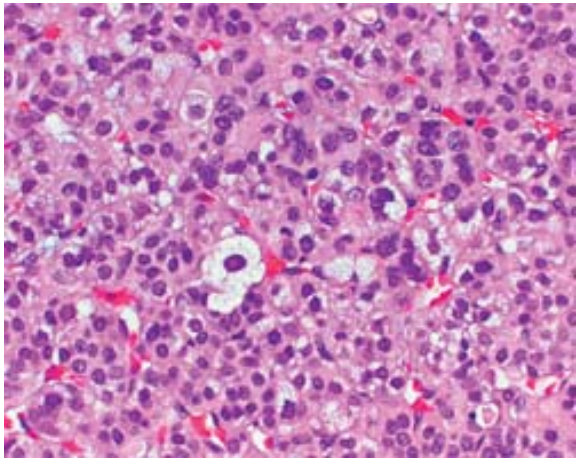


Figure 24-47 Nodular hyperplasia of the adrenal contrasted with normal adrenal gland. In cross-section, the adrenal cortex is yellow, thickened, and multinodular, owing to hypertrophy and hyperplasia of the lipid-rich zonae fasciculata and reticularis.

Figure 24-48 Consequences of C-21 hydroxylase deficiency. 21-Hydroxylase deficiency impairs the synthesis of both cortisol and aldosterone. The resultant decrease in feedback inhibition *(dashed line)* causes increased secretion of adrenocorticotropic hormone, resulting ultimately in adrenal hyperplasia and increased synthesis of testosterone. The sites of action of 11-, 17-, and 21-hydroxylase are shown by the numbers in circles.

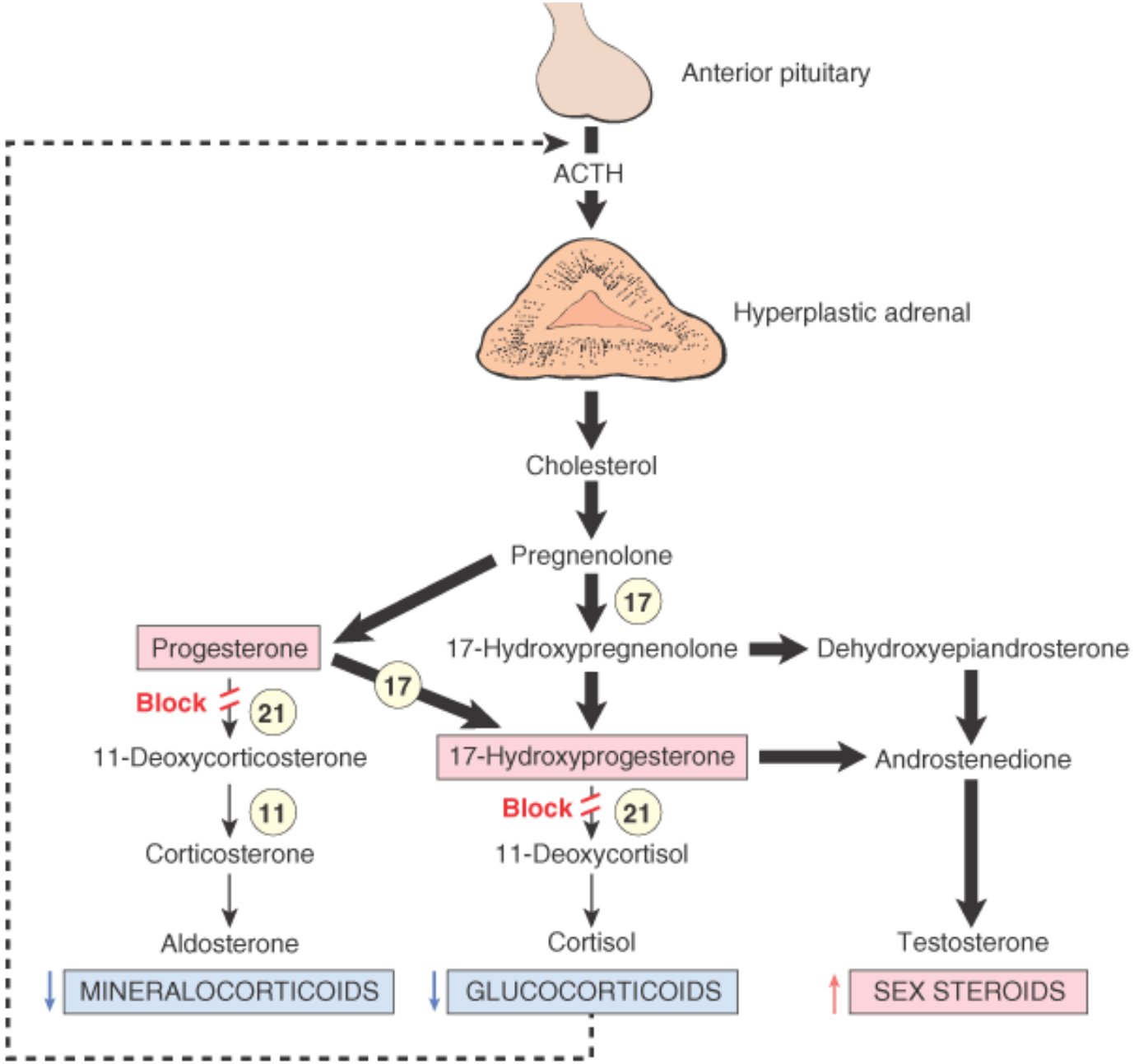


TABLE 24-10 -- Adrenocortical Insufficiency

Primary Insufficiency
Loss of cortex
••Congential adrenal *hypo*plasia
••••X-linked adrenal hypoplasia (*DAX-1* gene on Xp21)
••••"Miniature" type adrenal hypoplasia (unknown cause)
••Adrenoleukodystrophy (*ALD* gene on Xq28)
••Autoimmune adrenal insufficiency
••••Autoimmune polyendocrinopathy syndrome type 1 (*AIRE-1* gene on 21q22)
••••Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
••••Isolated autoimmune adrenalitis (polygenic)
••Infection
••••Acquired immune deficiency syndrome
••••Tuberculosis
••••Fungi
••••Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome)*
••Amyloidosis, sarcoidosis, hemochromatosis
••Metastatic carcinoma
Metabolic failure in hormone production
••Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virlization)
••Drug- and steroid-induced inhibition of adrenocorticotropic hormone or cortical cell function
Secondary Insufficiency
Hypothalamic pituitary disease
••Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)
Hypothalamic pituitary suppression
••Long-term steroid administration
••Steroid-producing neoplasms

Waterhouse-Friderichsen Syndrome

This uncommon but catastrophic syndrome is characterized by the following:

• An overwhelming bacterial infection, which is classically associated with *Neisseria meningitidis* septicemia but occasionally is caused by other highly virulent organisms, such as *Pseudomonas* species, pneumococci, *Haemophilus influenzae*, or staphylococci
• Rapidly progressive hypotension leading to shock
• Disseminated intravascular coagulation with widespread purpura, particularly of the skin

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• Rapidly developing adrenocortical insufficiency associated with massive bilateral adrenal hemorrhage

Figure 24-49 Waterhouse-Friderichsen syndrome in a child. The dark, hemorrhagic adrenal glands are distended with blood.

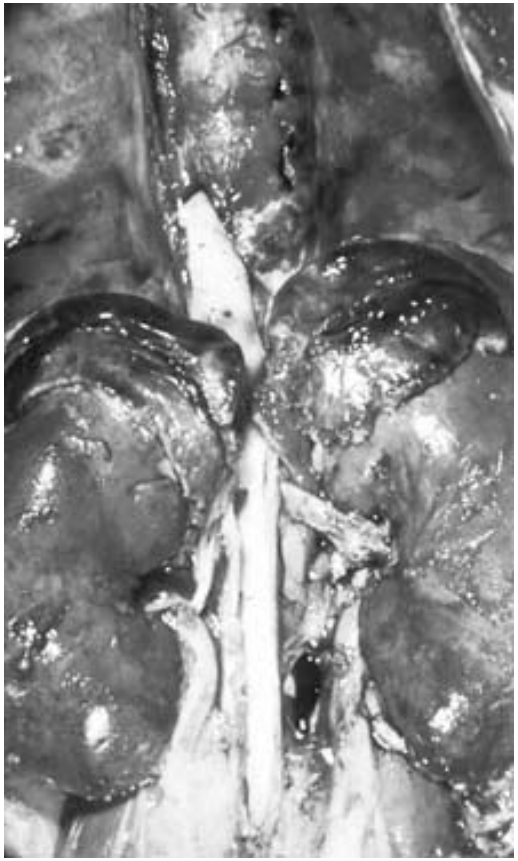

Figure 24-50 Waterhouse-Friderichsen syndrome. At autopsy, the adrenals were grossly hemorrhagic and shrunken; microscopically, little residual cortical architecture is discernible.

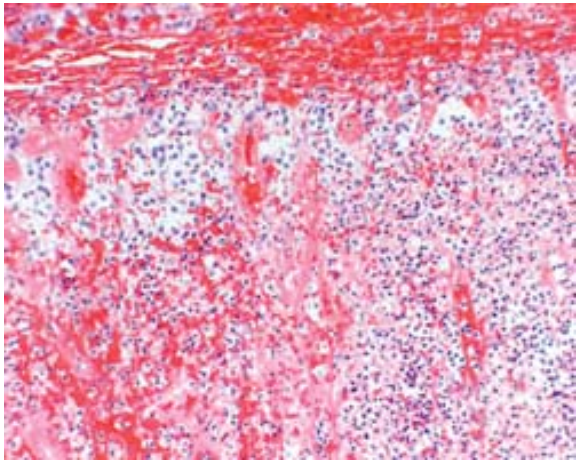

Figure 24-51 Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.

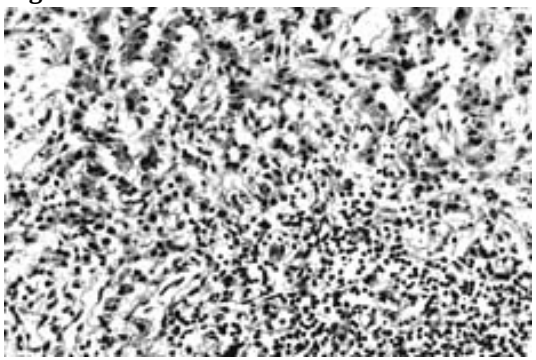

Figure 24-52 Adrenal carcinoma. The hemorrhagic and necrotic tumor dwarfs the kidney and compresses the upper pole.

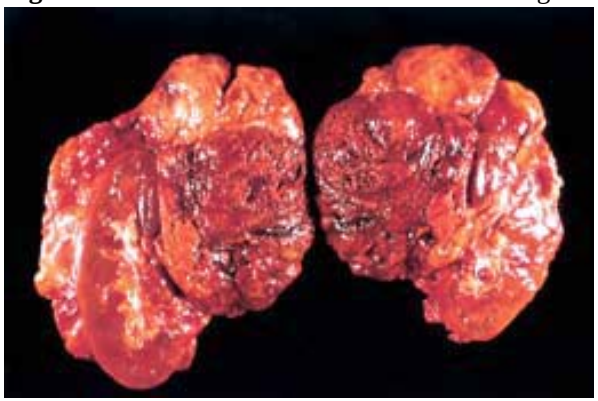

Figure 24-53 Adrenal carcinoma *(A)* revealing marked anaplasia, contrasted with normal cortical cells (*B*).

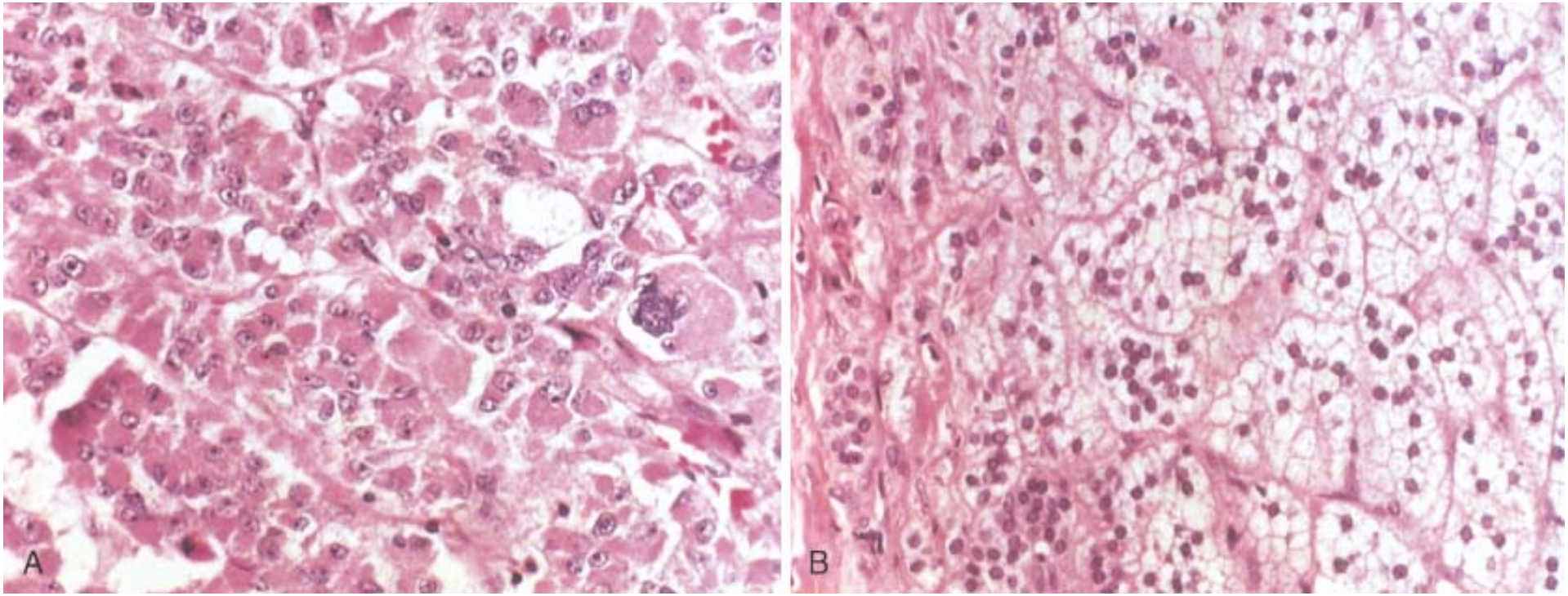

Figure 24-54 The paraganglion system. This schematic representation of the paraganglion system demonstrates sites of paraganglion cell nests, in which neoplasms may form. The extra-adrenal portion of the paraganglion system is grouped into three families based on anatomic distribution, innervation, and microscopic structure: (1) branchiomeric, (2) intravagal, and (3) aorticosympathetic. *(From Whalen RK, et al: Extra-adrenal pheochromocytoma. J Urol 147:1–10, 1992; copyright Williams & Wilkins, 1992.)*

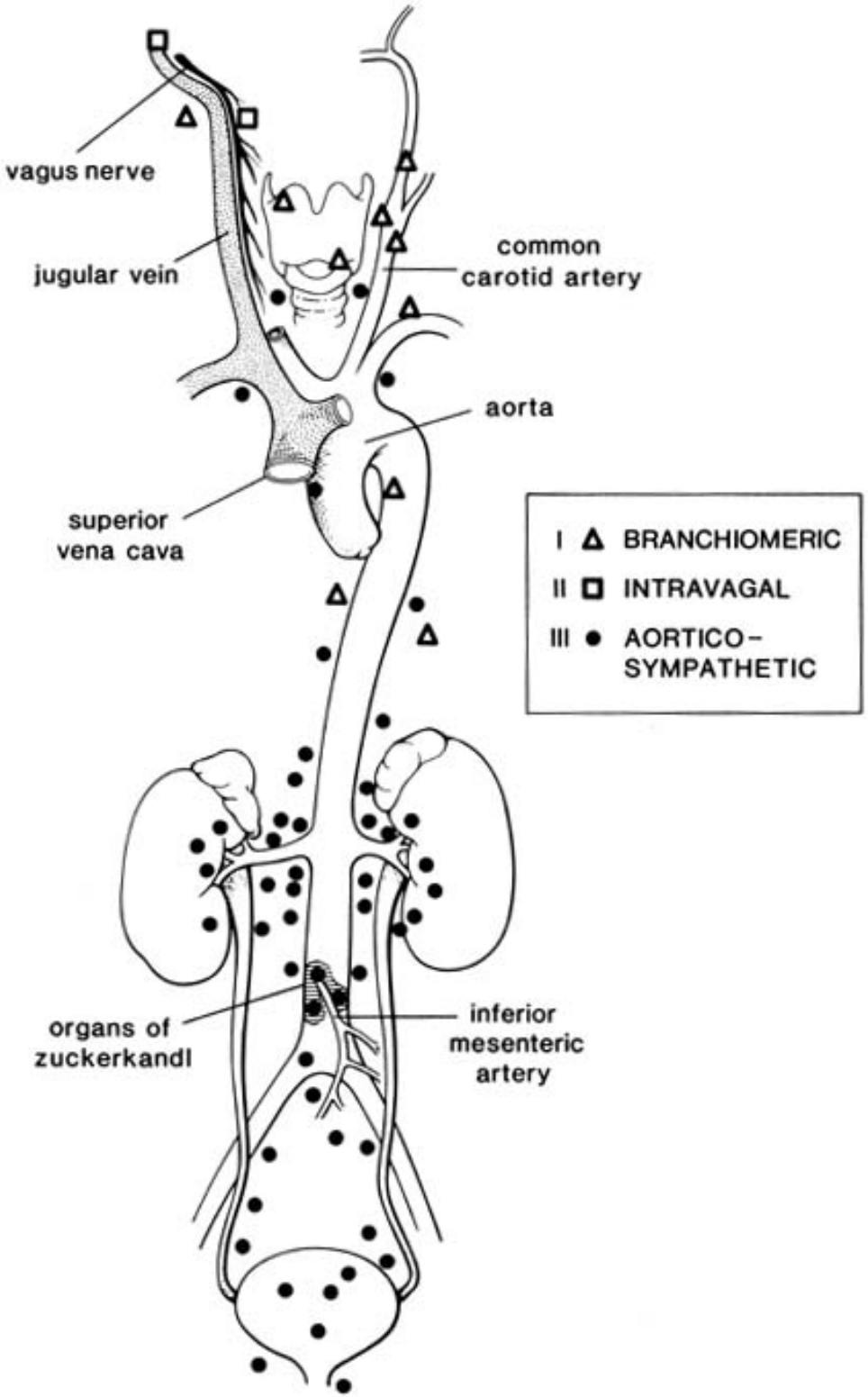
vagus nerve
jugular vein
common
carotid artery
aorta
superior
vena cava
I BRANCHIOMERIC
II INTRAVAGAL
III AORTICO-
SYMPATHETIC
organs of
zuckerkandl
inferior
mesenteric
artery

TABLE 24-11 -- Familial Syndromes Associated with Pheochromocytoma

Syndrome	Components
MEN, type 2A	Medullary thyroid carcinomas and C-cell hyperplasia
	Pheochromocytomas and adrenal medullary hyperplasia
	Parathyroid hyperplasia
MEN, type 2B	Medullary thyroid carcinomas and C-cell hyperplasia
	Pheochromocytomas and adrenal medullary hyperplasia
	Mucosal neuromas
	Marfanoid features
von Hippel-Lindau	Renal, hepatic, pancreatic, and epididymal cysts
	Renal cell carcinomas
	Pheochromocytomas
	Angiomatosis
	Cerebellar hemangioblastomas
von Recklinghausen	Neurofibromatosis
	Café au lait skin spots
	Schwannomas, meningiomas, gliomas
	Pheochromocytomas
Sturge-Weber	Cavernous hemangiomas of fifth cranial nerve distribution
	Pheochromocytomas
MEN, multiple endocrine neoplasia.	
Data from Silverman ML, Lee AK: Anatomy and pathology of the adrenal glands. Urol Clin North Am 16:417, 1989.	

Morphology.

Pheochromocytomas range from small, circumscribed lesions confined to the adrenal (Fig. 24-55) to large hemorrhagic masses weighing kilograms. The average weight of a pheochromocytoma is 100 gm, but variations from just over 1 gm to almost 4000 gm have been reported. The larger tumors are well demarcated by either connective tissue or compressed cortical or medullary tissue. Richly vascularized fibrous trabeculae pass into the tumor and produce a lobular pattern. In many tumors, remnants of the adrenal gland can be seen, stretched over the surface or attached at one pole. On section, the cut surfaces of smaller pheochromocytomas are yellow-tan. Larger lesions tend to be hemorrhagic, necrotic, and cystic and typically efface the adrenal gland. Incubation of fresh tissue with a potassium dichromate solution turns the tumor a dark brown color owing to oxidation of stored catecholamines, thus the term *chromaffin*.

The histologic pattern in pheochromocytoma is quite variable. The tumors are composed of polygonal to spindle-shaped chromaffin cells or chief cells, clustered with the sustentacular cells into small nests or alveoli (**zellballen**) by a rich vascular network (Fig. 24-56). Uncommonly, the dominant cell type is a spindle or small cell; various patterns can be found in any one tumor. The cytoplasm has a finely granular appearance, best demonstrated with silver stains, owing to the appearance of granules containing catecholamines. The nuclei are usually round to ovoid, with a stippled "salt and pepper" chromatin that is characteristic of most neuroendocrine tumors. Electron microscopy reveals variable numbers of membrane-bound, electron-dense granules, representing

Figure 24-55 Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen below.

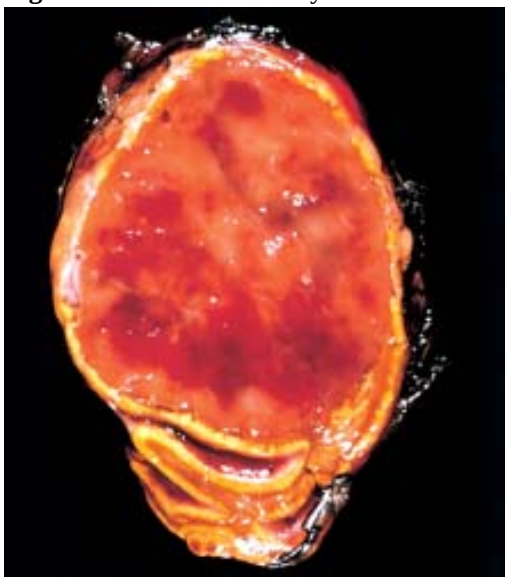

Figure 24-56 Pheochromocytoma demonstrating characteristic nests of cells ("zellballen") with abundant cytoplasm. Granules containing catecholamine are not visible in this preparation. It is not uncommon to find bizarre cells even in pheochromocytomas that are biologically benign, and this criterion by itself should not be used to diagnose malignancy.

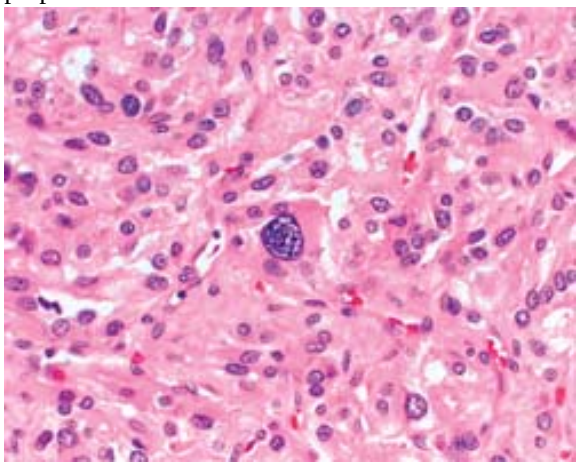

Figure 24-57 Electron micrograph of pheochromocytoma. This tumor contains membrane-bound secretory granules in which catecholamines are stored (30,000X).

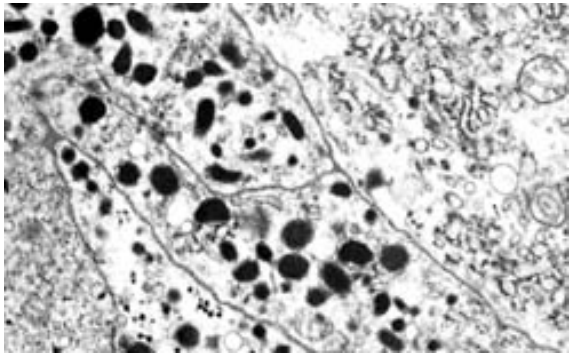

TABLE 24-12 -- Multiple Endocrine Neoplasia (MEN) Syndromes

	MEN-1	MEN-2A	MEN-2B
Pituitary	Adenomas		
Parathyroid	Hyperplasia +++	Hyperplasia +	
	Adenomas +		
Pancreatic islets	Hyperplasia ++		
	Adenomas ++		
	Carcinomas +++		
Adrenal	Cortical hyperplasia	Pheochromocytoma ++	Pheochromocytoma +++
Thyroid		C-cell hyperplasia +++	C-cell hyperplasia +++
		Medullary carcinoma +++	Medullary carcinoma +++
Extraendocrine changes			Mucocutaneous ganglioneuromas
			Marfanoid habitus
Mutant gene locus	*MEN1*	*RET*	*RET*
Relative frequency: +, uncommon; +++, common.			

MEN-1 syndrome is caused by germ-line mutations in the *MEN1* gene at 11q13. This gene encodes a 610-amino acid product known as menin, which localizes primarily to the nucleus. *MEN1* is a classic tumor suppressor gene (Chapter 7) in that both alleles are inactivated in the MEN-1-associated tumors.[131] The precise role of menin in tumor suppression remains elusive, although recent studies have shown that it may be important in regulating the cell cycle and transcription. [132]

The dominant clinical manifestations of MEN-1 are usually defined by the peptide hormones that are overproduced and include such abnormalities as recurrent hypoglycemia due to insulinomas, intractable peptic ulcers in patients with Zollinger-Ellison syndrome, nephrolithiasis caused by PTH-induced hypercalcemia, or symptoms of prolactin excess from a pituitary tumor. As expected, malignant behavior by one or more of the endocrine tumors arising in these patients is often the proximate cause of death.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE 2

MEN-2 is subclassified into three distinct syndromes: MEN-2A, MEN-2B, and familial medullary thyroid cancer.

• *MEN-2A*, or *Sipple syndrome*, is characterized by *pheochromocytoma*, *medullary carcinoma*, and *parathyroid hyperplasia*. Medullary carcinomas of the thyroid occur in almost 100% of patients. They are usually multifocal and are virtually always associated with foci of C-cell hyperplasia in the adjacent thyroid. The medullary carcinomas may elaborate calcitonin and other active products and are usually clinically aggressive. Forty per cent to 50% of patients with MEN-2A have pheochromocytomas, which are often bilateral and may arise in extra-adrenal sites. As in the case of pheochromocytomas in general, they may be benign or malignant. Ten per cent to 20% of patients have parathyroid hyperplasia and evidence of hypercalcemia or renal stones. MEN-2A is clinically and genetically distinct from MEN-1 and has been linked to germ-line mutations in the *RET* (rearranged during transfection) protooncogene on chromosome 10q11.2. As was noted earlier, the *RET* protooncogene is a receptor tyrosine kinase that binds *glialderived neurotrophic factor* (GDNF) and other ligands in the GDNF family and transmits growth and differentiation signals (Chapter 7). *Loss of function* mutations in *RET* result in intestinal aganglionosis and Hirschsprung disease (Chapter 17). In contrast, in MEN-2A (as well as in MEN-2B), germ-line mutations constitutively activate the *RET* receptor, resulting in *gain of function*.[133] This scenario is different from most other inherited predispositions to neoplasia, which are due to heritable loss of function mutations that inactivate tumor-suppressor proteins (Chapter 7).

• *MEN-2B* has significant clinical overlap with MEN-2A. Patients develop medullary thyroid carcinomas, which are usually multifocal and more aggressive than in MEN-2A, and pheochromocytomas. However, unlike in MEN-2A, primary hyperparathyroidism is not present. In addition, MEN-2B is accompanied by *neuromas* or ganglioneuromas involving the skin, oral mucosa, eyes, respiratory tract, and gastrointestinal tract, and a *marfanoid habitus*, with long axial skeletal features and hyperextensible joints. A single amino acid change in *RET* (*RET*^{Met918Thr}), distinct from the

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mutational spectra that are seen in MEN-2A, appears to be responsible for virtually all cases of MEN-2B and affects a critical region of the tyrosine kinase catalytic domain of the protein.[134]

• *Familial medullary thyroid cancer* is a variant of MEN-2A, in which there is a strong predisposition to medullary thyroid cancer but not the other clinical manifestations of MEN-2A or MEN-2B. A substantial majority of cases of medullary thyroid cancer are sporadic, but as many as 20% may be familial. Familial medullary thyroid cancers develop at an older age than those occurring in the full-blown MEN-2 syndrome and follow a more indolent course.

In contrast to MEN-1, in which the long-term benefit of early diagnosis via genetic screening is not well established, diagnosis via screening of at-risk family members in MEN-2A kindred is important because medullary thyroid carcinoma is a life-threatening disease that can be prevented by early thyroidectomy. Prior to the advent of genetic testing, family members 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 kindred; *all individuals carrying germ-line RET mutations are advised to undergo prophylactic thyroidectomy to prevent the inevitable development of medullary carcinomas.*

Pineal Gland

Normal

The rarity of clinically significant lesions (virtually only tumors) justifies brevity in the consideration of the pineal gland. It is a minute, pinecone-shaped organ (hence its name), weighing 100 to 180 mg and lying between the superior colliculi at the base of the brain. It is composed of a loose, neuroglial stroma enclosing nests of epithelial-appearing *pineocytes*, cells with photosensory and neuroendocrine functions (hence the designation of the pineal gland as the "third eye"). Silver impregnation stains reveal that these cells have long, slender processes reminiscent of primitive neuronal precursors intermixed with the processes of astrocytic cells.

Pathology

All tumors involving the pineal are rare; most (50% to 70%) arise from sequestered embryonic germ cells. They most commonly take the form of so-called *germinomas*, resembling testicular seminoma (Chapter 21) or ovarian dysgerminoma (Chapter 22). Other lines of germ cell differentiation include embryonal carcinomas; choriocarcinomas; mixtures of germinoma, embryonal carcinoma, and choriocarcinoma; and, uncommonly, typical teratomas (usually benign). Whether to characterize these germ cell neoplasms as pinealomas is still a subject of debate, but most "pinealophiles" favor restricting the term *pinealoma* to neoplasma arising from the pineocytes.

PINEALOMAS

These neoplasms are divided into two categories, pineoblastomas and pineocytomas, based on their level of differentiation, which, in turn, correlates with their neoplastic aggressiveness. [135]

Morphology.

Pineoblastomas are encountered mostly in the first two decades of life and appear as soft, friable, gray masses punctuated with areas of hemorrhage and necrosis. They typically invade surrounding structures, such as the hypothalamus, midbrain, and lumen of the third ventricle. Histologically, they are composed of masses of pleomorphic cells two to four times the diameter of an erythrocyte. Large hyperchromatic nuclei appear to occupy almost the entire cell, and mitoses are frequent. The cytology is that of **primitive embryonal tumor** ("small blue cell neoplasm") similar to medulloblastoma (Chapter 28) or retinoblastoma (Chapter 29).

Pineoblastomas, like medulloblastomas, tend to spread via the cerebrospinal fluid. As might be expected, the enlarging mass may compress the aqueduct of Sylvius, giving rise to internal hydrocephalus and all its consequences. Survival beyond 1 or 2 years is rare.

In contrast, **pineocytomas** occur mostly in adults and are much slower-growing than pineoblastomas. They tend to be well-circumscribed, gray, or hemorrhagic masses that compress but do not infiltrate surrounding structures. **Histologically, the tumors may be pure pineocytomas or exhibit divergent glial, neuronal, and retinal differentiation.** The tumors are composed largely of pineocytes having darkly staining, round-to-oval, fairly regular nuclei. Necrosis is unusual, and mitoses are virtually absent. The neoplastic cells resemble normal pineocytes in their strong immunoreactivity for neuro-specific enolase and synaptophysin. Particularly distinctive are the **pineocytomatous pseudorosettes** rimmed by rows of pineocytes. The centers of these rosettes are filled with eosinophilic cytoplasmic material representing tumor cell processes. These cells are set against a background of thin, fibrovascular, anastomosing septa, which confer a lobular growth pattern to the tumor. Glial and retinal differentiation is detectable by immunoreactivity for glial fibrillary acidic protein and retinal S-antigen, respectively.

The clinical course of patients with pineocytomas is prolonged, averaging 7 years. The manifestations are the consequence of their pressure effects and consist of visual disturbances, headache, mental deterioration, and sometimes dementia-like behavior. The lesions being located where they are, it is understandable that successful excision is at best difficult.

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Chapter 25 - The Skin

George F. Murphy MD
Klaus Sellheyer MD
Martin C. Mihm Jr. MD

Normal

The Skin: More Than a Mechanical Barrier

Little more than 100 years ago, the noted pathologist Rudolph Virchow understood the skin as a protective covering for more delicate and functionally sophisticated internal viscera.[1] Then, and for the century that followed, the skin was considered primarily a passive barrier to fluid loss and mechanical injury. During the past three decades, however, enormously productive avenues of scientific inquiry have demonstrated the skin to be a complex organ in which precisely

Figure 25-1 *A,* The skin is composed of an epidermal layer (e) from which specialized adnexa (hair follicles, h; sweat glands, g; and sebaceous glands, s) descend into the underlying dermis (d). *B,* This projection of the epidermal layer (e) and underlying superficial dermis demonstrates the progressive upward maturation of basal cells (b) into cornified squamous epithelial cells of the stratum corneum (sc). Melanin-containing dendritic melanocytes (m) (and rare Merkel cells containing neurosecretory granules) and midepidermal dendritic Langerhans cells (lc) are also present. The underlying dermis contains small vessels (v), fibroblasts (f), perivascular mast cells (mc), and dendrocytes (dc), potentially important in dermal immunity and repair.

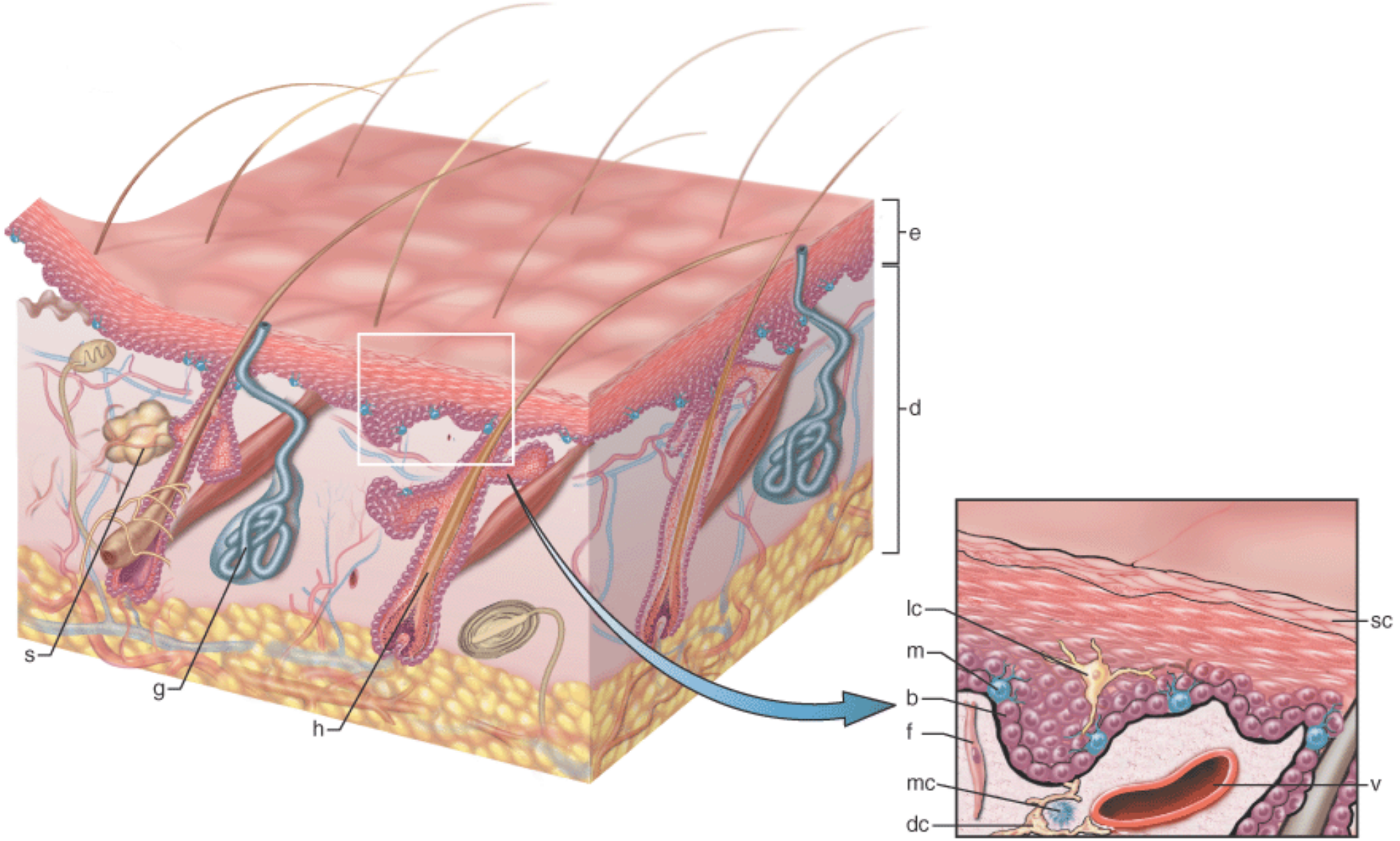
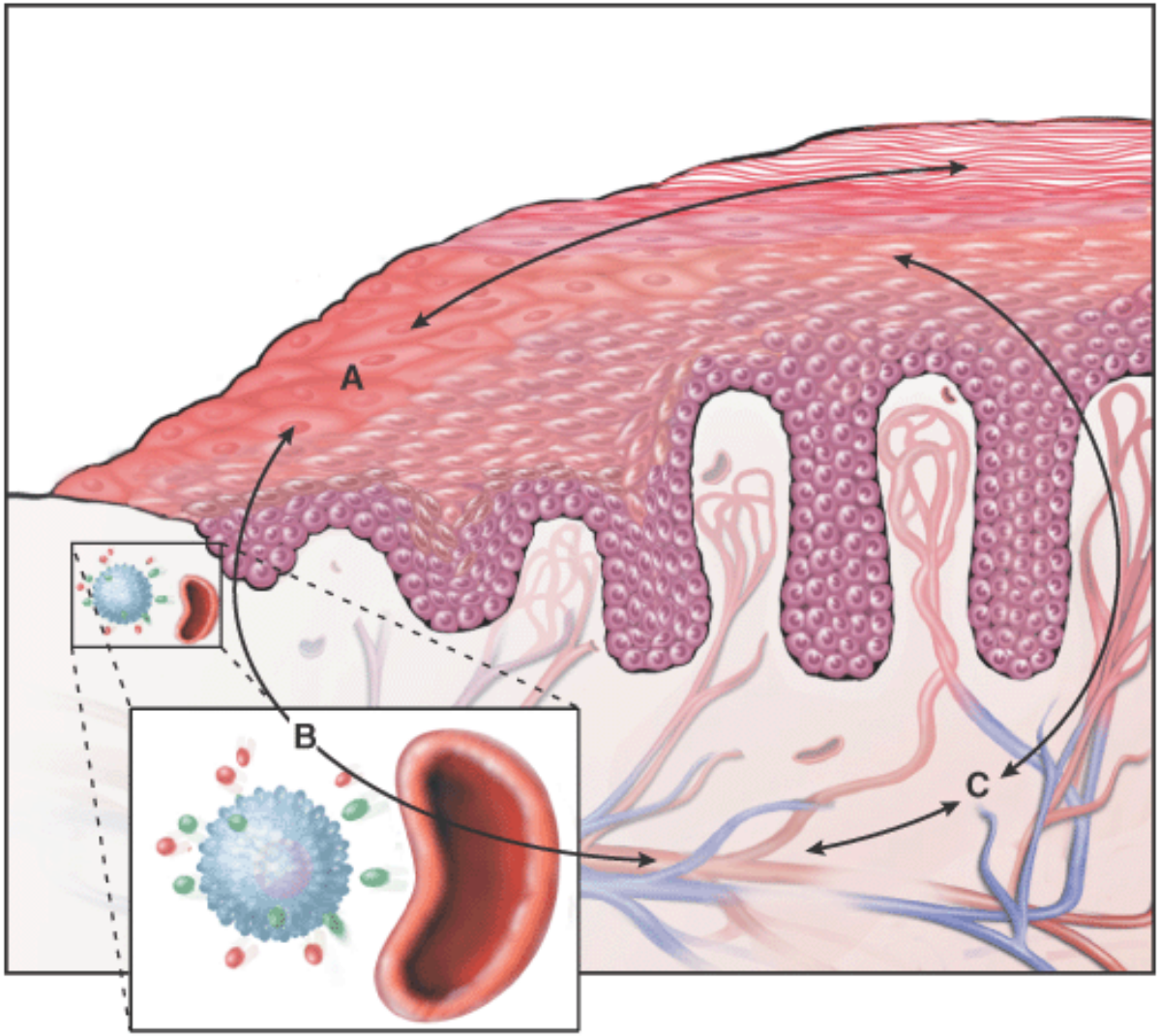


Figure 25-2 Schematic representation of dynamic interaction between the epidermal layer and the dermal layer. Keratinocytes at the edge of an ulcer *(A)* produce cytokines and factors that influence both keratinization and the function of underlying dermal cells *(B)*. In turn, dermal cells *(B)*, such as mast cells, also release cytokines *(green granules)* and proteases *(red granules)*, which may regulate both endothelial cells and overlying keratinocytes. Perturbations in these interactions between epidermal cells and dermal cells may contribute to pathologic processes, such as psoriasis *(C)*, in which both compartments become morphologically abnormal.



Scale
Dry, horny, platelike excrescence; usually the result of imperfect cornification.

Lichenification
Thickened and rough skin characterized by prominent skin markings; usually the result of repeated rubbing in susceptible persons.

Excoriation
Traumatic lesion characterized by breakage of the epidermis, causing a raw linear area (i.e., a deep scratch); often self-induced.

Onycholysis
Separation of nail plate from nail bed.

DEFINITIONS OF MICROSCOPIC TERMS

Hyperkeratosis
Thickening of the stratum corneum, often associated with a qualitative abnormality of the keratin.

Parakeratosis
Modes of keratinization characterized by the retention of the nuclei in the stratum corneum. On mucous membranes, parakeratosis is normal.

Hypergranulosis
Hyperplasia of the stratum granulosum, often due to intense rubbing.

Acanthosis
Diffuse epidermal hyperplasia.

Papillomatosis
Surface elevation caused by hyperplasia and enlargement of contiguous dermal papillae.

Dyskeratosis
Abnormal keratinization occurring prematurely within individual cells or groups of cells below the stratum granulosum.

Acantholysis
Loss of intercellular connections resulting in loss of cohesion between keratinocytes.

Spongiosis
Intercellular edema of the epidermis.

Hydropic swelling (ballooning)
Intracellular edema of keratinocytes, often seen in viral infections.

Exocytosis
Infiltration of the epidermis by inflammatory or circulating blood cells.

Erosion
Discontinuity of the skin exhibiting incomplete loss of the epidermis.

Ulceration
Discontinuity of the skin exhibiting complete loss of the epidermis and often of portions of the dermis and even subcutaneous fat.

Vacuolization
Formation of vacuoles within or adjacent to cells; often refers to basal cell-basement membrane zone area.

Lentiginous
Referring to a linear pattern of melanocyte proliferation within the epidermal basal cell layer. Lentiginous melanocytic hyperplasia can occur as a reactive change or as part of a neoplasm of melanocytes.

Disorders of Pigmentation and Melanocytes

Skin pigmentation has historically had major societal implications. Cosmetic desire for increased pigmentation (tanning) has resulted in many deleterious alterations that are described in the pages that follow. Focal or widespread loss of normal protective pigmentation not only renders individuals extraordinarily vulnerable to the harmful effects of sunlight (as in albinism), but has also resulted in severe emotional stress and, in some cultures, profound social and economic discrimination (as in vitiligo). Change in preexisting skin pigmentation may signify important primary events in the skin (e.g., malignant transformation of a mole) or disorders of internal viscera (e.g., in Addison disease, see Chapter 24).

VITILIGO

Vitiligo is a common disorder characterized by partial or complete loss of pigment-producing melanocytes within the epidermis. All ages and races are affected, but lesions are most noticeable in darkly pigmented individuals. Vitiligo may be entirely unapparent in lightly pigmented skin until tanning occurs in the surrounding normal skin. In darkly pigmented individuals with extensive involvement, residual zones of normal skin may at first appear to represent hyperpigmented lesions (Fig. 25-3*A*).

Clinical lesions are asymptomatic, flat, well-demarcated macules and patches of pigment loss; their size varies from few to many centimeters. Vitiligo often involves the hands and wrists; axillae; and perioral, periorbital, and anogenital skin. A curious phenomenon called *koebnerization* often occurs in vitiligo (as well as in certain other conditions; see lichen planus), where lesions develop primarily at sites of repeated trauma.

Morphology.

On histologic examination, vitiligo usually appears indistinguishable from normal skin. However, it is characterized by loss of melanocytes, as revealed by electron microscopy; it also may be diagnosed by immunohistochemistry for melanocyte-associated proteins (e.g., tyrosinase or Melan-A, or S-100; Fig. 25-3*B*). This is in contrast to some forms of **albinism,** in which melanocytes are present but melanin pigment is not produced because of a lack of or defect in tyrosinase. There are other causes of hypopigmentation that are unrelated to diminished expression of melanin or melanocytes (e.g., post-inflammatory hypopigmentation, which represents redistribution of existing pigment within skin possibly coupled with diminished transfer of pigment to keratinocytes).

Pathogenesis.

Why are melanocytes progressively lost or destroyed in vitiligo? Theories of pathogenesis include (1) autoimmunity, (2) neurohumoral factors toxic to melanocytes and released by nearby nerve endings, and (3) self-destruction of melanocytes by toxic intermediates of melanin synthesis. Most evidence supports autoimmune causation, focusing on the presence of circulating antibodies against melanocytes[7] and the association of vitiligo with other autoimmune disorders, such as pernicious anemia, Addison disease, and autoimmune thyroiditis. Abnormalities in macrophages,[8] and in T lymphocytes in skin[9] and in the peripheral blood have been described recently, suggesting that aberrations in cell-mediated immunity may also be operative in the pathogenesis of vitiligo. Another interesting facet of vitiligo is its response to therapy with UV light of the A wavelength coupled with use of the photosensitizing drug, psoralen (a therapy known as *PUVA*). Lesions so treated may regain pigment initially at the ostia of hair follicles, suggesting that melanocyte precursors harbored within the uppermost follicular epithelium are stimulated by this therapeutic approach.

Figure 25-3 *A*, Clinical appearance of vitiligo. Well-demarcated zones of pigment loss result from depletion of melanocytes that produce small melanin granules. Note small macules of normal pigment within the patches of vitiligo; Some of these appear to surround follicular ostia. *B*, Immunochemistry for S-100 protein revealing positively stained melanocytes within the basal cell layer of the epidermis; these cells are decreased or absent in vitiligo.

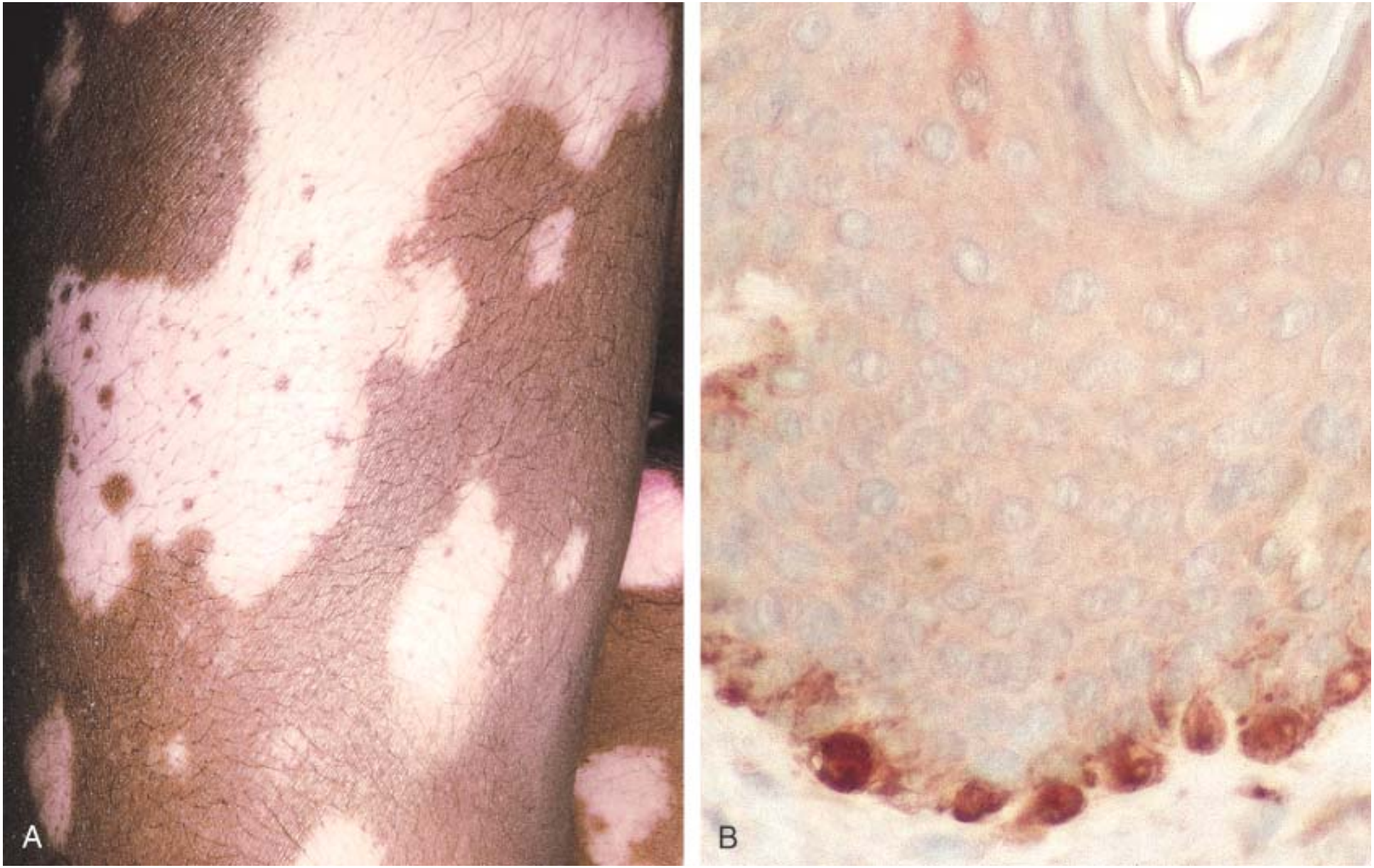


Figure 25-4 Nevocellular nevus, junctional type. *A*, In clinical appearance, lesions are small, relatively flat, symmetric, and uniform. *B*, On histologic examination, junctional nevi are characterized by rounded nests of nevus cells originating at the tips of rete ridges along the dermoepidermal junction.

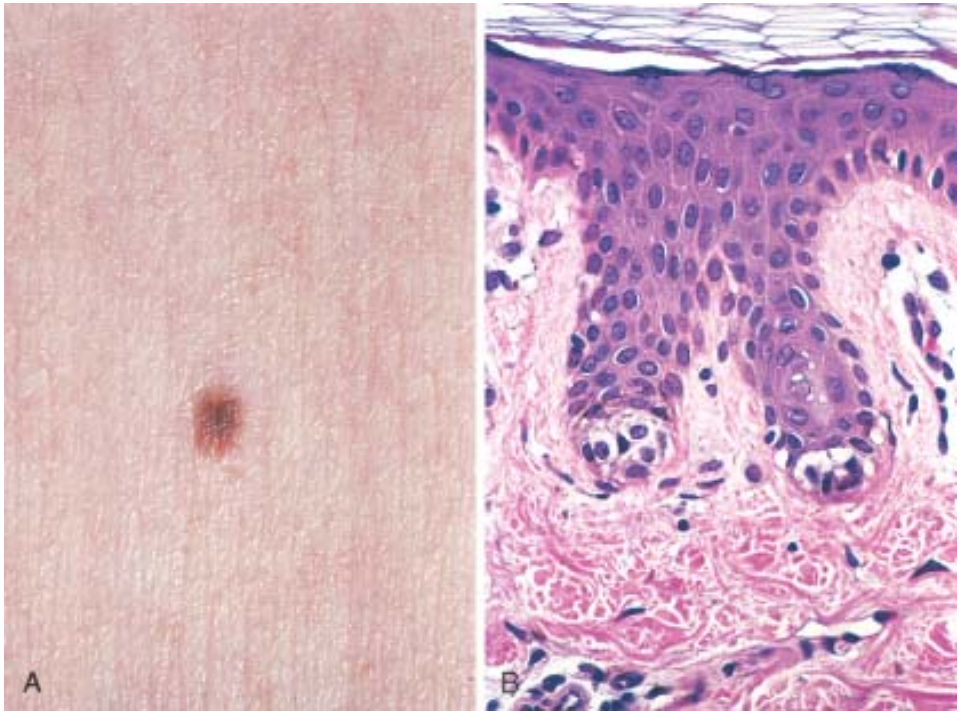


Figure 25-5 Nevocellular nevus, compound type. In contrast to the junctional nevus, the compound nevus *(A)* is more raised and dome shaped. The symmetry and uniform pigment distribution suggest a benign process. Histologically *(B)*, compound nevi combine the features of junctional nevi (intraepidermal nevus cell nests) with nests and cords of nevus cells in the underlying dermis.

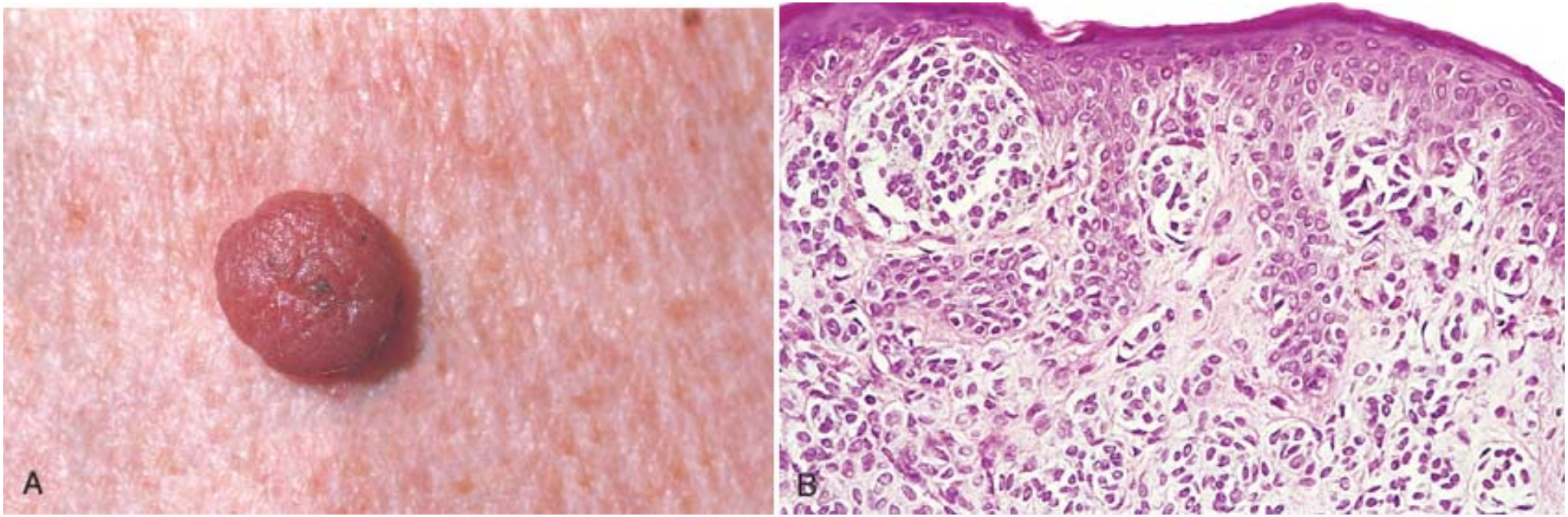


TABLE 25-1 -- Variant Forms of Nevocellular Nevi

Nevus Variant	Diagnostic Architectural Features	Diagnostic Cytologic Features	Clinical Significance
Congenital nevus	Deep dermal and sometimes subcutaneous growth around adnexa, neurovascular bundles, and blood vessel walls	Identical to ordinary acquired nevi	Present at birth; large variants have increased melanoma risk
Blue nevus	Non-nested dermal infiltration, often with associated fibrosis	Highly dendritic, heavily pigmented nevus cells	Black-blue nodule; often confused with melanoma clinically
Spindle and epithelioid cell nevus (Spitz nevus)	Fascicular growth	Large, plump cells with pink-blue cytoplasm; fusiform cells	Common in children; red-pink nodule; often confused with hemangioma clinically
Halo nevus	Lymphocytic infiltration surrounding nevus cells	Identical to ordinary acquired nevi	Host immune response against nevus cells and surrounding normal melanocytes
Dysplastic nevus	Large, coalescent intraepidermal nests	Cytologic atypia	Potential precursor of malignant melanoma

well as on sun-exposed body surfaces. Dysplastic nevi have been documented in multiple members of families prone to the development of malignant melanoma *(the heritable melanoma syndrome)*.[12] In these cases, genetic analyses have demonstrated the trait to be inherited as an autosomal dominant.[13] [14] (See discussion under Molecular Genetics of Skin Cancers.) Transitions from these lesions to early melanoma have actually been documented clinically and histologically within a period as short as several weeks. However, most dysplastic nevi are clinically stable lesions. Dysplastic nevi may also occur as isolated lesions not associated with the heritable melanoma syndrome, in which case the risk of malignant change appears to be low.

Morphology.

On histologic examination (see Fig. 25-6*A,B*), dysplastic nevi consist of compound nevi with both architectural and cytologic evidence of abnormal growth. **Nevus cell nests within the epidermis may be enlarged and exhibit abnormal fusion or coalescence with adjacent nests. As part of this**

Figure 25-6 Dysplastic nevus. *A*, The lesion often has a compound nevus component (right side of scanning field) and an asymmetric "shoulder" composed of a junctional nevus component (left side of scanning field). The former correlates clinically with the more pigmented and raised central zone and the latter with the less pigmented, flat peripheral rim *(inset)*. *B*, An important feature is the presence of cytologic atypia (irregularly shaped, dark-staining nuclei) at high magnification. The dermis underlying the atypical cells characteristically shows linear, or lamellar, fibrosis.

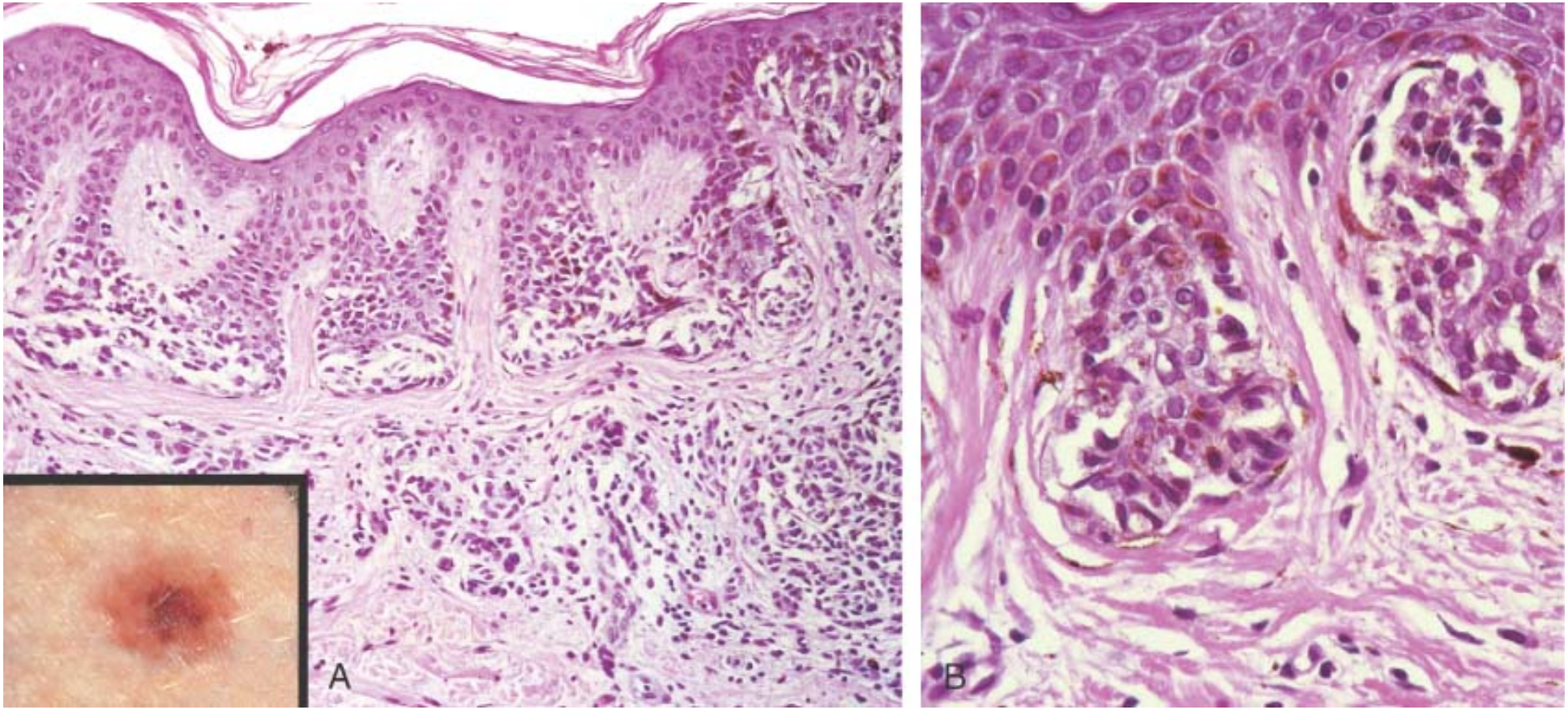


Figure 25-7 Steps of tumor progression in dysplastic nevi. *A*, Lentiginous melanocytic hyperplasia. *B*, Lentiginous junctional nevus. *C*, Lentiginous compound nevus with abnormal architectural and cytologic features (dysplastic nevus). *D*, Early melanoma, or radial growth phase melanoma (large dark cells in epidermis). *E*, Advanced melanoma (vertical growth phase) with malignant spread into the dermis and vessels.

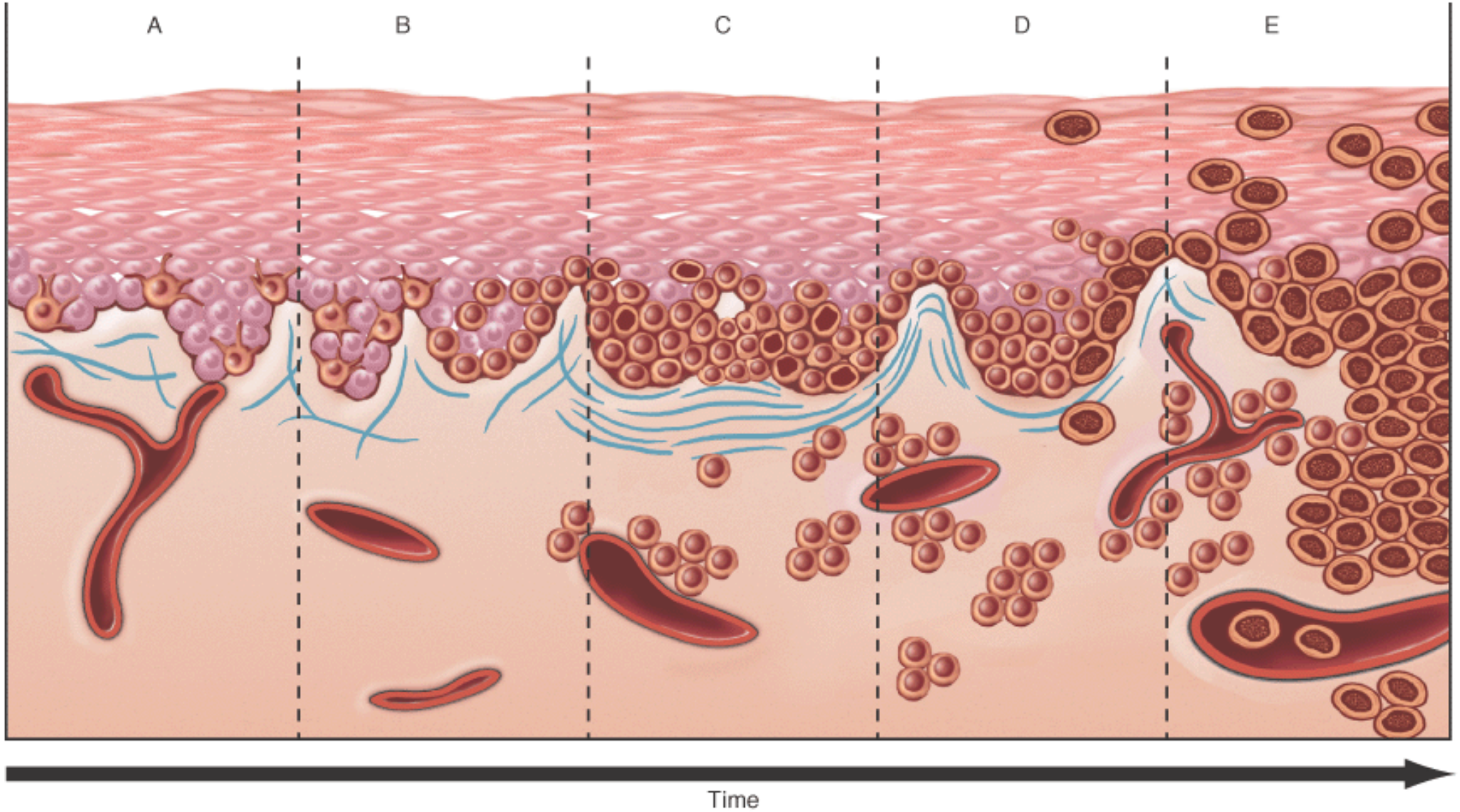


Figure 25-8 Malignant melanoma. *A*, In clinical appearance, lesions are irregular in contour and pigmentation. Macular areas correlate with the radial growth phase, while raised areas usually correspond to nodular aggregates of malignant cells in the vertical phase of growth. *B*, Radial growth phase of malignant melanoma, showing irregular nested and single-cell growth of melanoma cells within the epidermis and an underlying inflammatory response within the dermis. *C*, Photomicrograph of lesion in the vertical phase of growth, demonstrating nodular aggregates of infiltrating cells. *D*, High-power view of malignant melanoma cells.

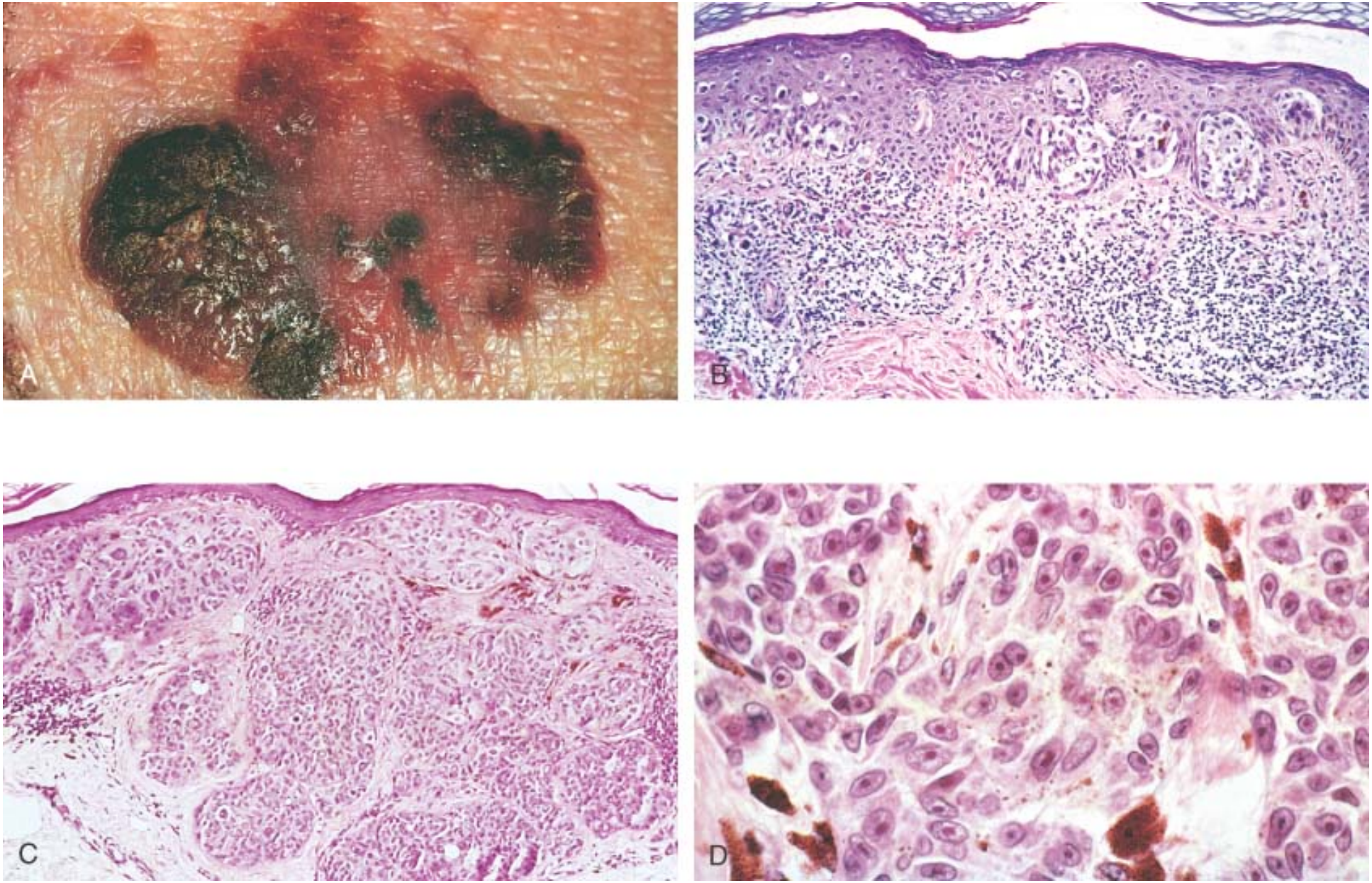


Figure 25-9 Seborrheic keratosis. *A,* A well-demarcated coinlike pigmented lesion containing dark keratin-filled surface plugs is composed histologically of proliferations of basaloid cells with formation of prominent keratin-filled "horn" cysts *(B),* some of which communicate with the surface (pseudo-horn cysts) and correlate with the plugs observed clinically.

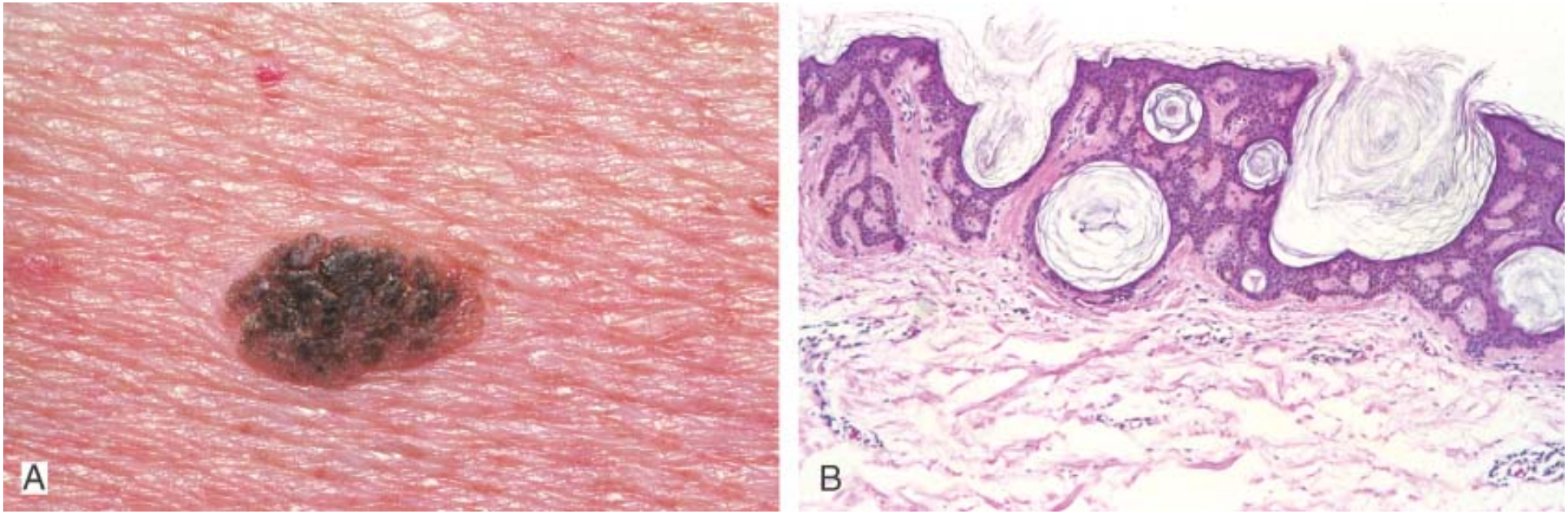


Figure 25-10 Adnexal tumors. The clinical appearance is often nondescript (*A* shows multiple cylindromas and *C* shows multiple trichoepitheliomas). *B*, On histologic examination, the cylindroma is composed of islands of basaloid cells containing occasional ducts and seemingly fitting together like pieces of a jigsaw puzzle. *D*, Trichoepithelioma is composed of buds of basaloid cells that resemble primitive hair follicles. Here the small ductlike structures are actually keratin-filled microcysts.

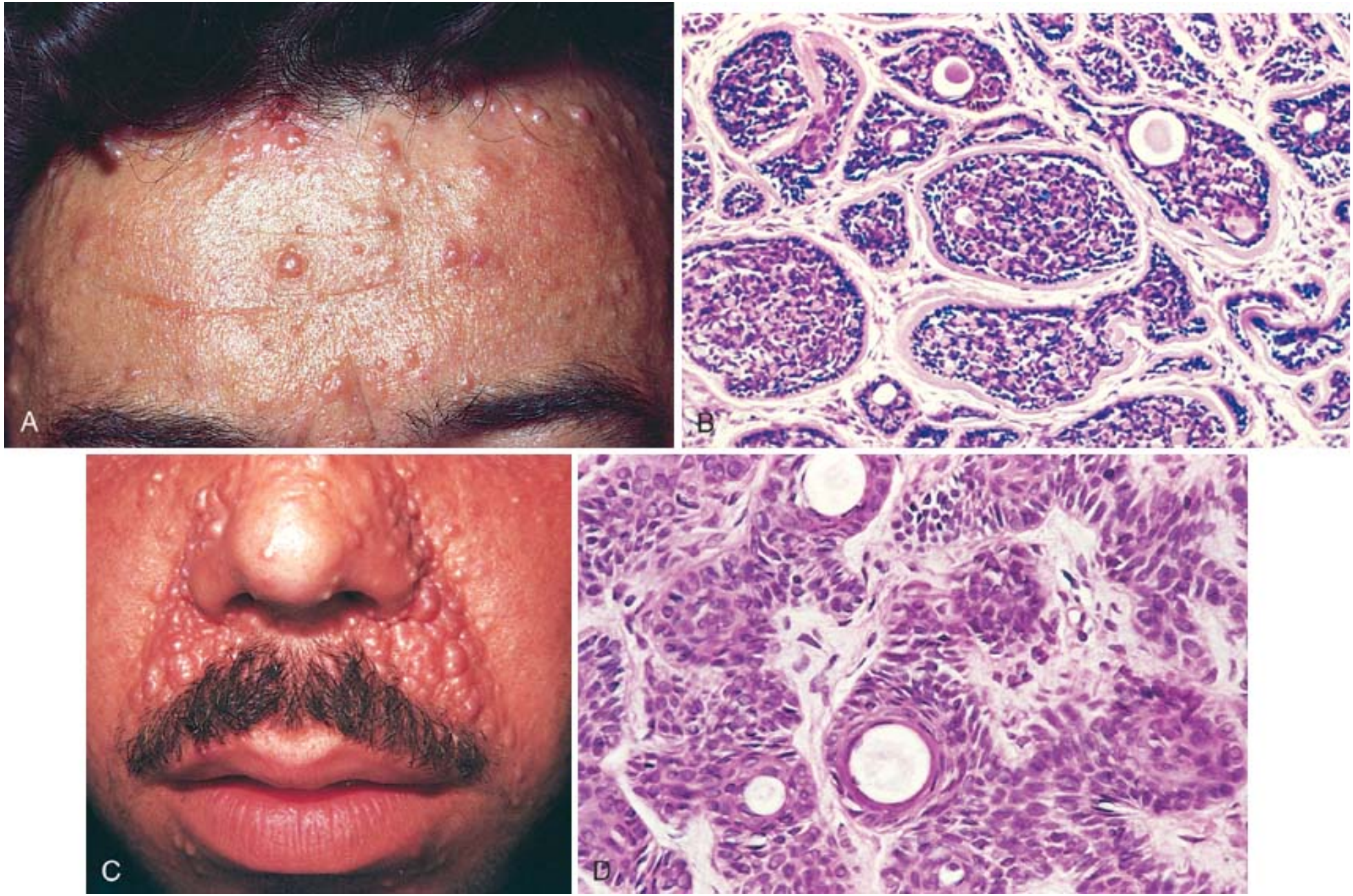


Figure 25-11 Adnexal tumors. *A*, Mixed tumor (chondroid syringoma). *B*, Trichilemmoma. *C*, Hidradenoma papilliferum.

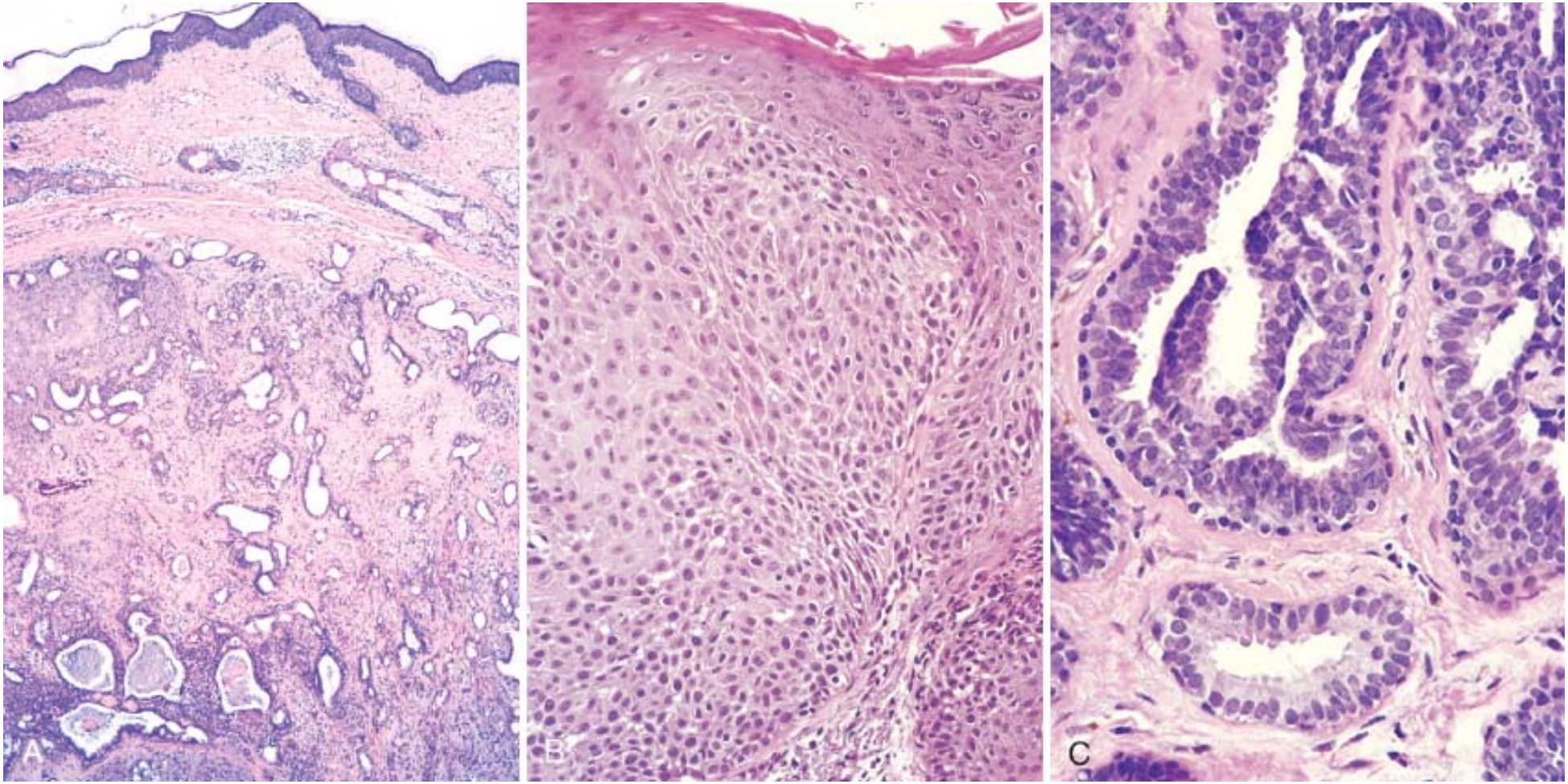


TABLE 25-2 -- Common Adnexal Tumors

Adnexal Tumors	Mature Counterpart	Histologic Features	Clinical Significance
Trichoepithelioma	Hair follicle	Hair matrix, outer root sheath differentiation	Multiple trichoepitheliomas, dominant inheritance
Trichofolliculoma			
Sebaceous adenoma	Sebaceous gland	Cytoplasmic lipid vacuoles	Association with internal malignancy
Sebaceous epithelioma			
Syringocystadenoma papilliferum	Apocrine gland	Apocrine type ("decapitation") secretion	May develop in mixed epidermal-adnexal hamartomas of face and scalp termed *nevus sebaceus*
Syringoma	Eccrine gland	Eccrine ducts lined by membranous eosinophilic cuticles; tadpole-like epithelial structures	May be confused with basal cell carcinoma clinically