Morphology.

In patients with a distal symmetric sensorimotor neuropathy, the predominant pathologic finding is an axonal neuropathy. As with other chronic axonal neuropathies, there is often some segmental demyelination. There is a relative loss of small myelinated fibers and of unmyelinated fibers, but large fibers are also affected. Endoneurial arterioles show thickening, hyalinization, and intense periodic acid-Schiff (PAS) positivity in their walls and extensive reduplication of the basement membrane[36] (Fig. 27-7). Whether the lesions are due to ischemia[37] or metabolic derangement is unclear.

Clinical Course.

The most common peripheral neuropathy is the symmetric neuropathy that involves distal sensory and motor nerves. Patients with the neuropathy develop decreased sensation in the distal extremities with less evident motor abnormalities. The loss of pain sensation can result in the development of ulcers that heal poorly because of the diffuse vascular injury in diabetes, and are a major cause of morbidity. Another manifestation of diabetic neuropathy is *dysfunction of the autonomic nervous system*; this affects 20% to 40% of diabetics, nearly always in association with a distal sensorimotor neuropathy.[38] Some patients, especially elderly

Figure 27-7 Diabetic neuropathy with marked loss of myelinated fibers, a thinly myelinated fiber *(arrowheads)*, and thickening of endoneurial vessel wall *(arrow)*.
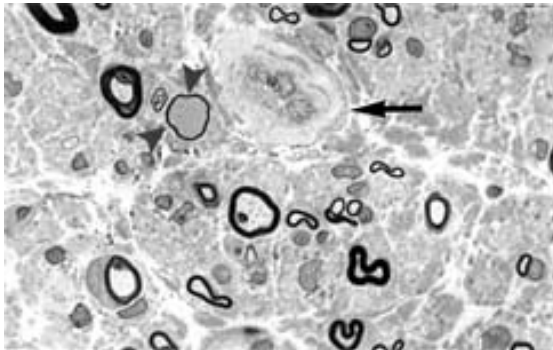

Figure 27-8 Traumatic neuroma showing disordered orientation of nerve fiber bundles *(purple)* intermixed with connective tissue *(blue)*.
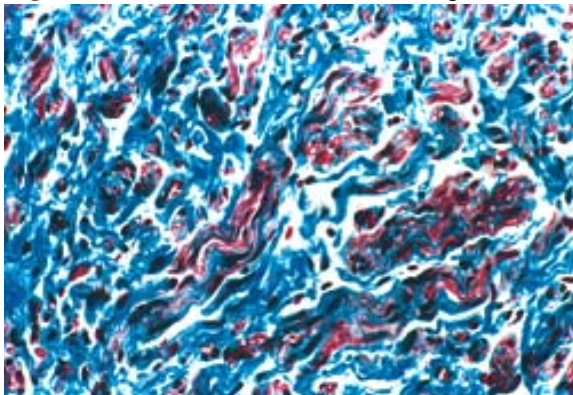

Figure 27-9 Spinal muscular atrophy with groups of atrophic muscle fibers resulting from denervation atrophy of muscle in early childhood.
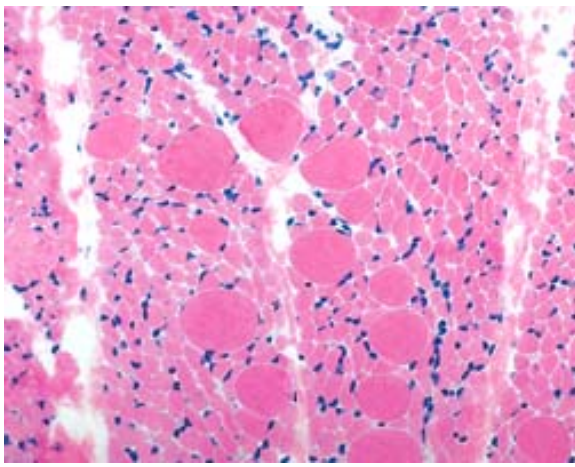
Figure 27-10 Diagram showing the relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins. Dystrophin, an intracellular protein, forms an interface between the cytoskeletal proteins and a group of transmembrane proteins, the dystroglycans and the sarcoglycans. These transmembrane proteins have interactions with the extracellular matrix, including the laminin proteins. Dystrophin also interacts with dystrobrevin and the syntrophins, which form a link with neuronal-type nitric oxide synthetase (nNOS) and caveolin. Mutations in dystrophin are associated with the X-linked muscular dystrophies, mutations in caveolin and the sarcoglycan proteins with the autosomal limb girdle muscular dystrophies, and mutations in the α2-laminin (merosin) with a form of congenital muscular dystrophy.
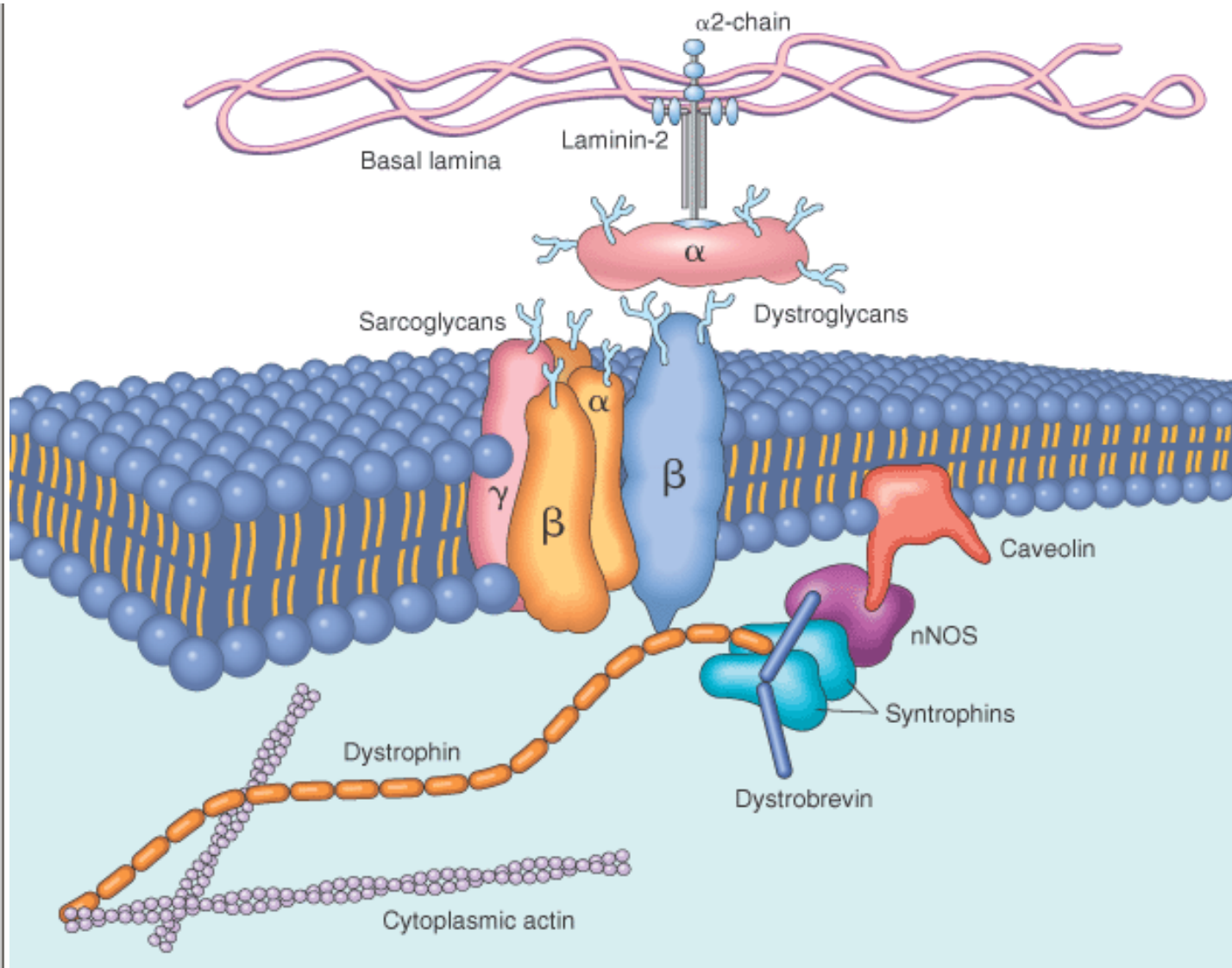
Figure 27-11 *A*, Duchenne muscular dystrophy (DMD) showing variation in muscle fiber size, increased endomysial connective tissue, and regenerating fibers *(blue hue)*. *B*, Western blot showing absence of dystrophin in DMD and altered dystrophin size in Becker muscular dystrophy (BMD) compared with control (Con). *(Courtesy of Dr. L. Kunkel, Children's Hospital, Boston, MA.)*

B
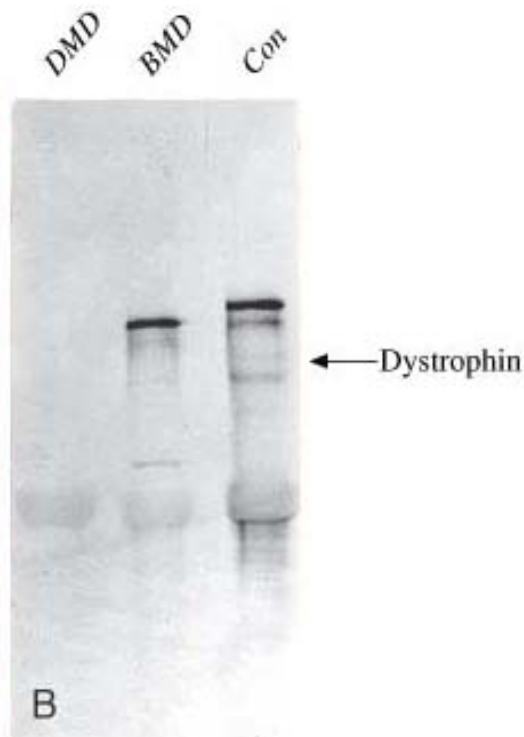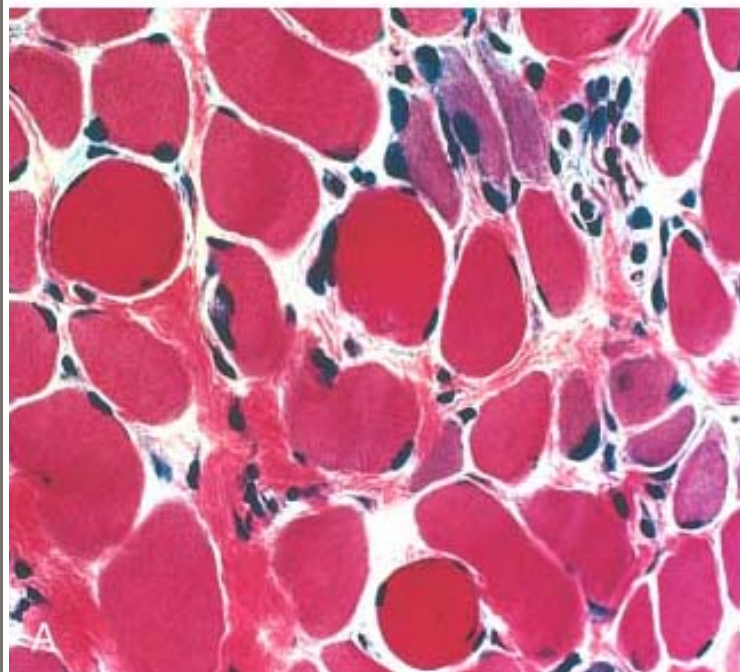
← Dystrophin

TABLE 27-4 -- Other Muscular Dystrophies

Disease and Inheritance	Gene and Locus	Clinical Findings	Pathologic Findings
Facioscapulohumeral muscular dystrophy; autosomal-dominant	Type 1A—deletion of variable number of 3.3-kB subunits of a tandemly arranged repeat (D4Z4) on 4q35	Variable age at onset (most commonly 10–30 years); Weakness of muscles of face, neck, and shoulder girdle	Dystrophic myopathy, but also often including inflammatory infiltrates of muscle.
	Type 1B (FSHMD1B)—locus unknown		
Oculopharyngeal muscular dystrophy; autosomal-dominant	Poly(A)-binding protein-2 (PABP2) gene; 14q11.2-q13	Onset in midadult life; ptosis and weakness of extraocular muscles; difficulty in swallowing	Dystrophic myopathy, but often including rimmed vacuoles in type 1 fibers
Emery-Dreifuss muscular dystrophy; X-linked (mostly)	Emerin (EMD1) gene; Xq28	Variable onset (most commonly 10–20 years); prominent contractures, especially of elbows and ankles	Mild myopathic changes; absent emerin by immunohistochemistry
Congenital muscular dystrophies; autosomal-recessive (Also called muscular dystrophy, congenital, subtypes MDC1A, MDC1B, MDC1C)	Type 1A (merosin-deficient type)—laminin $\alpha2$ (merosin) gene; 6q22-q23	Neonatal hypotonia, respiratory insufficiency, delayed motor milestones	Variable fiber size and extensive endomysial fibrosis
	Type 1B—locus at 1q42; gene unknown		

| | Type 1C; fukutin-related protein gene; 19q13.3 | | | |

muscle groups, and the specific diagnosis is based largely on the pattern of clinical muscle weakness (Table 27-4). Several autosomal muscular dystrophies, however, affect the proximal musculature of the trunk and limbs, similar to the X-linked muscular dystrophies, and are termed *limb girdle muscular dystrophies*.

Limb girdle muscular dystrophies are inherited in either an autosomal-dominant (type 1) or an autosomal-recessive (type 2) pattern (Table 27-5). Six subtypes of the dominant dystrophies (1A to 1F) and ten subtypes of the recessive limb girdle dystrophies (2A to 2J) have been identified. Mutations of the *sarcoglycan complex of proteins* have been identified in four of the limb girdle muscular dystrophies[52] (2C, 2D, 2E, and 2F). These membrane proteins interact with dystrophin through another transmembrane protein, β-dystroglycan (Fig. 27-10).

Myotonic Dystrophy

Myotonia, the sustained involuntary contraction of a group of muscles, is the cardinal neuromuscular symptom in this disease.[53] Patients often complain of "stiffness" and have difficulty in releasing their grip, for instance, after a handshake. Myotonia can often be elicited by percussion of the thenar eminence.

Pathogenesis.

Inherited as an autosomal-dominant trait, the disease tends to increase in severity and appear at a younger age in succeeding generations, a phenomenon termed *anticipation*. Myotonic dystrophy is associated with a trinucleotide CTG repeat expansion on chromosome 19q13.2-13.3. This expansion affects the mRNA for the dystrophila myotonia-protein kinase (DMPK).[54] In normal subjects, fewer than 30 repeats are present; disease develops with expansion of this repeat, and in severely affected individuals, several thousand repeats may be present.[54] The mutation is not stable within a pedigree; with each generation, more repeats accumulate, and this appears to correspond to the clinical

TABLE 27-5 -- Limb Girdle Muscular Dystrophies

Type	Inheritance	Locus	Gene	Clinicopathologic Features
1A	Autosomal-dominant	5q31	Myotilin	Onset in adult life with slow progression of limb weakness, but sparing of facial muscles; dysarthric speech
1B	Autosomal-dominant	1q21	Lamin A/C	Onset before the age of 20 years in lower limbs, progression during many years with cardiac involvement
1C	Autosomal-dominant	3p25	Caveolin-3 (M-caveolin)	Onset before the age of 20, clinically similar to type 1B
1D	Autosomal-dominant	7p	Unknown	Limb girdle muscle weakness, adult onset
2A	Autosomal-recessive	15q15.1-21.1	Calpain 3	Onset in late childhood to middle age; slow progression during 20–30 years
2B	Autosomal-recessive	2p13.3-q13.1	Dysferlin	Mild clinical course with onset in early adulthood

2C	Autosomal-recessive	13q12	γ-Sarcoglycan	Severe weakness during childhood, rapid progression; dystrophic myopathy on muscle biopsy
2D	Autosomal-recessive	17q21	α-Sarcoglycan (adhalin)	Severe weakness during childhood, rapid progression; dystrophic myopathy on muscle biopsy
2E	Autosomal-recessive	4q12	β-Sarcoglycan	Onset in early childhood, with Duchenne-like clinical course
2F	Autosomal-recessive	5q33	δ-Sarcoglycan	Early onset and severe myopathy; dystrophic myopathy on muscle biopsy
2G	Autosomal-recessive	17q11-q12	Telethonin	Distal weakness with limb-girdle weakness in late childhood to adulthood; rimmed vacuoles in muscle cells
2H	Autosomal-recessive	9q31-q34.1	Tripartite motif-containing protein 32 (TRIM32)	Limb-girdle and facial weakness with onset in childhood, mild, slowly progressive course

feature of anticipation. Expansion of the trinucleotide repeat influences the eventual level of protein product.

The pathologic features of the disease relate only in part to altered DMPK function. RNA that contains trinucleotide repeat expansions can directly affect splicing of other RNAs, including those for the ClC-1 chloride channel.[55] A second form of myotonic dystrophy is associated with untranslated CCTG expansion in a gene called *ZNF9* on chromosome 3.[56]

Morphology.

Skeletal muscle may show variation in fiber size. In addition, there is a striking increase in the number of internal nuclei, which on longitudinal section may form conspicuous chains. Another well-recognized abnormality is the **ring fiber**, with a subsarcolemmal band of cytoplasm that appears distinct from the center of the fiber. The rim contains myofibrils that are oriented circumferentially around the longitudinally oriented fibrils in the rest of the fiber. The ring fiber may be associated with an irregular mass of sarcoplasm **(sarcoplasmic mass)** extending outward from the ring. These sarcoplasmic masses stain blue with hematoxylin and eosin, red with Gomori trichrome, and intensely blue with the nicotinamide adenine dinucleotide-tetrazolium reductase (NADHTR) histochemical reaction. Histochemical techniques have demonstrated a relative atrophy of type 1 fibers early in the course of the disease in some cases. Of all the dystrophies, only myotonic dystrophy shows pathologic changes in the intrafusal fibers of muscle spindles, with fiber splitting, necrosis, and regeneration.

Clinical Course.

The disease often presents in late childhood with abnormalities in gait secondary to weakness of foot dorsiflexors and subsequently progresses to weakness of the hand intrinsic muscles and wrist extensors. Atrophy of muscles of the face and ptosis ensue, leading to the typical facial appearance. Cataracts, which are present in virtually every patient, may be detected early in the course of the disease with slit-lamp examination. Other associated abnormalities include frontal balding, gonadal atrophy, cardiomyopathy, smooth muscle involvement, decreased plasma immunoglobulin G, and an abnormal glucose tolerance test response. Dementia has been reported in some cases.

ION CHANNEL MYOPATHIES (CHANNELOPATHIES)

The *ion channel myopathies*, or channelopathies, are a group of familial diseases characterized clinically by myotonia, relapsing episodes of hypotonic paralysis (induced by vigorous exercise, cold, or a high-carbohydrate meal), or both. Hypotonia variants associated with elevated, depressed, or normal serum potassium levels at the time of the attack are called *hyperkalemic, hypokalemic, and normokalemic periodic paralysis*, respectively.

Pathogenesis.

As their name indicates, at the molecular level these diseases are caused by mutations in genes that encode ion channels.[57] [58] Hyperkalemic periodic paralysis results from mutations in the gene that encodes a skeletal muscle sodium channel protein (SCN4A), which regulates the entry of sodium into muscle during contraction. The gene for hypokalemic periodic paralysis encodes a voltage-gated calcium channel.

TABLE 27-6 -- Congenital Myopathies

| Disease and Inheritance	Gene and Locus	Clinical Findings	Pathologic Findings
Central core diseases; autosomal-dominant	Ryanodine receptor-1 (RYR1) gene; 19q13.1	Early-onset hypotonia and nonprogressive weakness; associated skeletal deformities; may develop malignant hyperthermia	Cytoplasmic cores are lightly eosinophilic and distinct from surrounding sarcoplasm; Found only in type 1 fibers, which usually predominate, best seen on NADH stain
Nemaline myopathy; autosomal-dominant or autosomal-recessive	Autosomal-dominant (NEM1)—Tropomyosin 3 (TPM3) gene; Autosomal-recessive (NEM2)—nebulin (NEB) gene; 2q22	Weakness, hypotonia, and delayed motor development in childhood; may also be seen in adults; usually nonprogressive; involves proximal limb muscles most severely; skeletal abnormalities may be present	Aggregates of subsarcolemmal spindle-shaped particles *(nemaline rods)*; occur predominantly in type 1 fibers; derived from Z-band material (α-actinin) and best seen on modified Gomori stain
	Autosomal-dominant or recessive—skeletal muscle actin, α chain (ACTA1) gene; 1q42.1		
Myotubular (centronuclear) myopathy; X-linked (MTM1), autosomal-recessive, or autosomal-dominant	X-linked—myotubularin (MTM1) gene; Xq28	X-linked form presents in infancy with prominent hypotonia and poor prognosis; autosomal forms have limb weakness and are slowly progressive; autosomal-recessive form is intermediate in severity and prognosis	Abundance of centrally located nuclei involving the majority of muscle fibers; central nuclei are usually confined to type 1 fibers, which are small in diameter, but can occur in both fiber types
	Autosomal-dominant—myogenic factor 6 (MYF6) gene; 12q21		
	Autosomal-recessive—locus and gene unknown		

Malignant hyperpyrexia (malignant hyperthermia) is a rare clinical syndrome characterized by a dramatic hypermetabolic state (tachycardia, tachypnea, muscle spasms, and later hyperpyrexia) triggered by the induction of anesthesia, usually with halogenated inhalational agents and succinylcholine. The clinical syndrome may also occur in predisposed individuals with hereditary muscle diseases, including congenital myopathies, dystrophinopathies, and metabolic myopathies. The only reliable method of diagnosis is contraction of biopsied muscle on exposure to anesthetic. Mutations in different genes have been identified in families with susceptibility to malignant hyperthermia, including genes encoding a voltage-gated calcium channel (lq32), an L-type voltage-dependent calcium channel (7q21-q22), and a ryanodine receptor (19q13.1).[59]

Figure 27-12 *A*, Nemaline myopathy with numerous rod-shaped, intracytoplasmic inclusions *(dark purple structures)*. *B*, Electron micrograph of subsarcolemmal nemaline bodies, showing material of Z-band density.
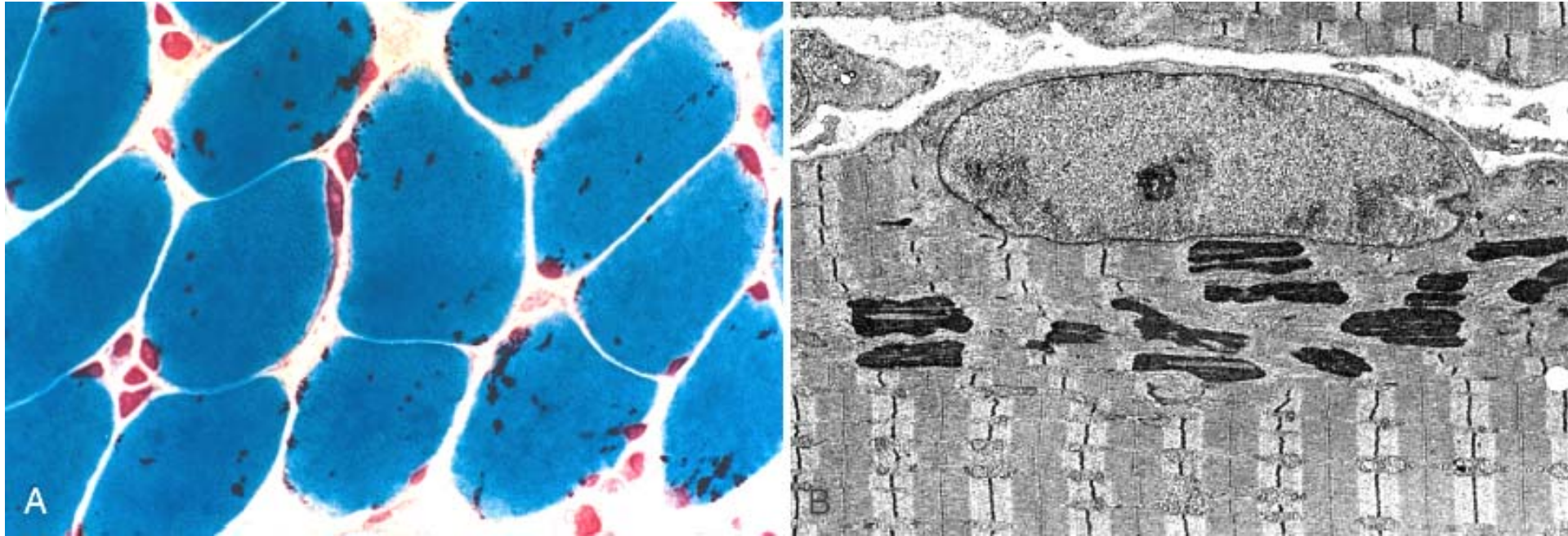

Figure 27-13 *A*, Mitochondrial myopathy showing an irregular fiber with subsarcolemmal collections of mitochondria that stain red with the modified Gomori trichrome stain *(ragged red fiber)*. *B*, Electron micrograph of mitochondria from biopsy specimen in *A* showing "parking lot" inclusions.
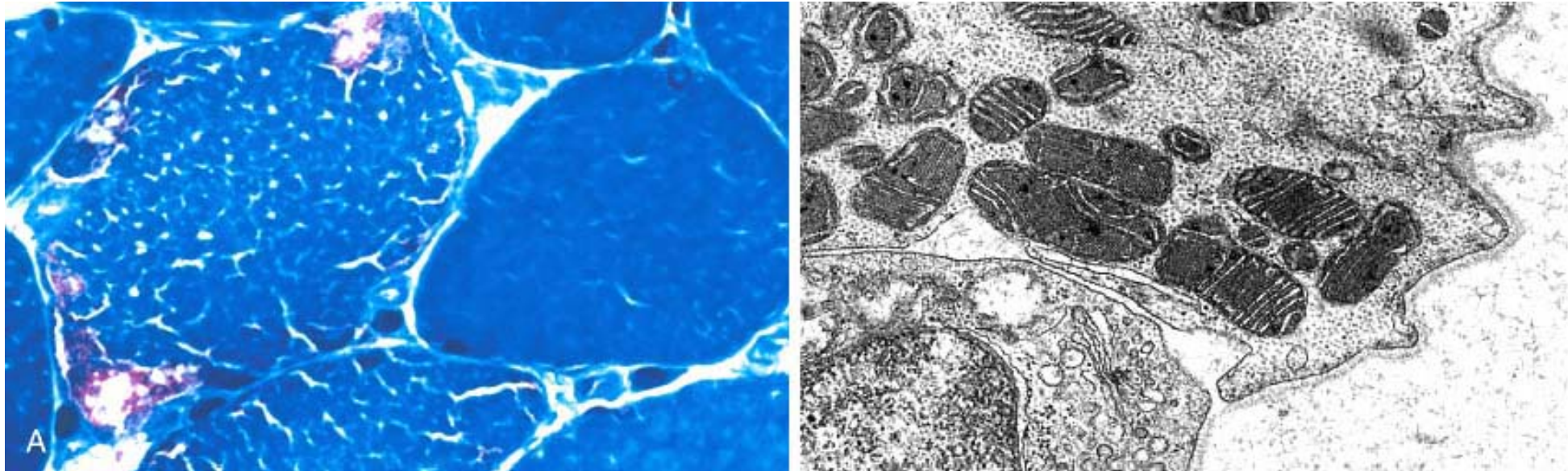
Figure 27-14 *A*, Dermatomyositis. Note the rash affecting the eyelids. *B*, Dermatomyositis. The histologic appearance of muscle shows perifascicular atrophy of muscle fibers and inflammation. *C*, Inclusion body myositis showing a vacuole within a myocyte. *(Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical*

School, Dallas, TX.)
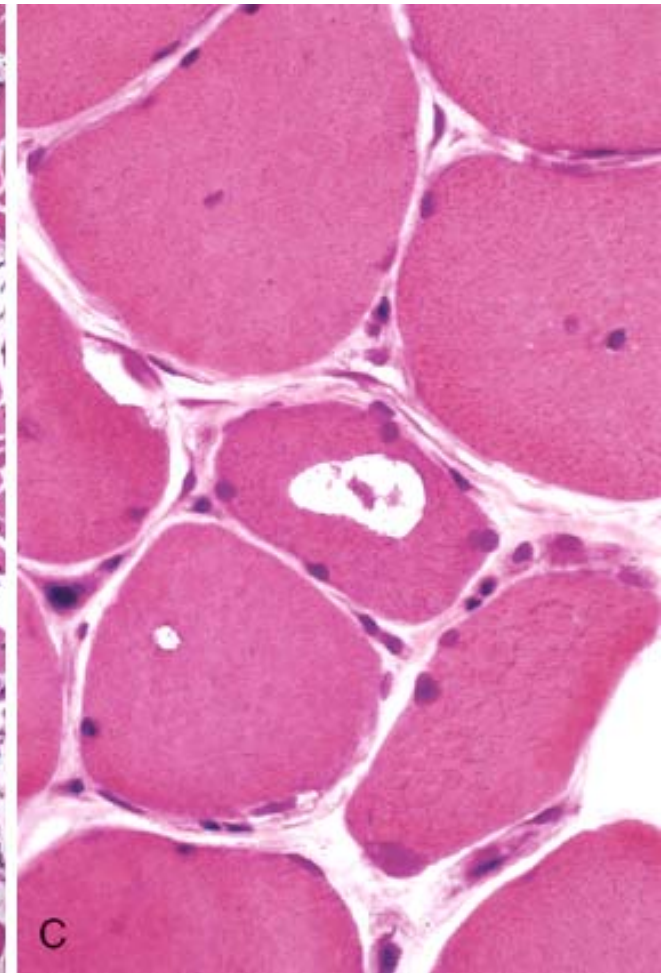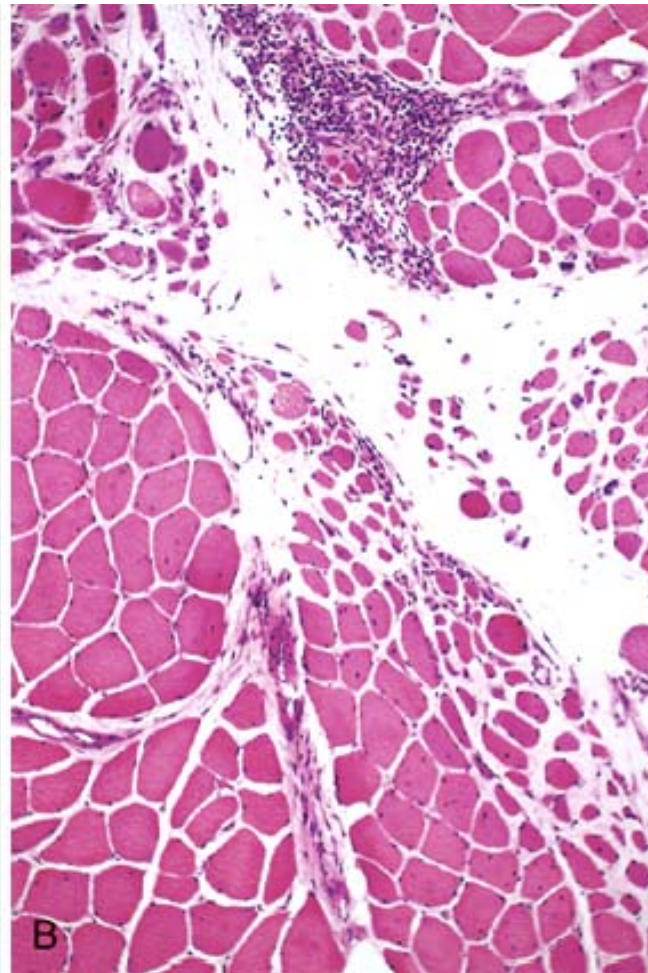
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Chapter 28 - The Central Nervous System

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The human central nervous system (CNS) is an enormously complex tissue serving the organism as a processing center linking information between the outside world and the body. The principal functional unit of the CNS is the neuron; the best estimates are that there are about 10^{11} neurons in the human brain. Neurons, although similar in many ways to other cells in the body, are unique in their ability to receive, store, and transmit information. Neurons differ greatly from one another in many important properties: their functional roles (e.g., sensory, motor, autonomic), the distribution of

their connections, the neurotransmitters they use for synaptic transmission, their metabolic requirements, and their levels of electrical activity at a given moment. A set of neurons, not necessarily clustered together in a region of the brain, may thus be singled out for destruction in a pathologic condition—*selective vulnerability*—because it shares one or more of these properties. Furthermore, and of particular importance in medicine, most mature neurons are postmitotic cells that are incapable of cell division, so destruction of even a small number of neurons responsible for a specific function may leave the patient with a severe clinical neurologic deficit. Stem cell populations have been described in several areas of the brain and

represent a potential mechanism for repair after injury.[1] In comparison to other organ systems of the body, the nervous system has several unique anatomic and physiologic characteristics: the protective bony enclosure of the skull and spinal column that contains it, a specialized system of autoregulation of cerebral blood flow, metabolic substrate requirements, the absence of a conventional lymphatic system, a special cerebrospinal fluid (CSF) circulation, limited immunologic surveillance, and distinctive responses to injury and wound healing. As a result of these special characteristics, the CNS is vulnerable to unique pathologic processes, and the reactions of CNS tissue to injury differ considerably from those

encountered elsewhere.[2] [3]

Normal Cells

The principal cells of the CNS are neurons, glia, and the cells that compose the meninges and blood vessels.

Neurons

In the CNS, neurons are topographically organized either as aggregates (nuclei, ganglia) or as elongated columns or layers (such as the intermediolateral gray column of the spinal cord

or the six-layered cerebral cortex).[4] Functional domains are located in many of these anatomically defined regions (such as the hypoglossal nucleus of the medulla for motor fibers of the twelfth cranial nerve; calcarine cortex of the occipital lobe for primary visual cortex). In addition, as a further dimension of anatomic-functional specificity, some cortical and

subcortical neurons and their projections are arranged somatotopically (such as motor and sensory homunculi).[5] Neurons vary considerably in structure and size throughout the nervous system and within a given brain region. With conventional histologic preparations, an anterior horn neuron in the spinal cord has a cell body (perikaryon) that is about 50 μm wide, a relatively large and somewhat eccentrically placed nucleus, a prominent nucleolus, and abundant Nissl substance; the nucleus of a granule cell neuron of the cerebellar cortex is about 10 μm across, and its perikaryon and nucleolus are not readily visible by light microscopy. Electron microscopic study reveals further variability among neurons in cytoplasmic content and

the shape of the cells and their processes.[6] Characteristic ultrastructural features common to many neurons include microtubules, neurofilaments, prominent Golgi apparatus and rough endoplasmic reticulum, and synaptic specializations. Despite these shared structures, axon length may vary greatly (hundreds of microns for interneurons versus a meter for an upper

motor neuron). Immunohistochemical markers for neurons and their processes commonly used in diagnostic work include neurofilament protein, NeuN, and synaptophysin.[7]

Glia

Glial cells are derived from neuroectoderm (macroglia: astrocytes, oligodendrocytes, ependyma) or from bone marrow (microglia). Glial cells have important structural and metabolic interactions with neurons and their dendritic and axonal processes; they also have a primary role in a wide range of normal functions and reactions to injury, including inflammation, repair, fluid balance, and energy metabolism. The size and shape of the nucleus helps in the light microscopic distinction of one glial cell type from another, as their cytoplasmic processes are often not apparent on H&E preparations and can be demonstrated only with the use of metallic impregnation, immunohistochemical, or electron microscopic methods. *Astrocytes* typically have round to oval nuclei (10 μm wide) with evenly dispersed, pale chromatin; *oligodendrocytes* have a denser, more homogeneous chromatin in a rounder and smaller nucleus (8 μm); and *microglia* have an elongated, irregularly shaped nucleus (5 to 10 μm) with clumped chromatin. *Ependymal cells*, on the other hand, do have visible cytoplasm; seen with H & E, they are columnar epithelial-like cells with a ciliated/microvillous border facing the ventricular surface with pale, vesiculated nuclei (each about 8 μm) located at the abluminal end of the cell.

ASTROCYTES

This glial cell is found throughout the CNS in both gray and white matter. *Protoplasmic* astrocytes occur mainly in the gray matter; *fibrous* astrocytes occur in white and gray matter. The cell derives its name from its star-shaped appearance, which is imparted by the multipolar, branching cytoplasmic processes that emanate from the cell body containing the characteristic cytoplasmic intermediate filament protein called glial fibrillary acidic protein (GFAP). These are seen well in tissue sections only with metallic impregnation techniques (e.g., the Golgi method) (Fig. 28-1*A*) or immunohistochemical preparations (Fig. 28-1*B*). The filaments are either aggregated in fascicles (in protoplasmic astrocytes) or dispersed diffusely throughout the cytoplasm (in fibrous astrocytes). Some astrocytic processes are directed toward neurons and their processes and synapses, where they are believed to act as metabolic buffers or detoxifiers, suppliers of nutrients, and electrical insulators. Others surround capillaries or extend to the subpial and subependymal zones, where they contribute to barrier functions controlling the flow of macromolecules between the blood, the CSF, and the brain. Astrocytes are also the principal cells responsible for repair and scar formation in the brain. Fibroblasts, which have a major role in wound healing elsewhere, are located mainly around large CNS blood vessels and in the meninges; they participate in wound healing only to a limited extent (primarily in the organization of subdural hematomas and the formation of abscess cavities).

Figure 28-1 *A*, Astrocytes and their processes. Some processes extend toward blood vessels (Golgi). *B*, Immunoperoxidase staining for glial fibrillary acidic protein shows astrocytic perinuclear cytoplasm and well-developed processes (*brown*). *(Courtesy of Dr. J. Corbo, Brigham and Women's Hospital, Boston, MA.)*
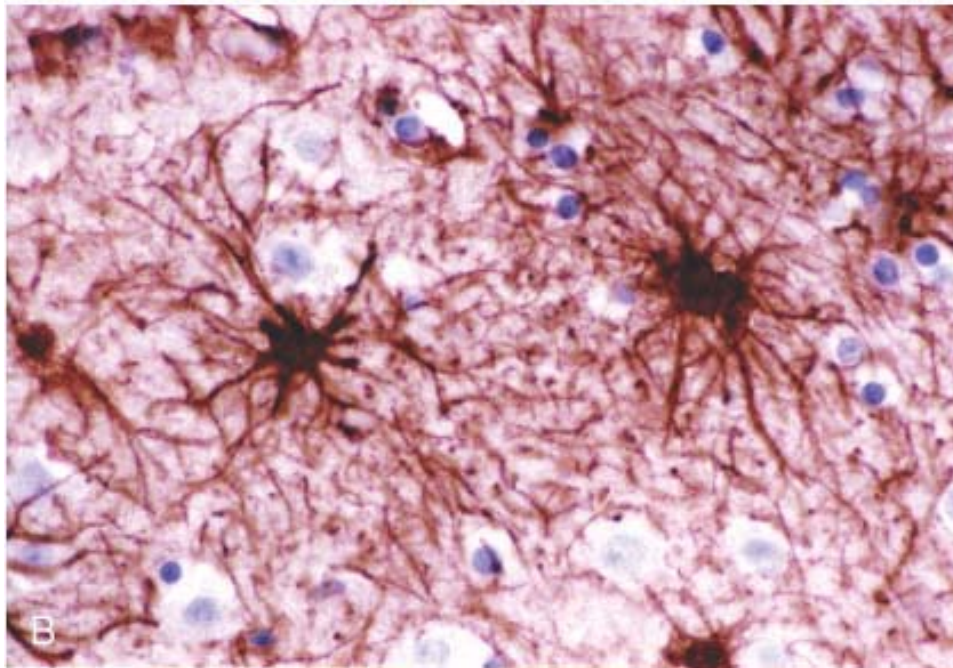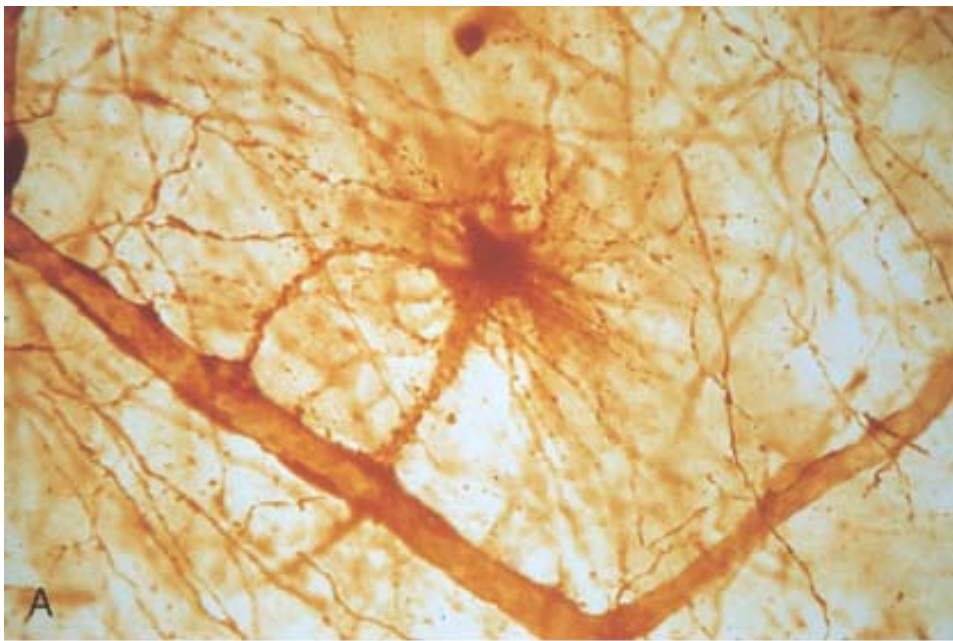
TABLE 28-1 -- Neurodegenerative Diseases Associated with Aggregated Proteins

Disease	Protein	Normal Structure	Aggregate/Inclusion	Location

Transmissible spongiform encephalopathies (Prion disease) (see Fig. 28-31)	Prion protein (PrP)	α-Helix and random coil	β-pleated sheet, proteinase K-resistant	Extracellular
Alzheimer disease (see Fig. 28-35*C*)	Amyloid precursor protein (APP)	α-Helix and random coil	β-pleated sheet, amyloid (fragment of APP)	Extracellular
Tauopathies and Alzheimer disease	Tau (microtubule binding protein)	3 and 4 repeat isoforms	Hyperphosphorylated aggregated protein	Intracellular
Parkinson disease (see Fig. 28-37*C*)	α-Synuclein	Random coil, repeats	Aggregated, Lewy bodies	Cytoplasmic
Multiple system atrophy	α-Synuclein	Random coil, repeats	Aggregated, Glial cytoplasmic inclusions	Cytoplasmic
Huntington disease	Huntingtin	Trinucleotide repeats	Insoluble aggregates	Nuclear
Spinocerebellar ataxias	Ataxins	Trinucleotide repeats	Insoluble aggregates	Nuclear

Modified from Welch WJ, Gambetti P: Chaperoning brain diseases. Nature 392:23–24, 1998.

REACTIONS OF ASTROCYTES TO INJURY

The cellular pathology of astrocytes may be subdivided into reactive responses that accompany the cells' proliferation (*gliosis*) and the sets of reactions to injury that lead to their death. In addition, morphologically diverse intracellular inclusions and deposits are seen in injured astrocytes.

 • *Gliosis* is the most important histopathologic indicator of CNS injury, regardless of etiology. Astrocytes participate in this process by undergoing both hypertrophy and hyperplasia. The nucleus enlarges and becomes vesicular, and the nucleolus is prominent. The previously scant cytoplasm expands to a bright pink, somewhat irregular swath around an eccentric nucleus, from which emerge numerous stout, ramifying processes (*gemistocytic astrocyte*). Immunohistochemistry for glial fibrillary acidic protein (GFAP) splendidly demonstrates the extraordinary metamorphosis. In long-standing lesions, the nuclei become small and dark and lie in a dense net of processes. These cell processes, glial "*fibrils,*" are not true extracellular fibers. Proliferation of astrocytes residing between the molecular and granule cell layers of the cerebellum is a regular accompaniment of anoxic injury and other conditions associated with death of Purkinje cells, termed *Bergmann gliosis*.

 • *Cellular swelling*, or swelling of the astrocyte cytoplasm, occurs regularly in acute insults when there is a failure of the cell's pump systems, as occurs in hypoxia, hypoglycemia, and toxic injuries.[13]

 • *Rosenthal fibers* are thick, elongated, brightly eosinophilic structures that are somewhat irregular in contour and occur within astrocytic processes. Ultrastructurally, they exhibit dense osmiophilic deposits that contain two heat-shock proteins (αB-crystallin and hsp27) and ubiquitin. Rosenthal fibers are typically found in regions of long-standing gliosis; they are also characteristic of cerebellar pilocytic astrocytoma (see later), as well as the reactive brain adjacent to craniopharyngioma or syrinx cavities. In *Alexander*

disease, a leukodystrophy due to a mutation in the gene for GFAP,[14]abundant Rosenthal fibers are found in periventricular, perivascular, and subpial locations.

 • *Corpora amylacea,* or polyglucosan bodies, are round, faintly basophilic, periodic acid-Schiff (PAS)-positive, concentrically lamellated structures ranging between 5 and 50 μm in diameter and located wherever there are astrocytic end processes, especially in the subpial and perivascular zones. Although consisting primarily of glycosaminoglycan polymers, they also contain heat-shock proteins and ubiquitin. They represent a degenerative change in the astrocyte, and they occur in increasing numbers with advancing age and in a rare condition called *adult polyglucosan body disease*. The *Lafora bodies* that are seen in the cytoplasm of neurons (as well as hepatocytes, myocytes, and other cells) in myoclonic epilepsy (Lafora body myoclonus with epilepsy) are of similar structure and biochemical composition.

 • *Glial cytoplasmic inclusions* consisting of silver-positive meshes of 20- to 40-nm intermediate filaments that contain the protein α-synuclein[15] are characteristic of a number

of CNS degenerative diseases, collectively known as multiple system atrophy. [16]

• The *Alzheimer type II astrocyte* is a gray matter astrocyte with a large (two to three times normal) nucleus, pale-staining central chromatin, an intranuclear glycogen droplet, and a prominent nuclear membrane and nucleolus. Despite its name, it is unrelated to Alzheimer disease; rather, it occurs especially in patients with long-standing hyperammonemia due to chronic liver disease, Wilson disease, or hereditary metabolic disorders of the urea cycle.

Cerebral Edema, Raised Intracranial Pressure and Herniation, and Hydrocephalus

The brain and spinal cord exist within a rigid compartment defined by the skull, vertebral bodies, and dura mater. The advantage of housing as vital and delicate a structure as the CNS in a protective environment is obvious. On the other hand, such rigid confines provide little room for brain parenchymal expansion in disease states. A number of disorders may upset the delicate balance between brain volume and the fixed boundaries of the intracranial vault. These conditions include generalized brain edema, hydrocephalus, and focally expanding mass lesions.

CEREBRAL EDEMA

Cerebral edema or, more precisely, brain parenchymal edema may arise in the setting of a number of diseases. Two principal types are recognized:

• *Vasogenic edema* occurs when the integrity of the normal blood-brain barrier is disrupted and increased vascular permeability occurs, allowing fluid to escape from the intravascular compartment predominantly into the intercellular spaces of the brain. The paucity of conventional lymphatics and the close apposition of cell processes of neurons and glia in the brain greatly impairs the resorption of excess extracellular fluid. Vasogenic edema may be either localized, as when it results from abnormally permeable vessels adjacent to inflammatory disease or neoplasms, or generalized.
• *Cytotoxic edema*, in contrast, implies an increase in intracellular fluid secondary to neuronal, glial or endothelial cell membrane injury, as might be encountered in a patient with a generalized hypoxic/ischemic insult or with some intoxications.

In practice, conditions associated with generalized edema often have elements of both vasogenic and cytotoxic edema.

Interstitial edema (hydrocephalic edema) occurs especially around the lateral ventricles when there is an abnormal flow of fluid from the intraventricular CSF across the ependymal lining to the periventricular white matter in a setting of increased intraventricular pressure.

Morphology.

The edematous brain is softer than normal and often appears to "overfill" the cranial vault. In generalized edema, the gyri are flattened, the intervening sulci are narrowed, and the ventricular cavities are compressed. As the brain expands, herniation may occur.

RAISED INTRACRANIAL PRESSURE AND HERNIATION

Raised intracranial pressure is an increase in mean CSF pressure above 200 mm water with the patient recumbent. It occurs when the volume of brain tissue increases beyond the limit permitted by compression of veins and displacement of CSF. Most cases are associated with a mass effect, either diffuse, as in generalized brain edema, or focal, as with tumors, abscesses, or hemorrhages. Because the cranial vault is subdivided by rigid dural folds (the falx and tentorium), a focal expansion of the brain causes it to be displaced in relation to these partitions. If the expansion is sufficiently severe, a *herniation* of the brain will occur (Fig. 28-2).

• *Subfalcine (cingulate) herniation* occurs when unilateral or asymmetric expansion of a cerebral hemisphere displaces the cingulate gyrus under the falx cerebri. This may be associated with compression of branches of the anterior cerebral artery.
• *Transtentorial (uncinate, mesial temporal) herniation* occurs when the medial aspect of the temporal lobe is compressed against the free margin of the tentorium cerebelli.

With increasing displacement of the temporal lobe, the third cranial nerve is compromised, resulting in pupillary dilation and impairment of ocular movements on the side of the lesion. The posterior cerebral artery may also be compressed, resulting in ischemic injury to the territory supplied by that vessel, including the primary visual cortex. When the extent of herniation is large enough, the contralateral cerebral peduncle may be compressed, resulting in hemiparesis ipsilateral to the side of the herniation; the changes in the peduncle in this setting are known as *Kernohan's notch*. Progression of transtentorial herniation is often accompanied by hemorrhagic lesions in the midbrain and pons, termed *secondary brainstem*, or *Duret*, *hemorrhages* (Fig. 28-3). These linear or flame-shaped lesions usually occur in the midline and paramedian regions and

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are believed to be due to tearing of penetrating veins and arteries supplying the upper brainstem.

•*Tonsillar herniation* refers to displacement of the cerebellar tonsils through the foramen magnum. This pattern of herniation is life-threatening because it causes brainstem compression and compromises vital respiratory and cardiac centers in the medulla oblongata.

Figure 28-2 Major herniations of the brain: subfalcine, transtentorial, and tonsillar. *(Adapted from Fishman RA: Brain edema. N Engl J Med 293:706, 1975. Copyright © 1975, Massachusetts Medical Society. All rights reserved.)*

Subfalcine
herniation

Transtentorial
herniation

Tonsillar herniation
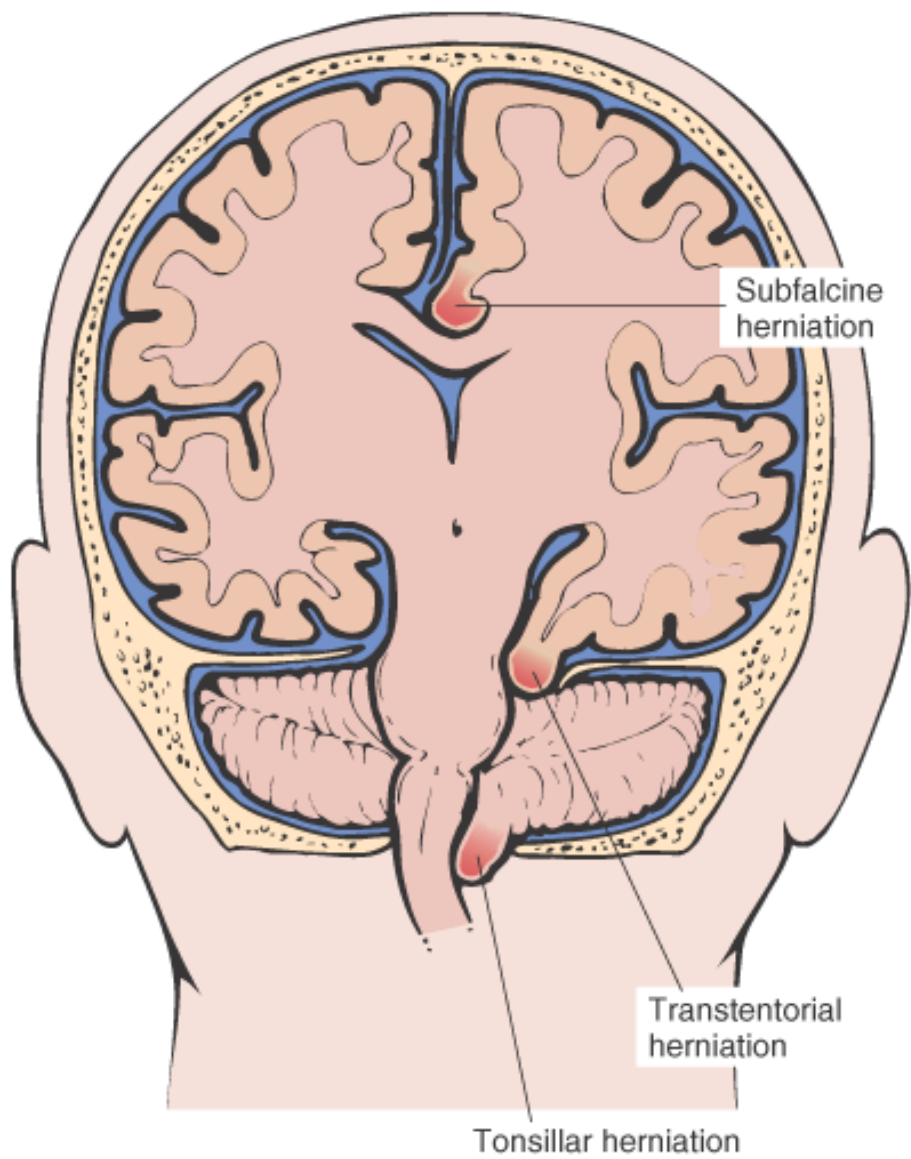
Figure 28-3 Duret hemorrhage involving the brainstem at the junction of the pons and midbrain.

Figure 28-4 *A*, Hydrocephalus. Dilated lateral ventricles seen in a coronal section through the midthalamus. *B*, Midsagittal plane T1-weighted magnetic resonance image of a child with communicating hydrocephalus, involving all ventricles. *(B, courtesy of Dr. P. Barnes, Stanford University Medical Center, CA.)*

Figure 28-5 Holoprosencephaly (severe alobar form). View of the dorsal surface showing a lack of separation of cerebral hemispheres, a single ventricle, and fused basal ganglia.

Figure 28-6 Agenesis of the corpus callosum. The midsagittal view of the left hemisphere shows the lack of a corpus callosum and cingulate gyrus above the third ventricle.

Figure 28-7 Arnold-Chiari malformation. Midsagittal section showing small posterior fossa contents, downward displacement of the cerebellar vermis, and deformity of the medulla (arrows indicate the approximate level of the foramen magnum).

Figure 28-8 Periventricular leukomalacia. Central focus of white matter necrosis with a peripheral rim of mineralized axonal processes (staining blue).
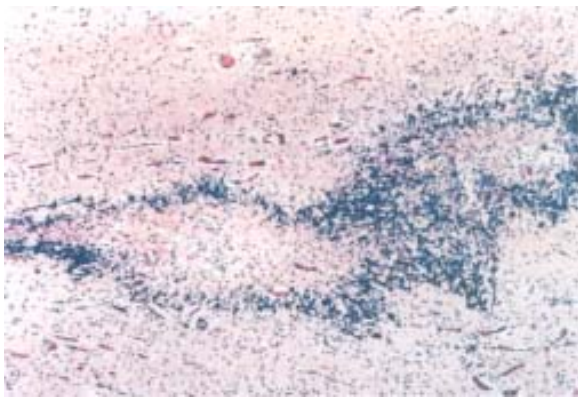
Figure 28-9 *A*, Multiple contusions involving the inferior surfaces of frontal lobes, anterior temporal lobes, and cerebellum. *B*, Acute contusions are present in both temporal lobes, with areas of hemorrhage and tissue disruption. *C*, Remote contusions are present on the inferior frontal surface of this brain, with a yellow color (associated with the term *plaque jaune*).
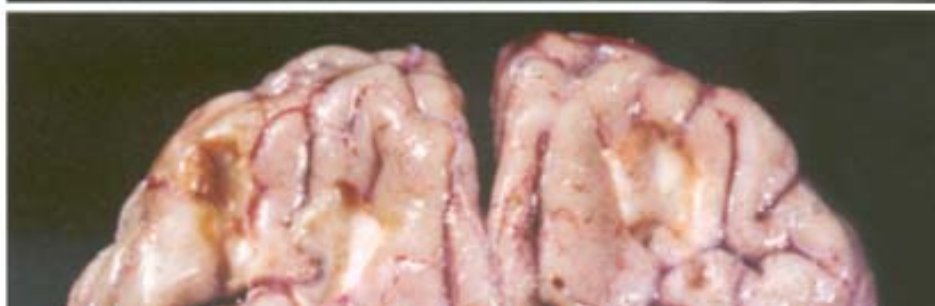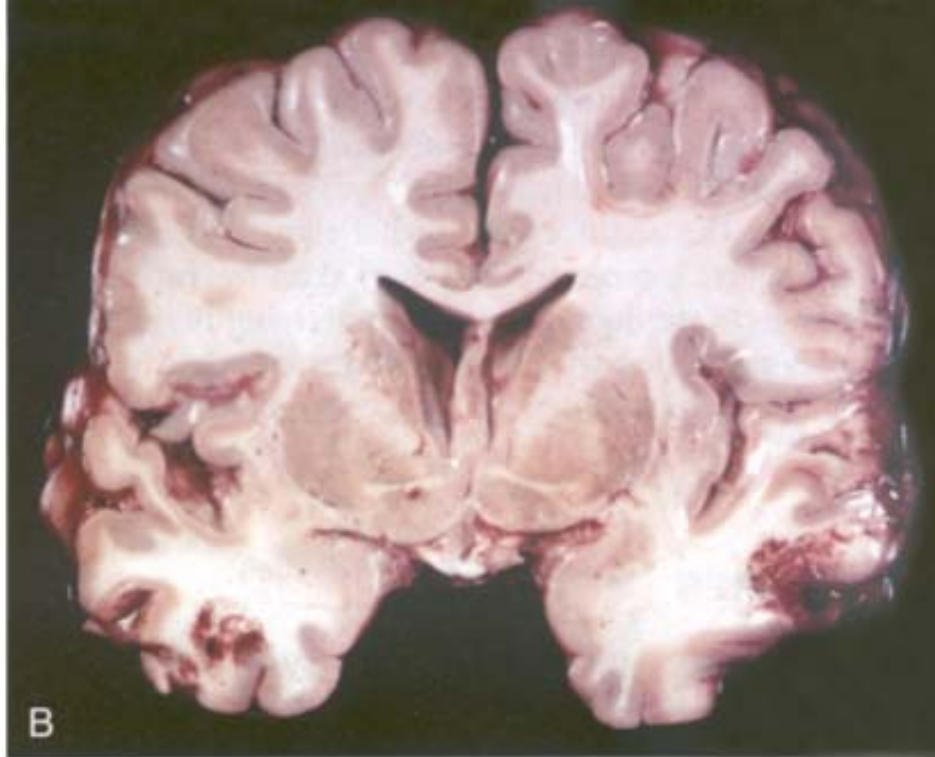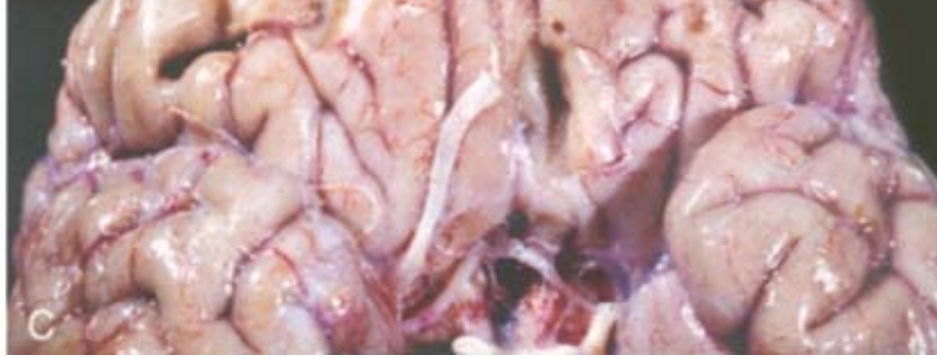
Figure 28-10 Epidural hematoma covering a portion of the dura. Multiple small contusions are seen in the temporal lobe. *(Courtesy of Dr. Raymond D. Adams, Massachusetts General Hospital, Boston, MA.)*
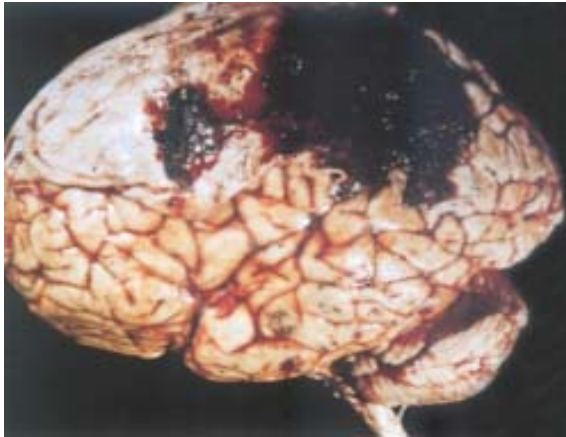
Figure 28-11 Epidural hematoma *(left)* in which rupture of a meningeal artery, usually associated with a skull fracture, leads to accumulation of arterial blood between the dura and the skull. In a subdural hematoma *(right)*, damage to bridging veins between the brain and the superior sagittal sinus leads to the accumulation of blood between the dura and the arachnoid.
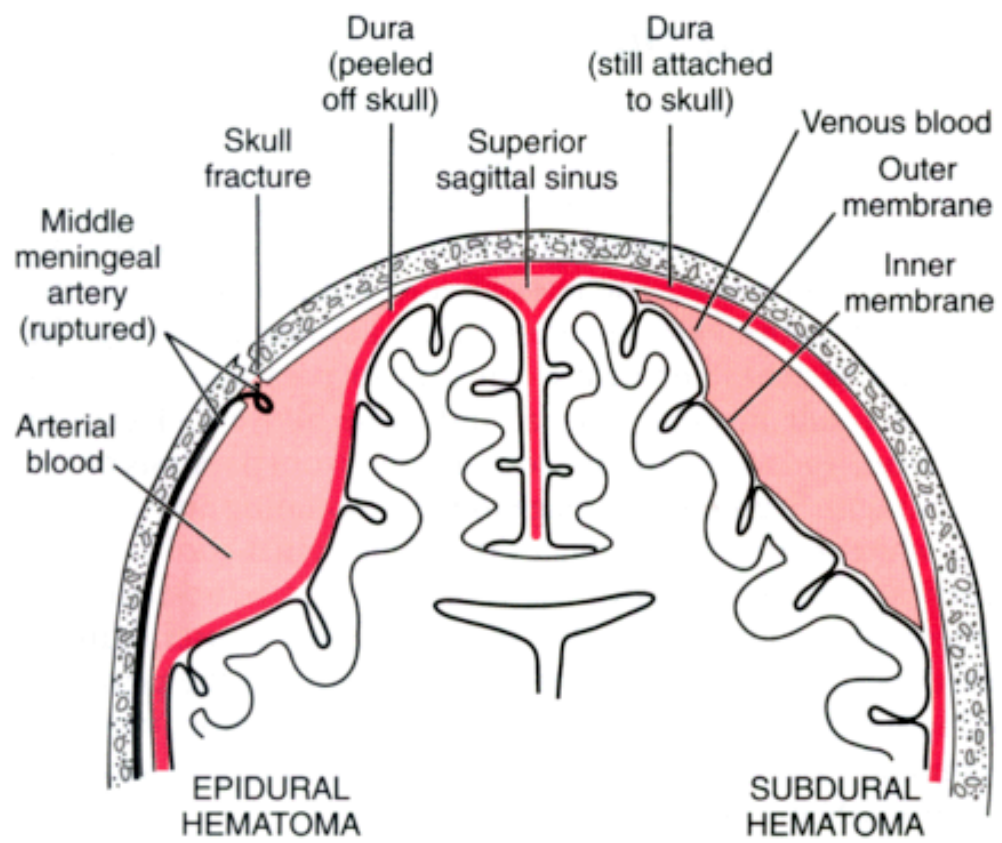
Figure 28-12 *A*, Large organizing subdural hematoma attached to the dura. *B*, Coronal section of the brain showing compression of the hemisphere underlying the hematoma.
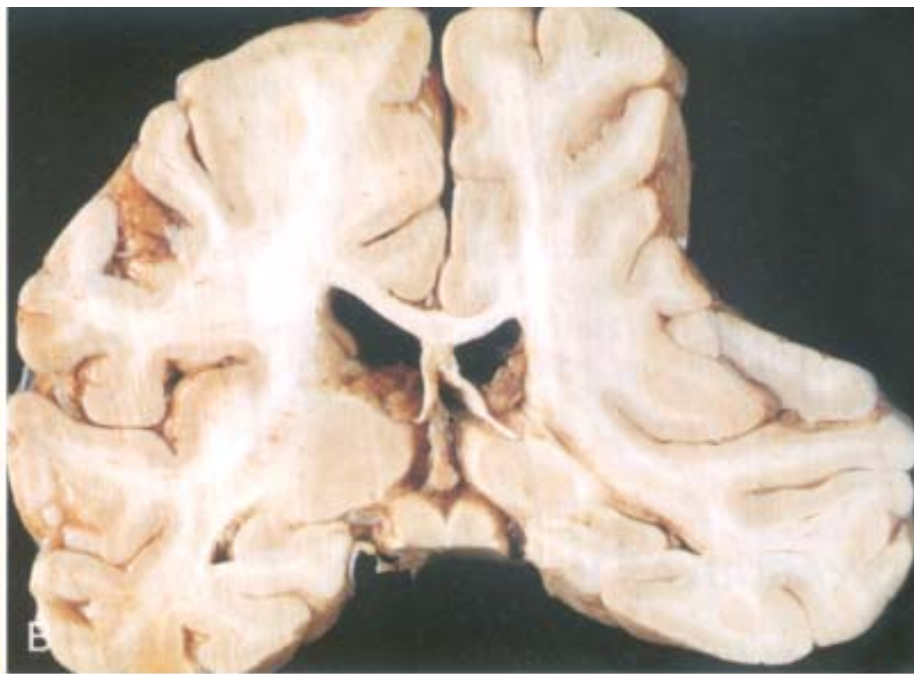
Figure 28-13 Cerebral infarction. *A*, At low magnification, it is possible to see the demarcated areas of an acute infarction. In the underlying white matter, the areas of infarction are well shown by the myelin stain. *B*, Acute ischemic injury causes diffuse eosinophilia of neurons, which are beginning to shrink. *C*, Infiltration of a cerebral infarct by neutrophils begins at the edges of the lesion where vascular supply has remained intact. *D*, After about 10 days, an area of infarction is characterized by the presence of macrophages and surrounding reactive gliosis. *E*, Remote small intracortical infarcts are seen as areas of tissue loss with a small amount of residual gliosis.
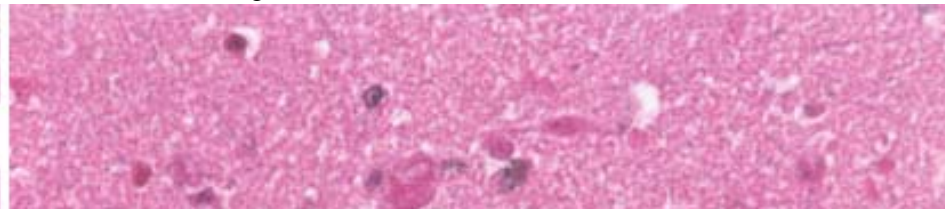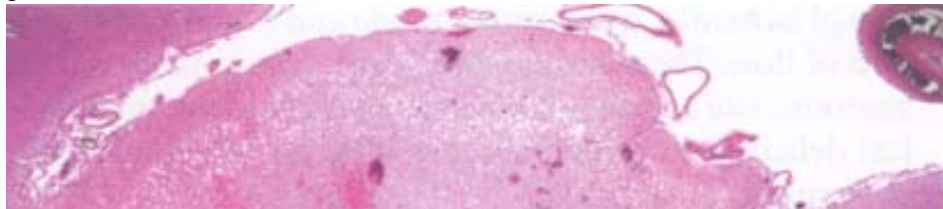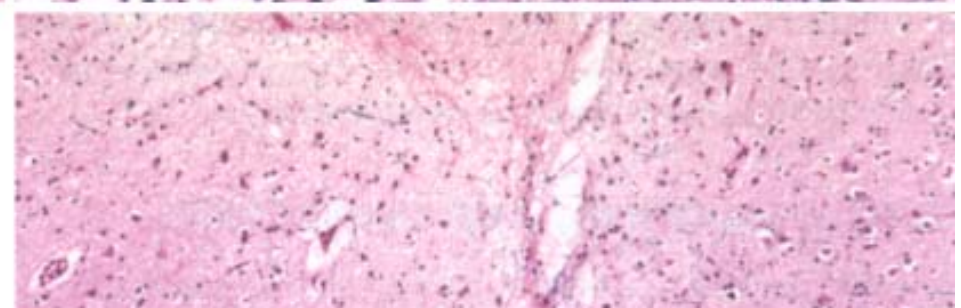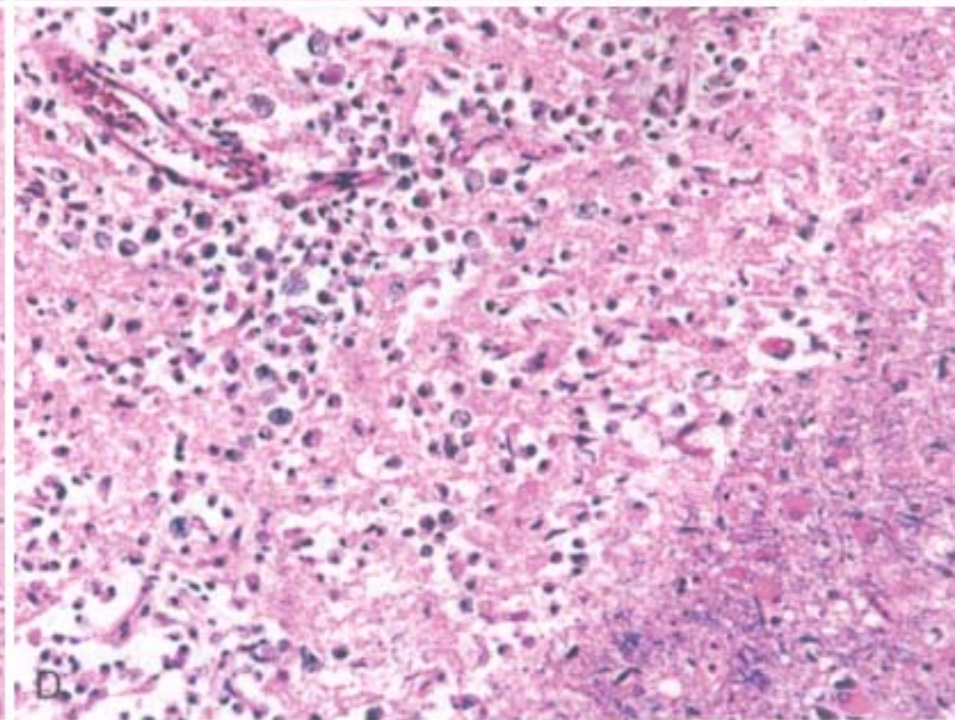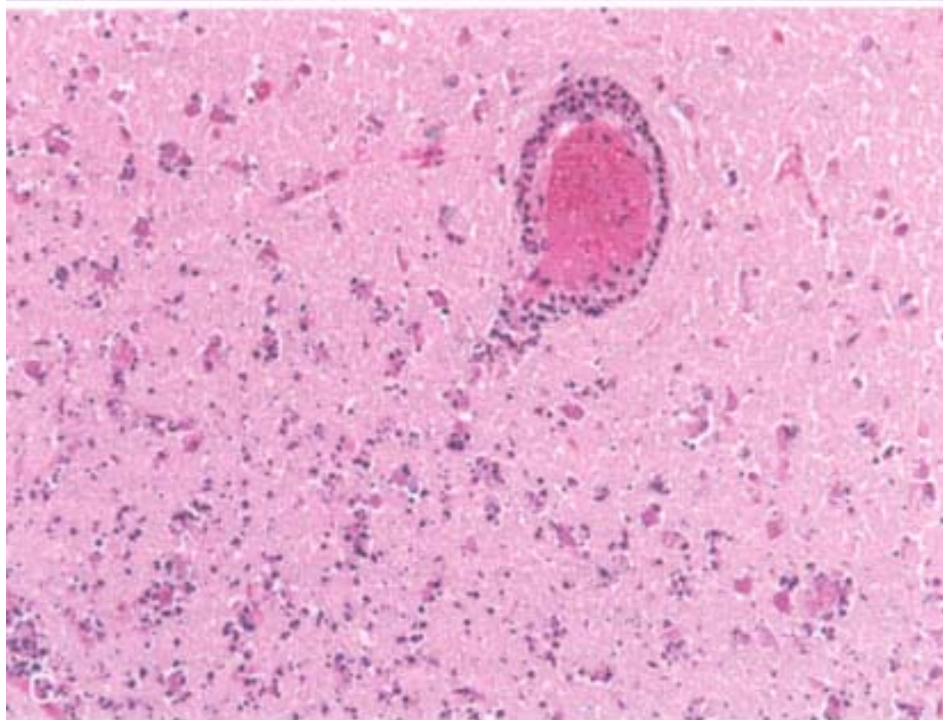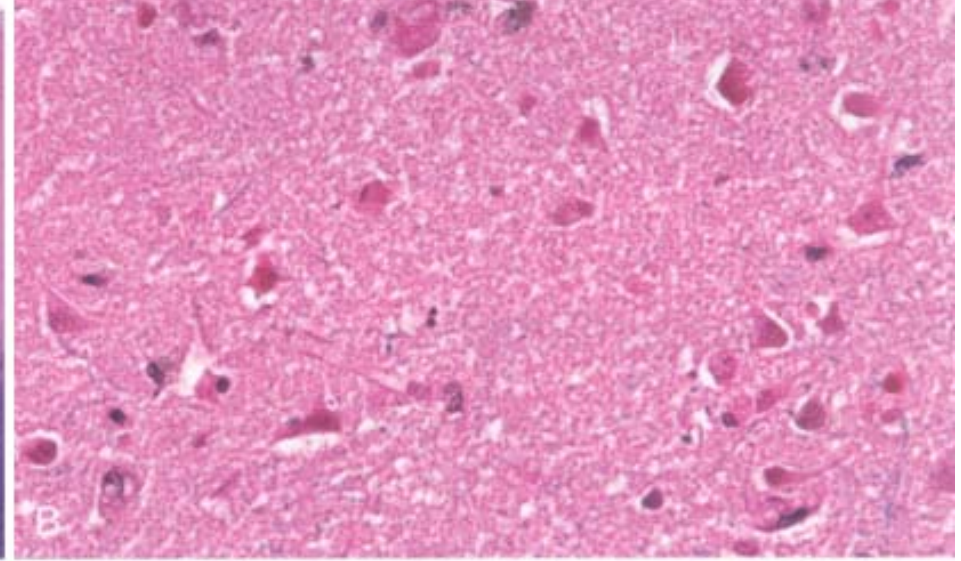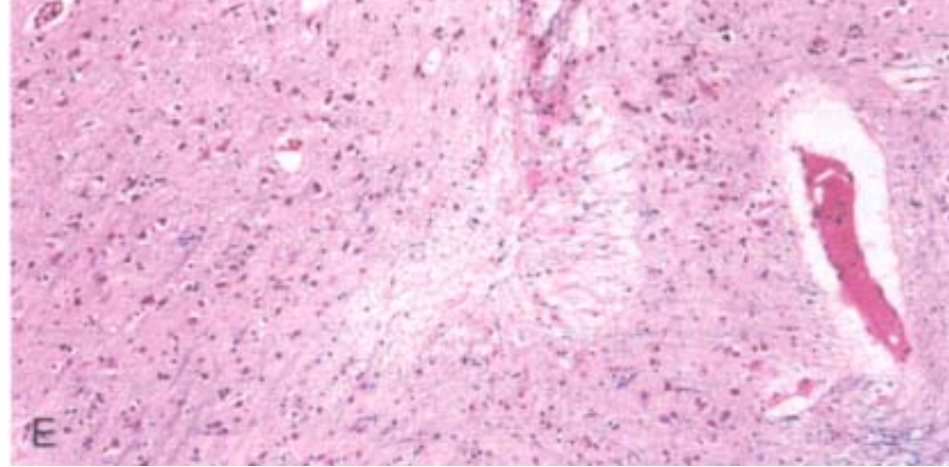
Figure 28-14 Widespread white matter hemorrhages are characteristic of bone marrow embolization.
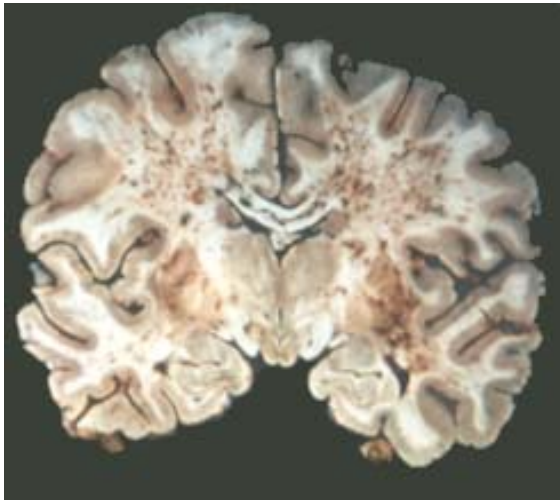

Figure 28-15 *A*, Sections of the brain showing a large, discolored, focally hemorrhagic region in the left middle cerebral artery distribution (hemorrhagic, or red, infarction). *B*, A hemorrhagic infarction is present in the inferior temporal lobe of the left side of this brain. *C*, A bland infarct with punctate hemorrhages, consistent with ischemia-reperfusion injury, is present in the temporal lobe.
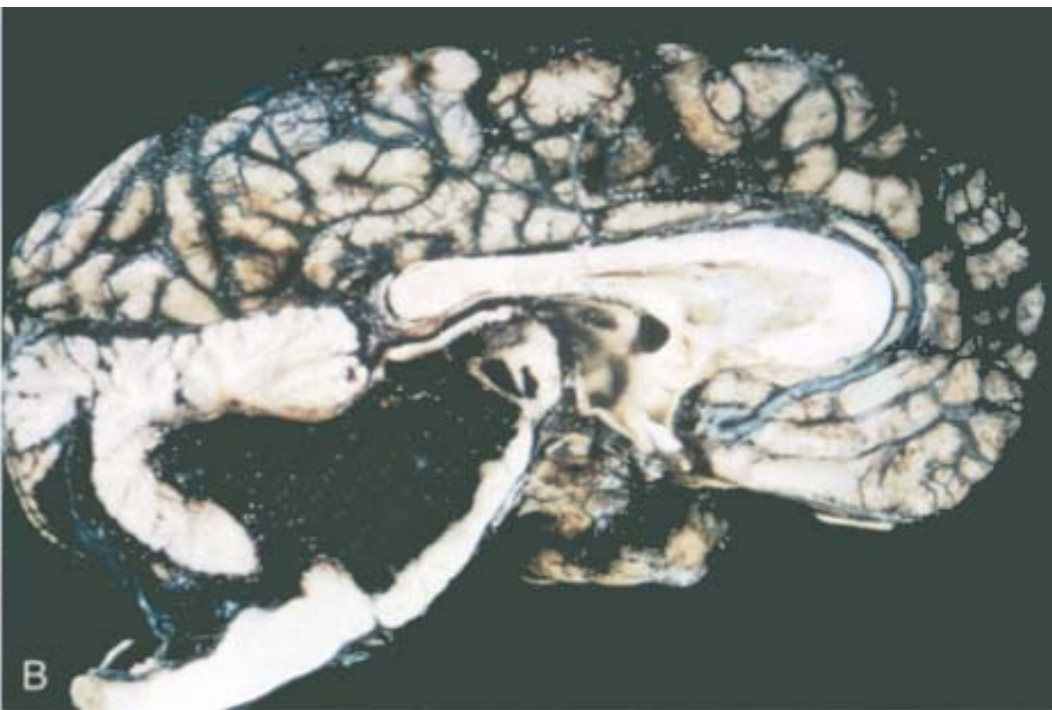
A

B

C
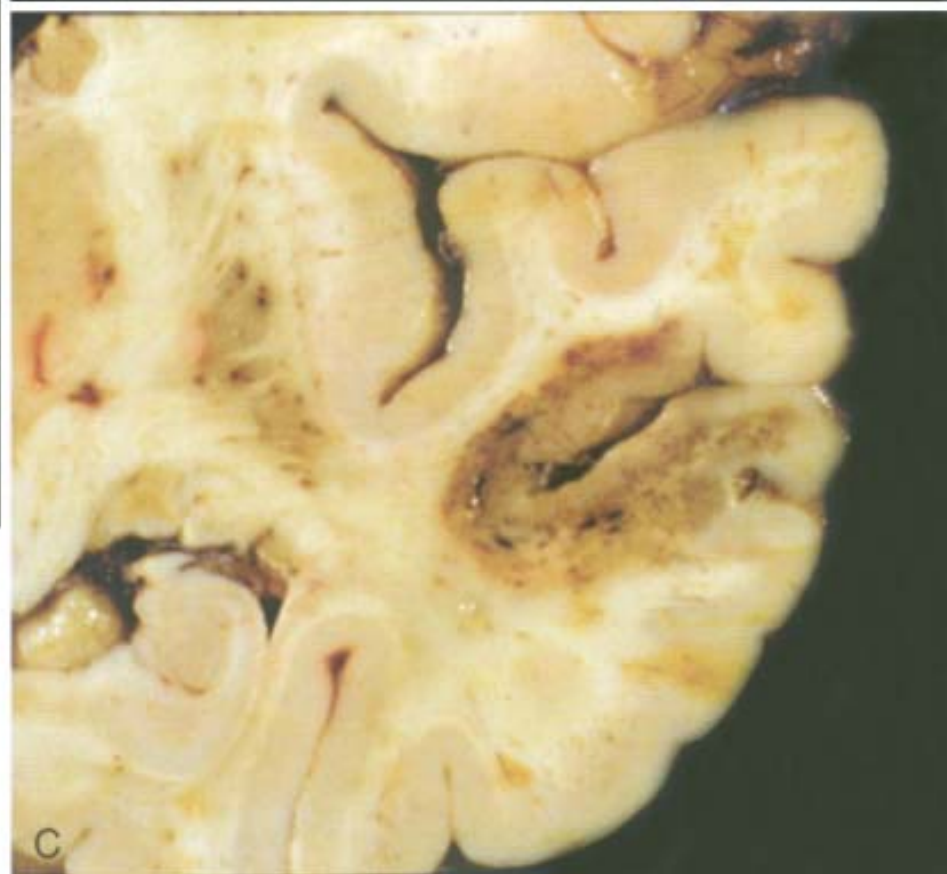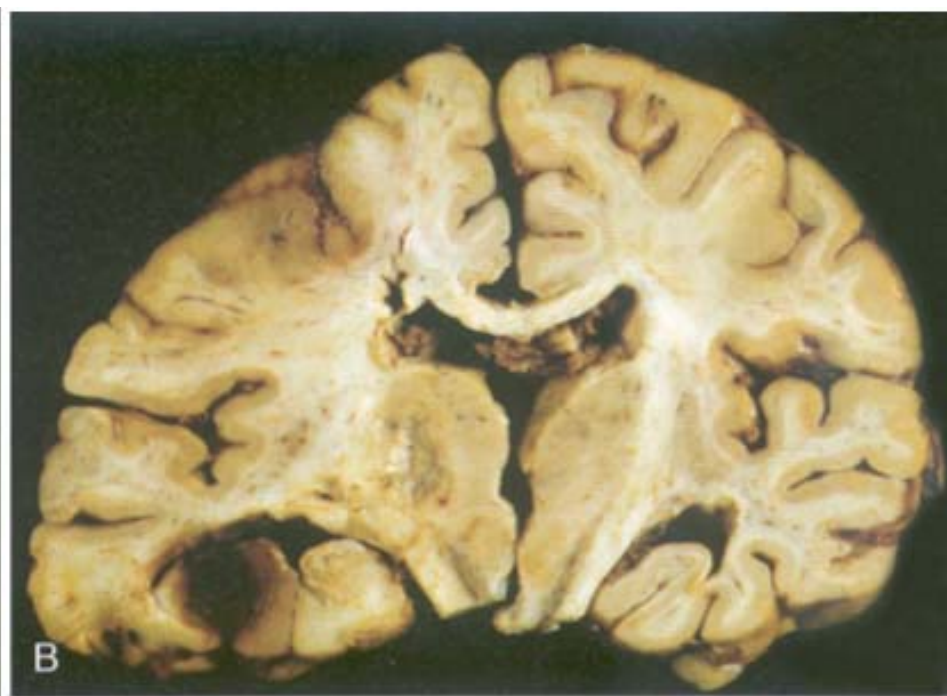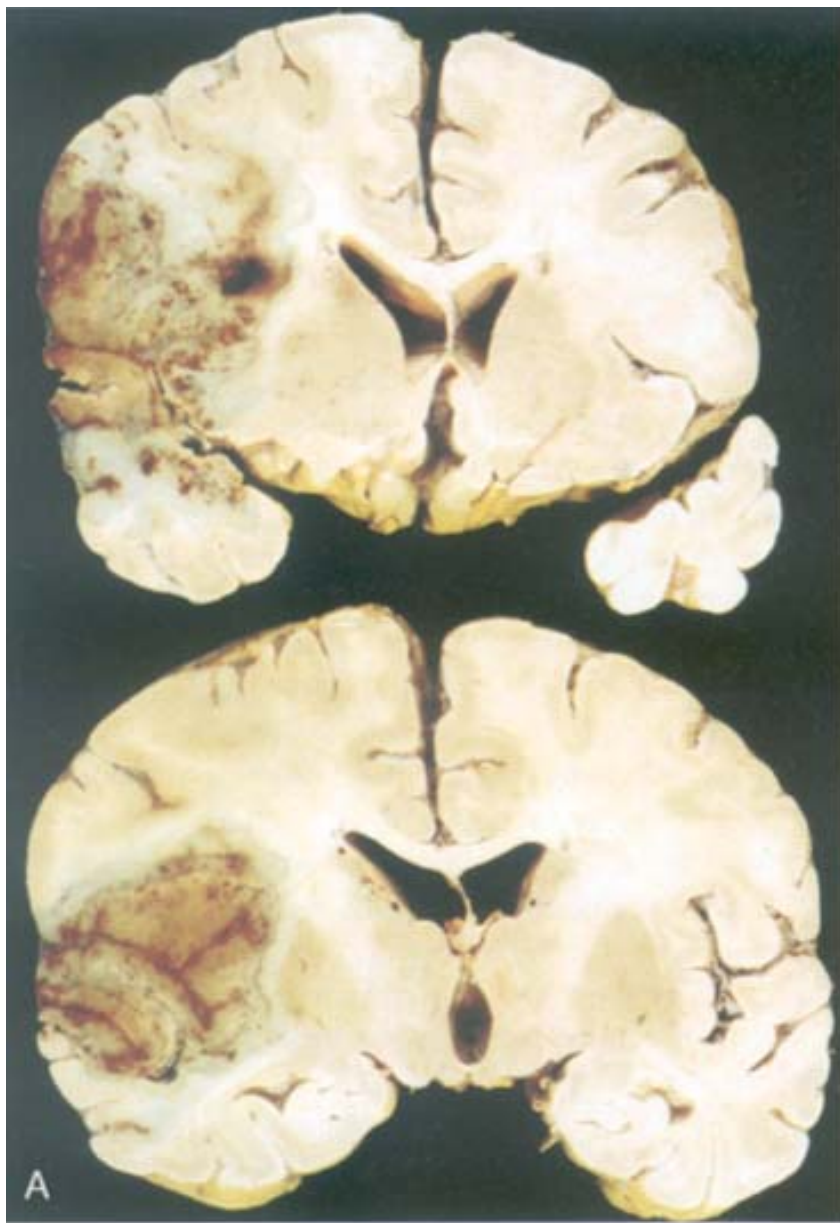
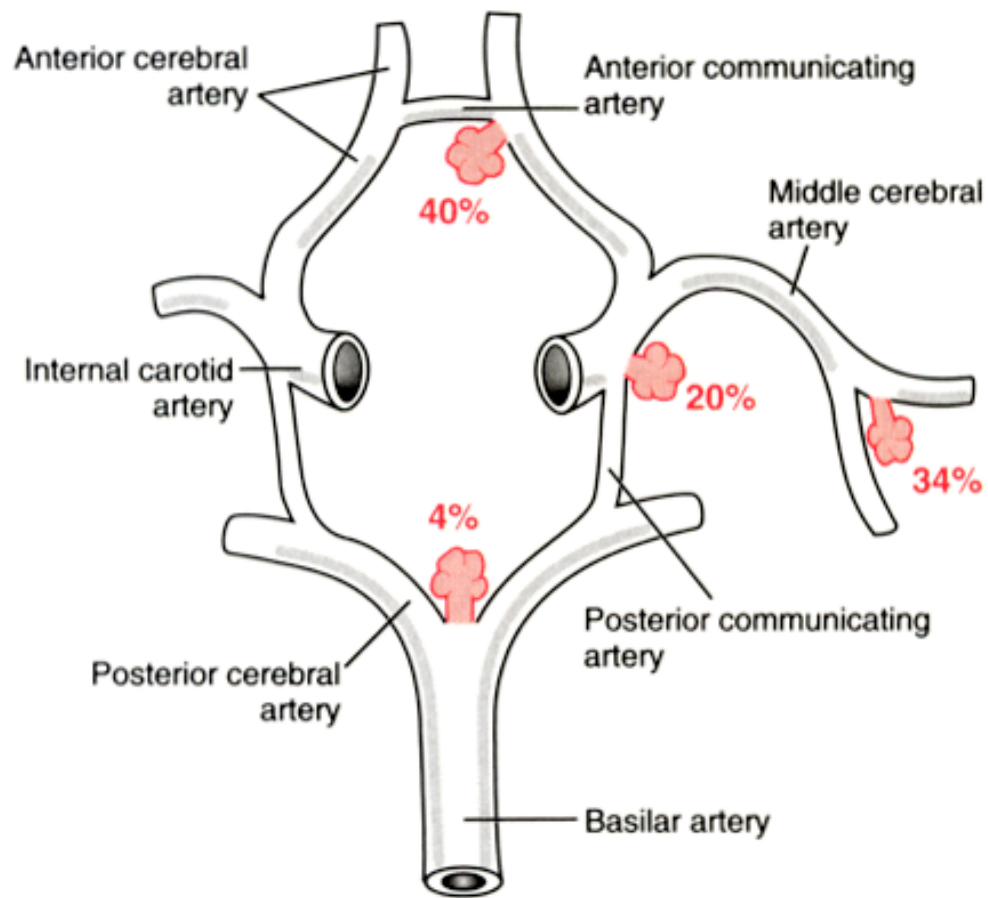**Figure 28-16** Old cystic infarct. Destruction of cortex and surrounding gliosis.
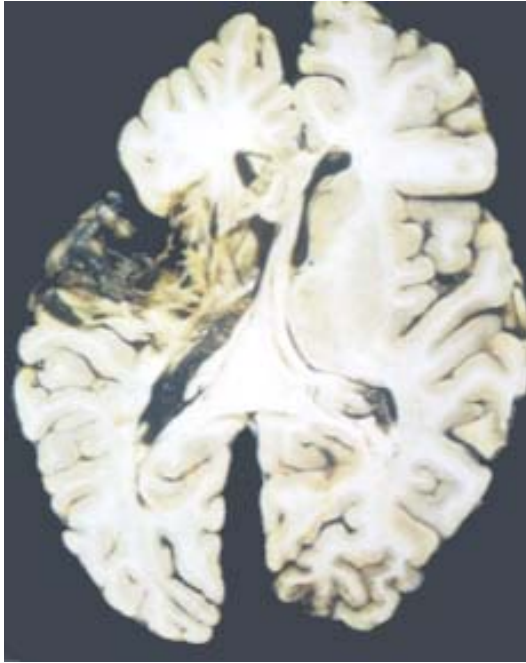
Figure 28-17 *A*, Massive hypertensive hemorrhage rupturing into a lateral ventricle. *B*, Hypertensive hemorrhage in the pons, with extension to fill the fourth ventricle.
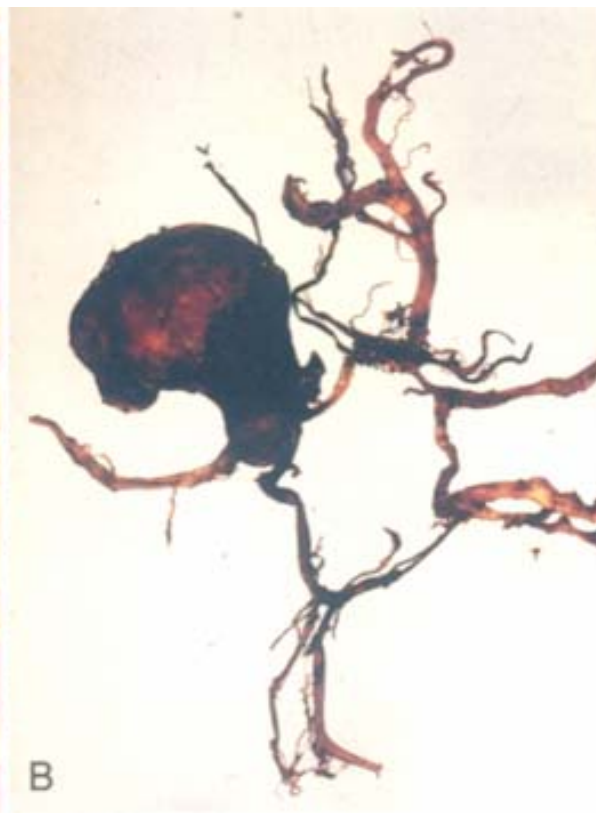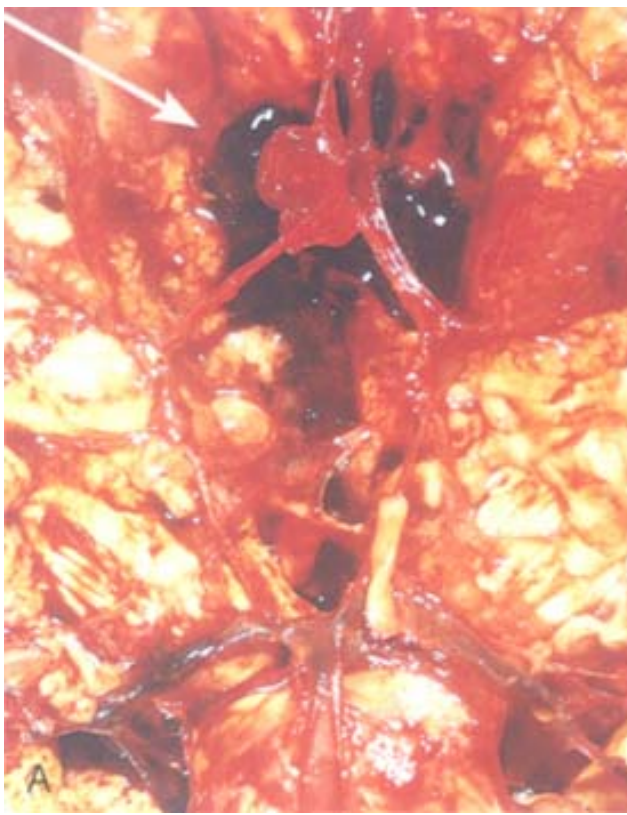
Figure 28-18 Common sites of saccular (berry) aneurysms in the circle of Willis.

Figure 28-19 *A*, View of the base of the brain, dissected to show the circle of Willis with an aneurysm of the anterior cerebral artery *(arrow)*. *B*, Dissected circle of Willis to show large aneurysm. *C*, Section through a saccular aneurysm showing the hyalinized fibrous vessel wall (H & E).
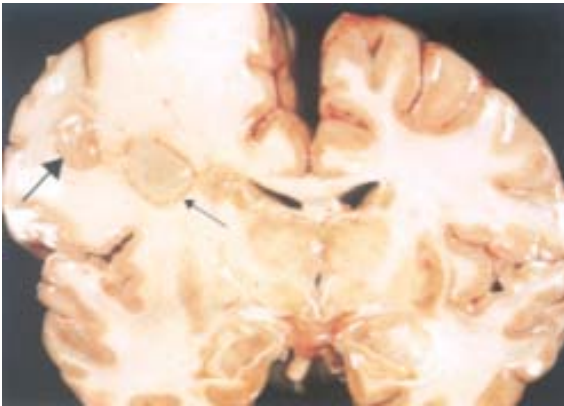
Figure 28-20 Lacunar infarcts in the caudate and putamen.

Figure 28-21 Pyogenic meningitis. A thick layer of suppurative exudate covers the brain stem and cerebellum and thickens the leptomeninges. *(From Golden JA, Louis DN: Images in clinical medicine: Acute bacterial meningitis. N Engl J Med 333:364, 1994.)*
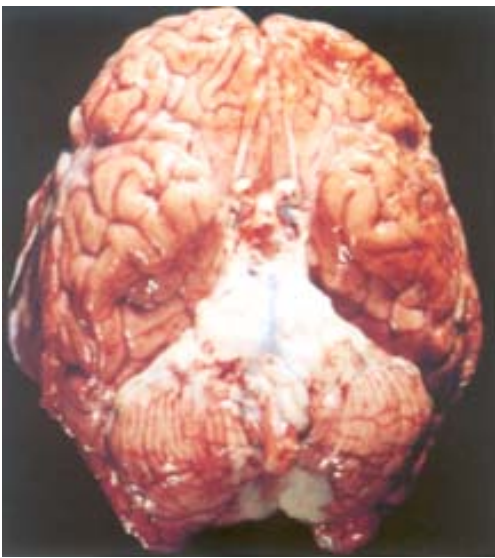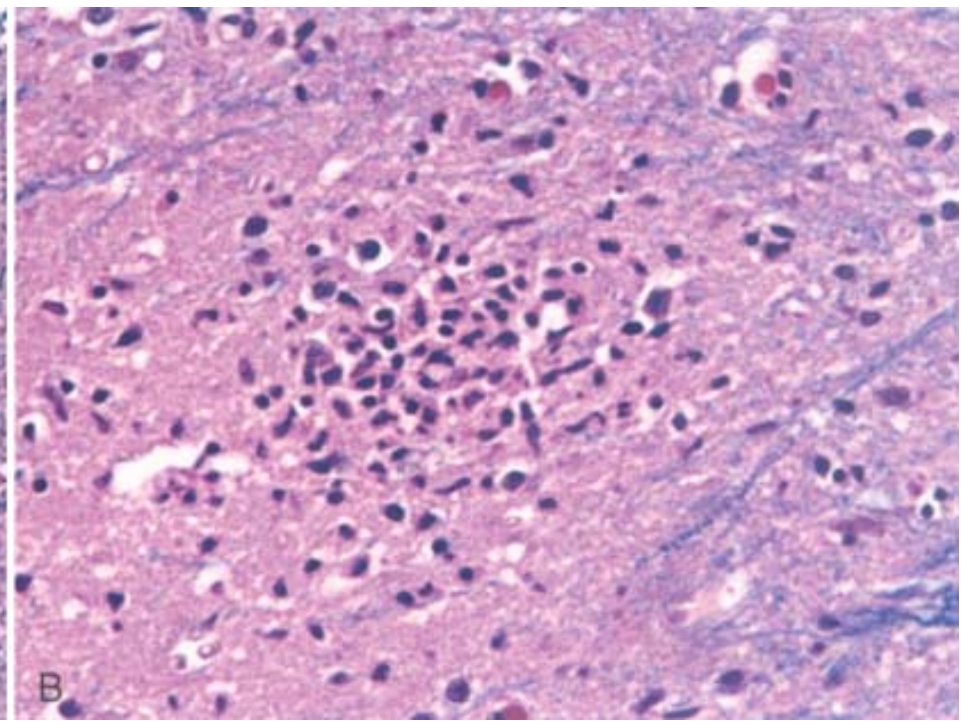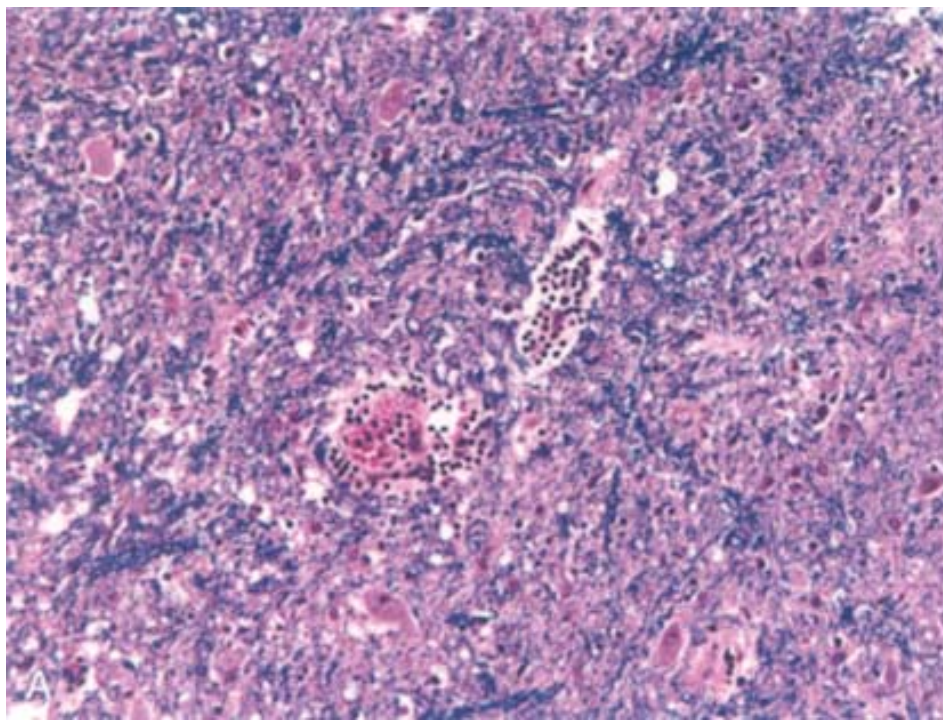
Figure 28-22 Frontal abscesses (*arrows*).

Figure 28-23 Characteristic findings of viral meningitis include perivascular cuffs of lymphocytes *(A)* and microglial nodules *(B)*.

Figure 28-24 *A*, Herpes encephalitis showing extensive destruction of inferior frontal and anterior temporal lobes. *(Courtesy of Dr. T.W. Smith, University of Massachusetts Medical School, Worcester, MA.) B*, Necrotizing inflammatory process characterizes the acute herpes encephalitis.
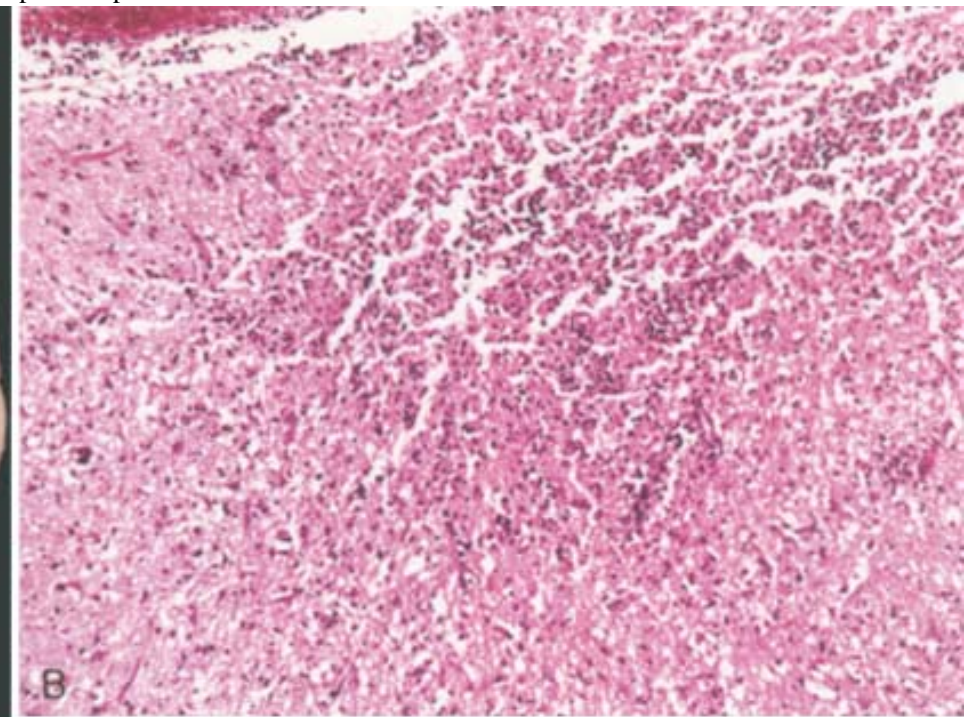
Figure 28-25 The diagnostic histologic finding in rabies is the eosinophilic Negri body, as seen here in a Purkinje cell *(arrows).*
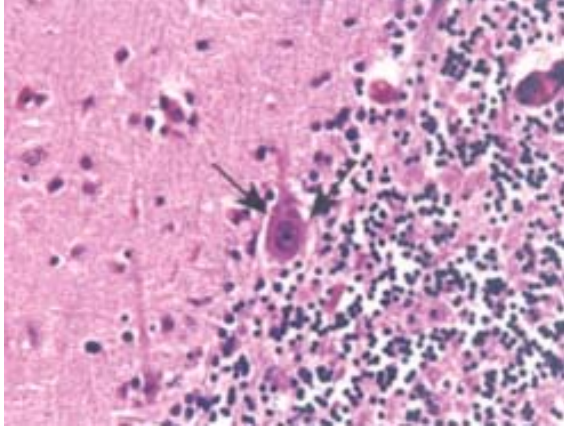
Figure 28-26 HIV encephalitis. Note the microglial nodule and multinucleated giant cells.
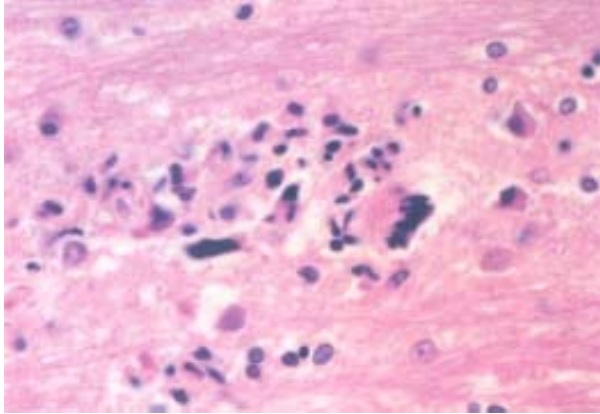
Figure 28-27 Progressive multifocal leukoencephalopathy. *A*, Section stained for myelin showing irregular, poorly defined areas of demyelination, which become confluent in places. *B*, Enlarged oligodendrocyte nuclei stained for viral antigens surround an area of early myelin loss.

A
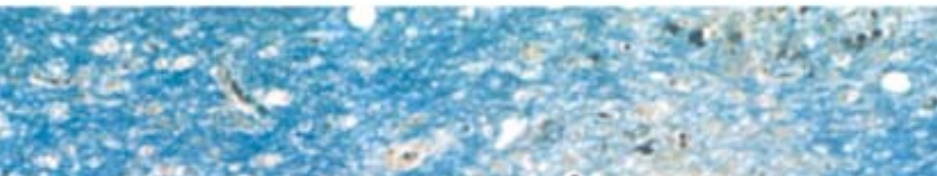
Figure 28-28 Cryptococcal infection. *A*, Whole brain section showing the numerous areas of tissue destruction associated with the spread of organisms in the perivascular spaces. *B*, At higher magnification, it is possible to see the cryptococci in the lesions.
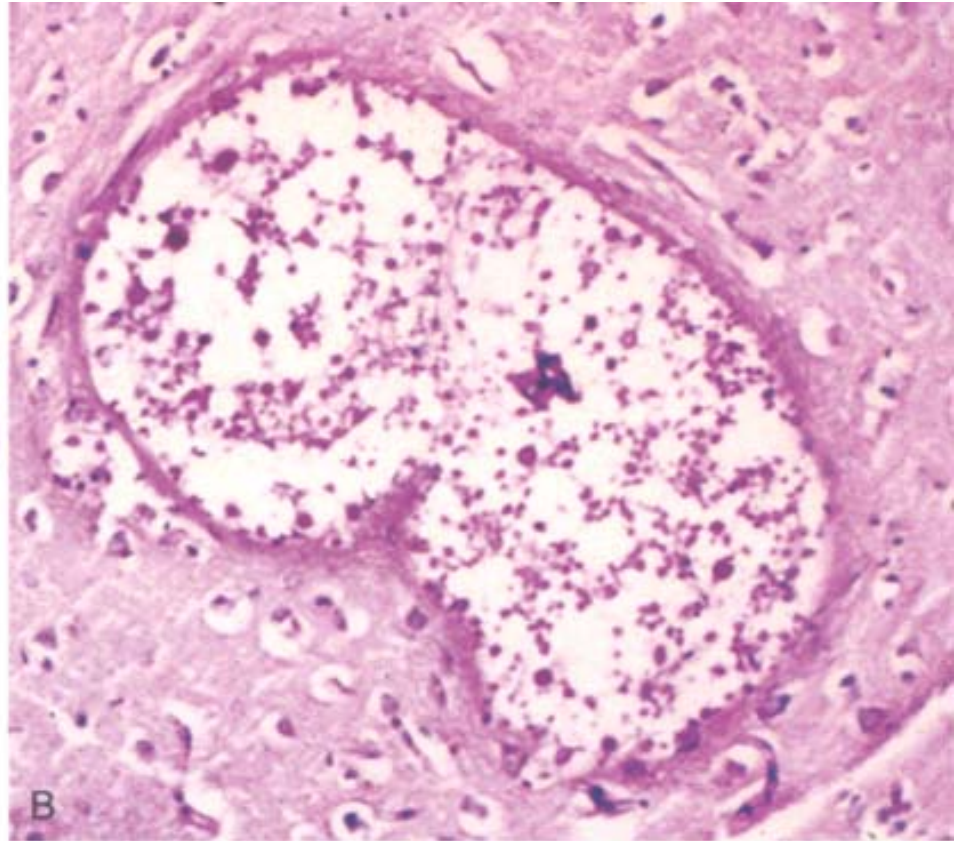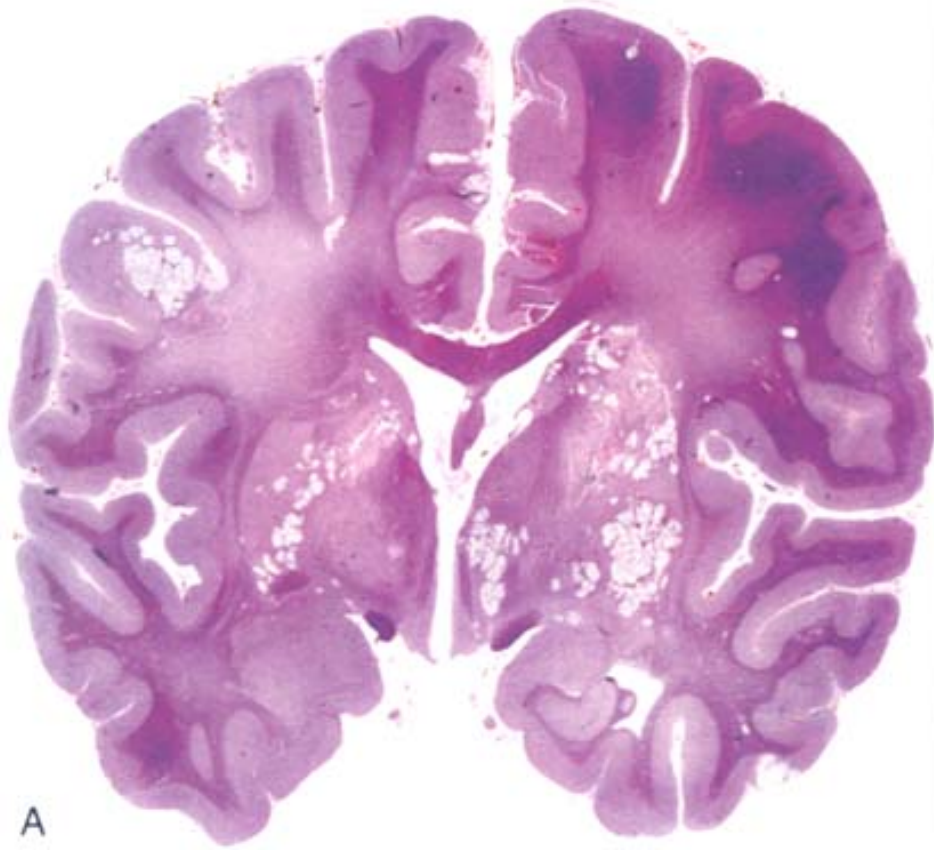
Figure 28-29 *A*, *Toxoplasma* abscesses in the putamen and thalamus. *B*, Free tachyzoites demonstrated by immunostaining. *C*, *Toxoplasma* pseudocyst with bradyzoites highlighted by immunostaining.
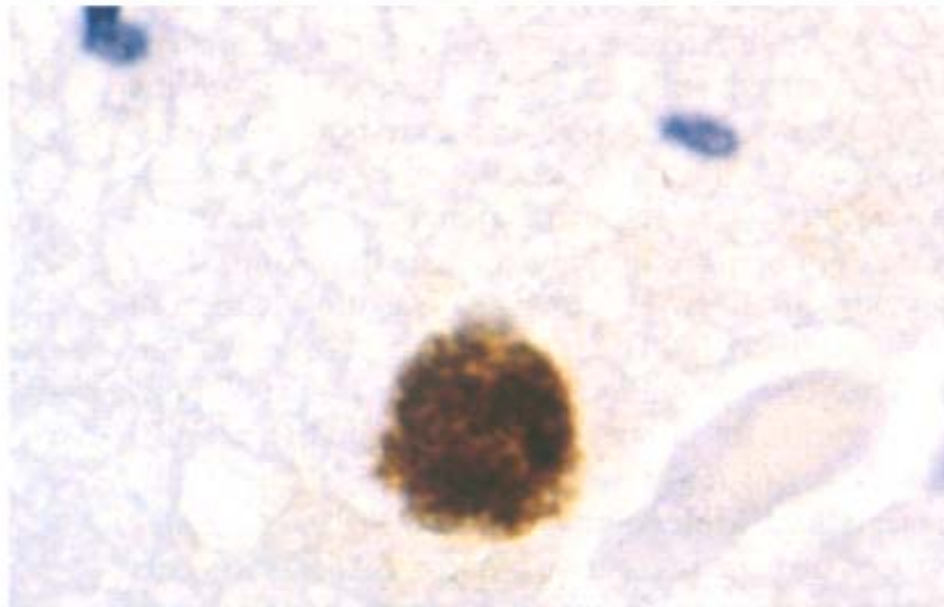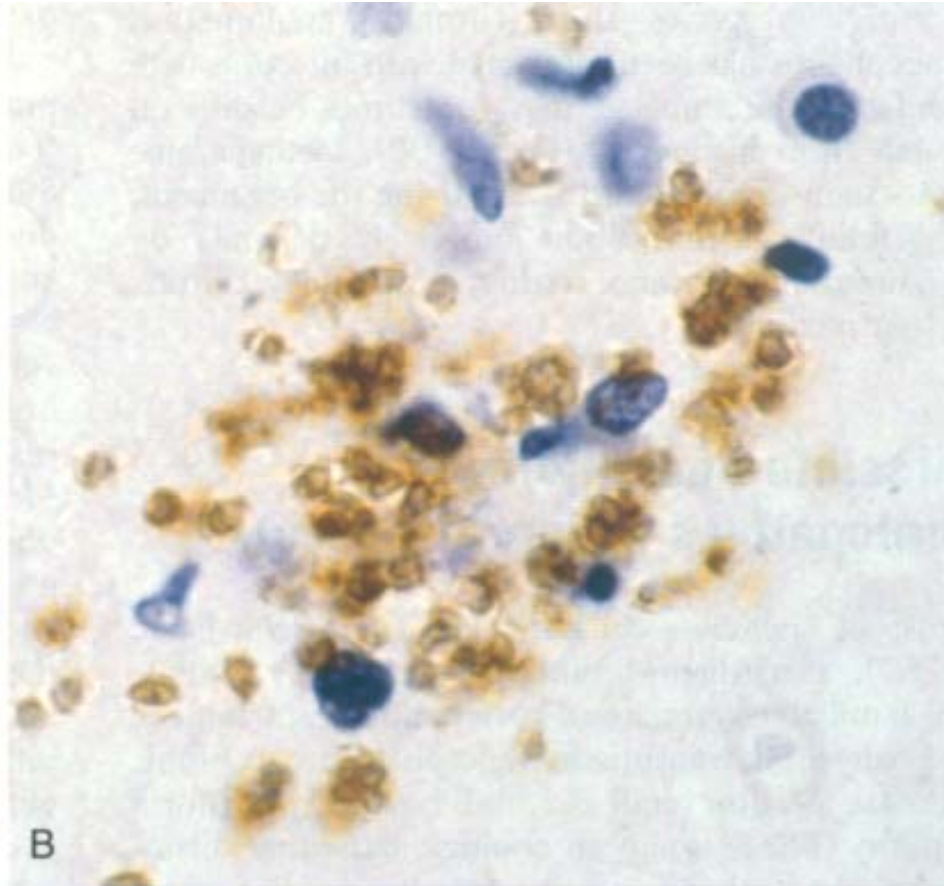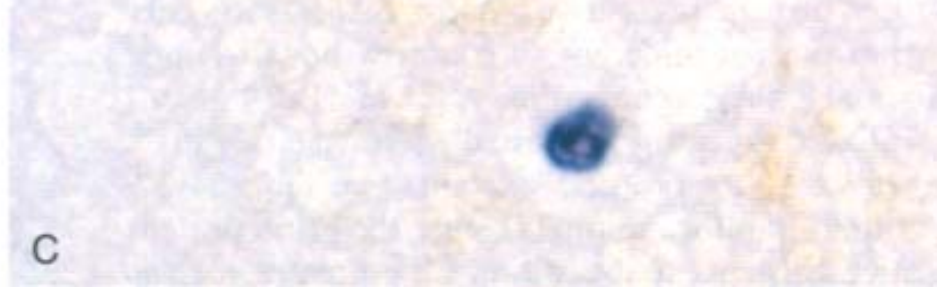
Figure 28-30 Necrotizing amoebic meningoencephalitis involving the cerebellum *(organism highlighted by arrow)*.
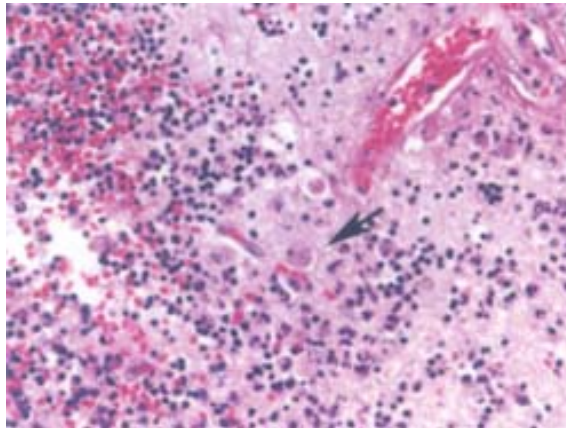
Figure 28-31 Mechanism and pathology of prion disease. *A*, Proposed mechanism for the conversion of PrP^c through protein-protein interactions. The initiating molecules of PrP^sc may arise through inoculation (as in directly transmitted cases) or through an extremely low-rate spontaneous conformational change. The effect of the mutations in PrP (see *B*) is to increase the rate of the conformational change once PrP^sc is able to recruit and convert other molecules of PrP^c into the abnormal form of the protein. Although the model is drawn with no other proteins involved, it is possible that other proteins play critical roles in the conversion of Prp^c to PrP^sc . *B*, The basic structure of the PrP protein with important sites of mutation (codon 178) and disease-associated polymorphism (codon 129). In normal individuals, codon 178 encodes Asp (D), and codon 129 encodes either Met (M) or Val (V). In some familial forms of disease, the mutation changes codon 178 to Asn (D178N). When the allele containing the D178N mutation also has a Val at codon 129, the patient develops Creutzfeldt-Jakob disease (CJD). In contrast, when the D178N allele has Met at codon 129, the clinical disorder is fatal familial insomnia. *C*, Histology of CJD showing spongiform change in the cerebral cortex. *Inset*, High magnification of neuron with vacuoles. *D*, Cerebellar cortex showing *kuru plaques* (periodic acid-Schiff [PAS] stain) representing aggregated PrP^sc .

A

PrPsc PrPc

Normal PrP

Conformational change,
may require other proteins
Converts PrPᶜ to PrPˢᶜ

PrPsc PrPsc → Aggregates

B
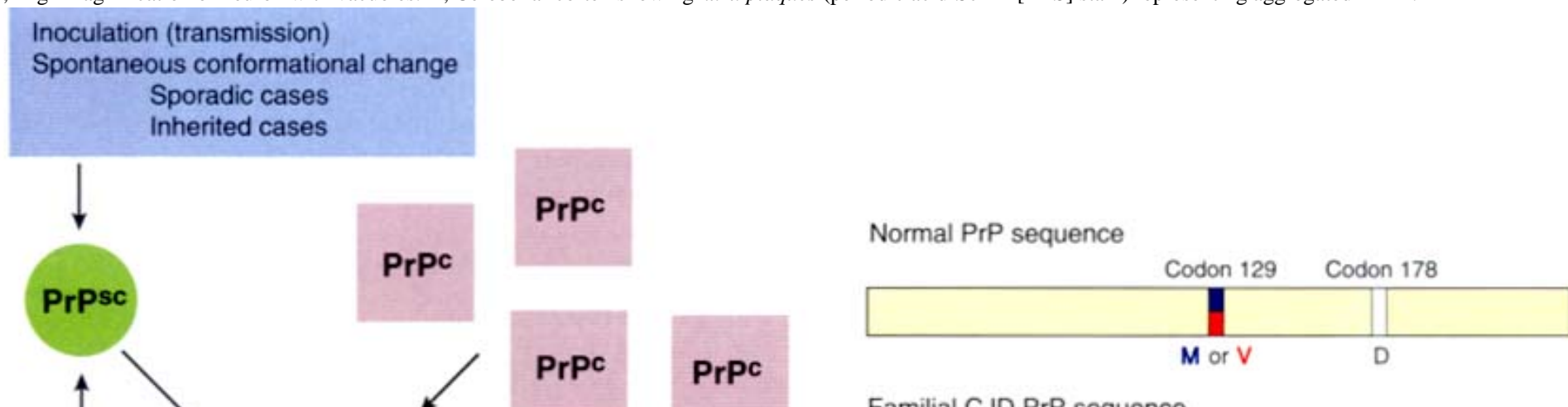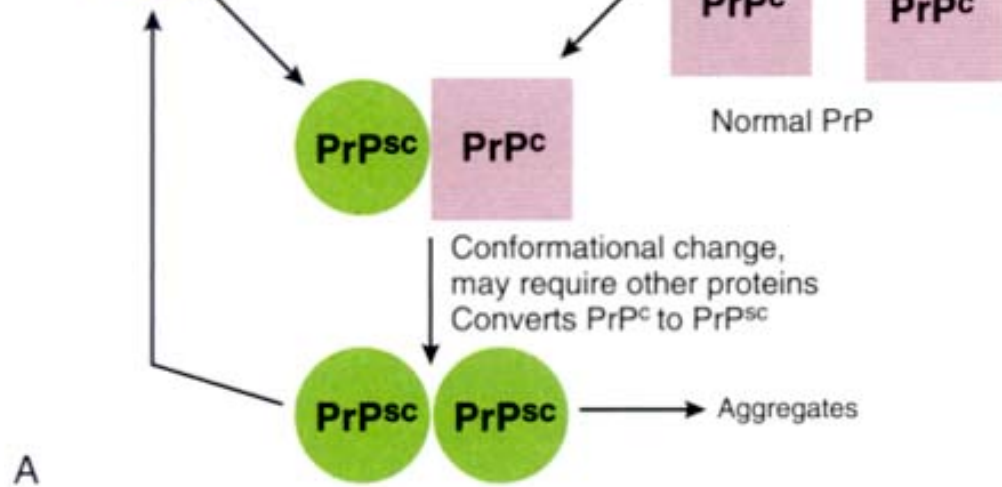
Familial CJD PrP sequence

V   N
Mutant allele

M or V   D
Normal allele
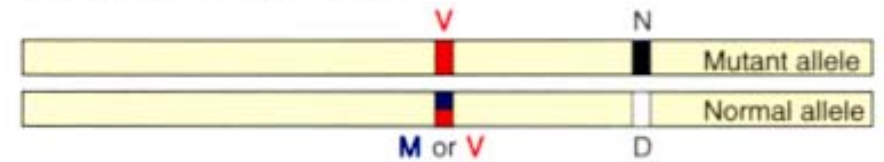
Fatal Familial Insomnia PrP sequence

M   N
Mutant allele

M or V   D
Normal allele
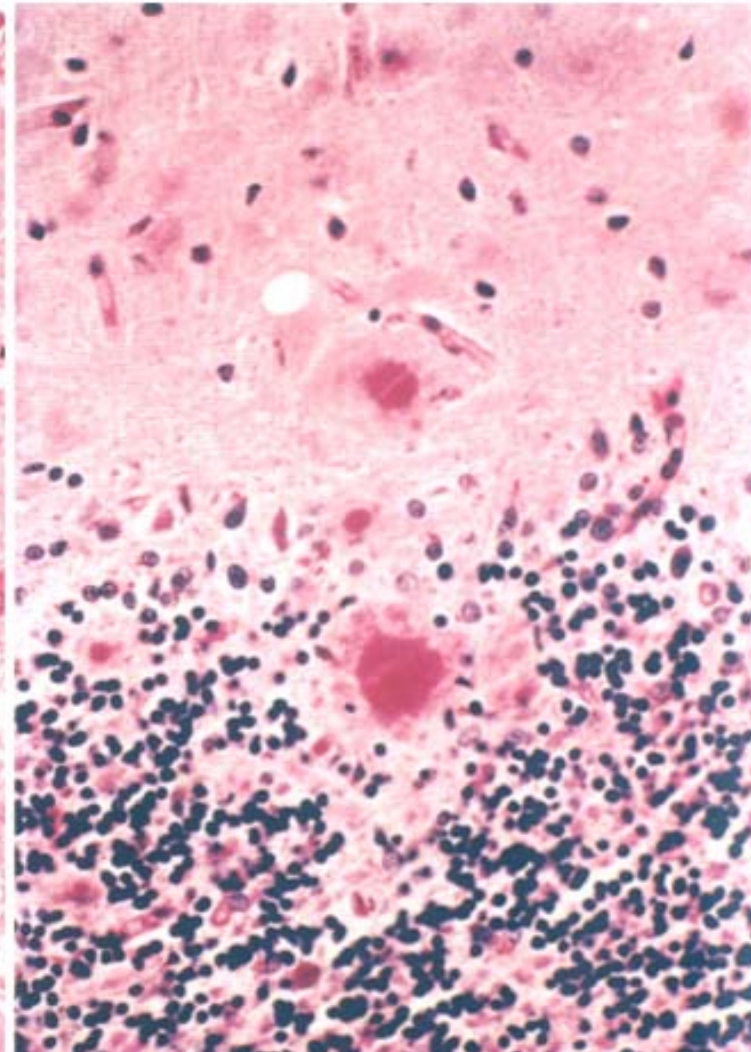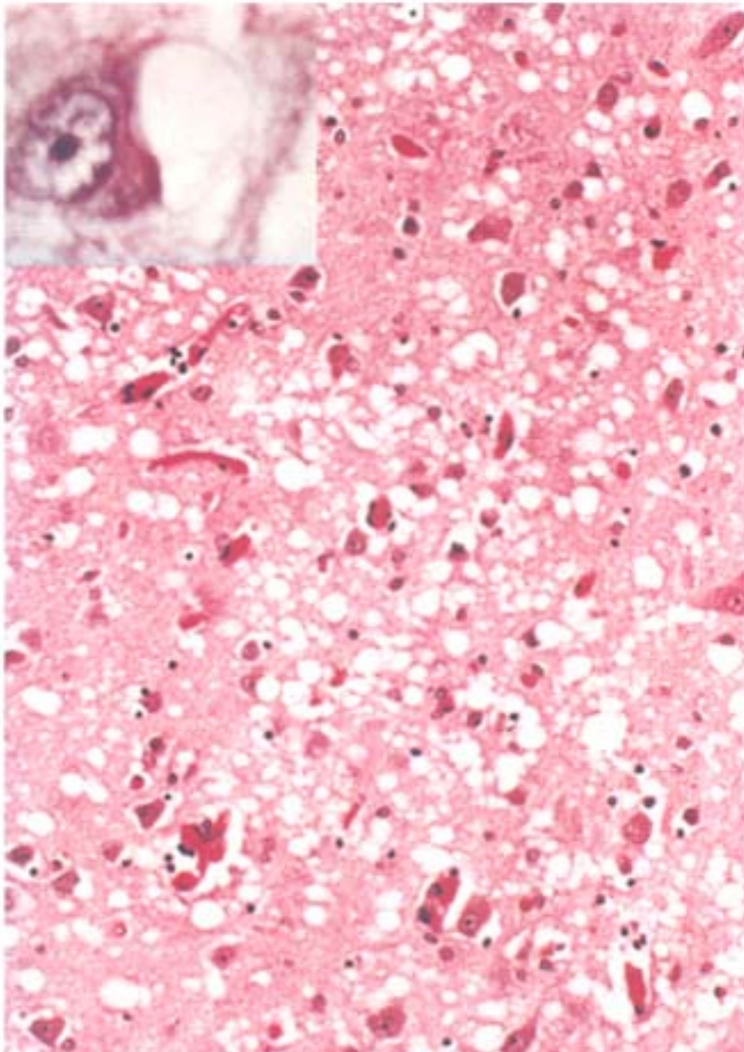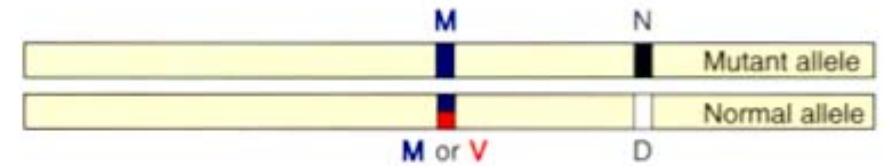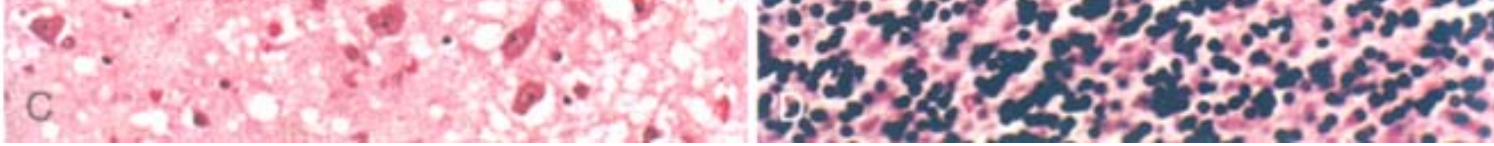
Figure 28-32 Multiple sclerosis. Section of fresh brain showing brown plaque around occipital horn of the lateral ventricle.
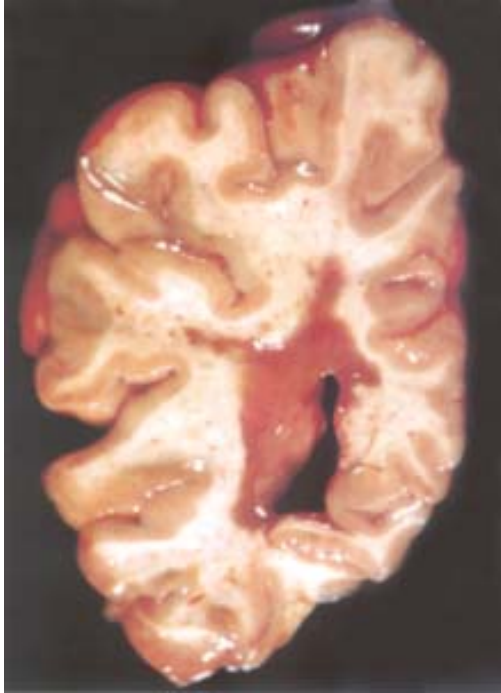
Figure 28-33 Multiple sclerosis. *A*, Unstained regions of demyelination (MS plaques) around the fourth ventricle. (Luxol fast blue PAS stain for myelin). *B*, Myelin-stained section shows the sharp edge of a demyelinated plaque and perivascular lymphocytic cuffs. *C*, The same lesion stained for axons shows relative preservation.
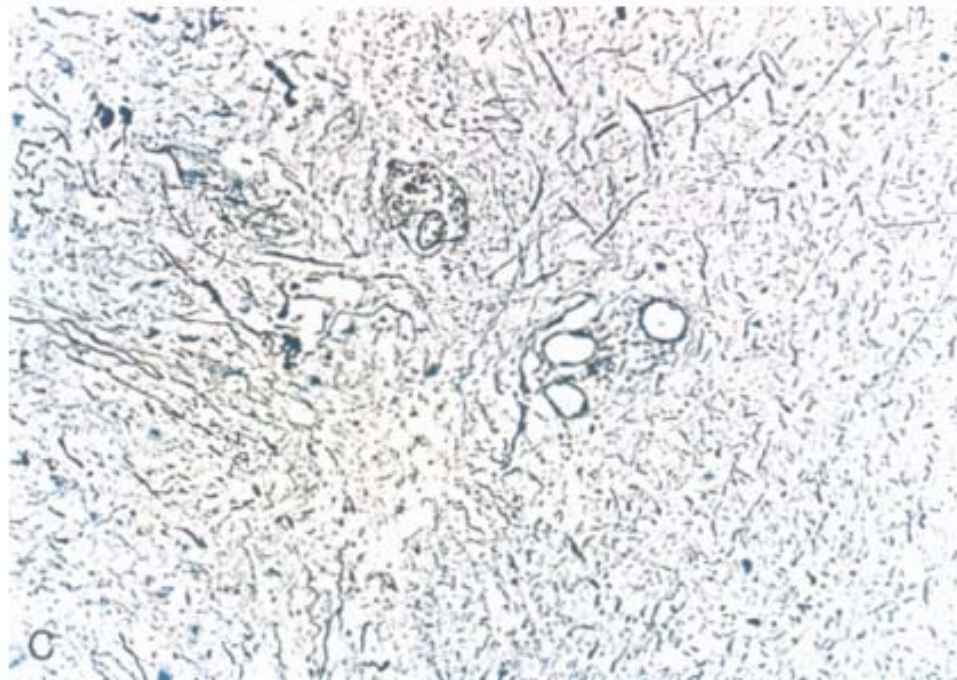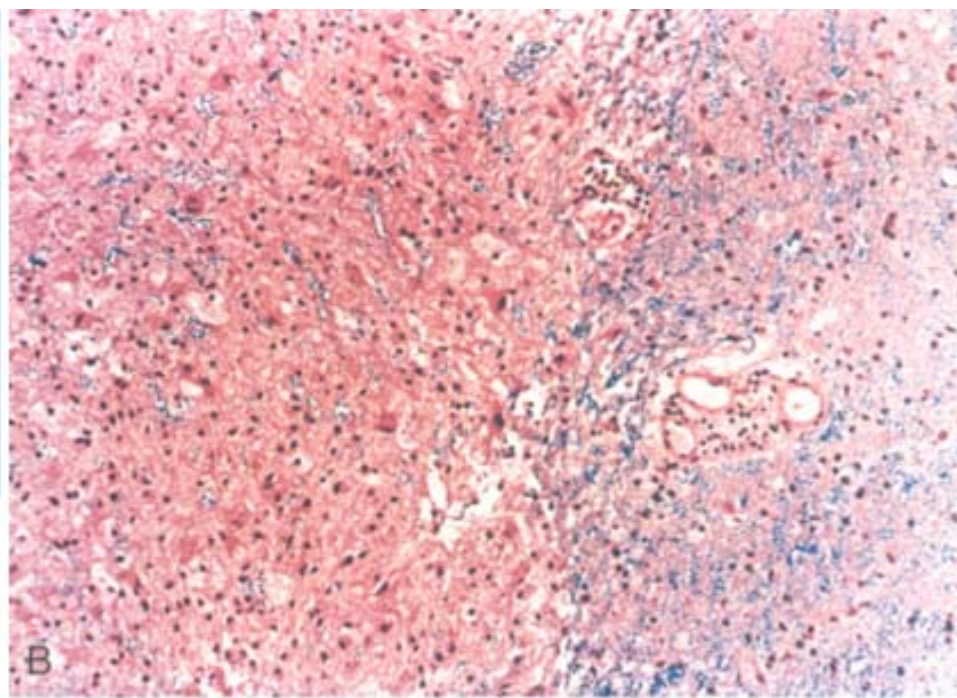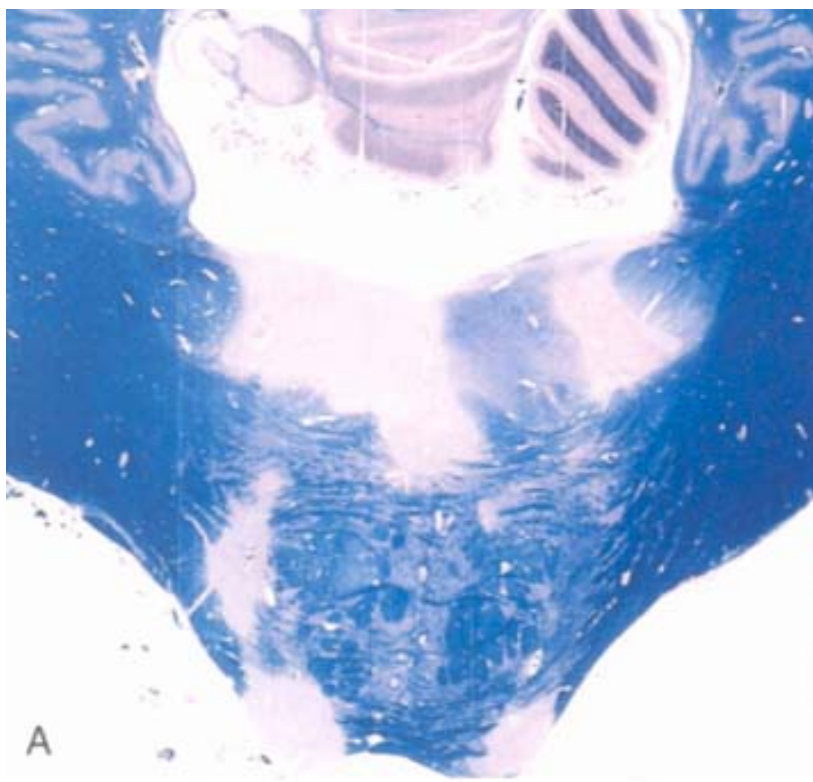
Figure 28-34 Alzheimer disease with cortical atrophy most evident on the right, where meninges have been removed. *(Courtesy of Dr. E.P. Richardson, Jr., Massachusetts General Hospital, Boston, MA.)*
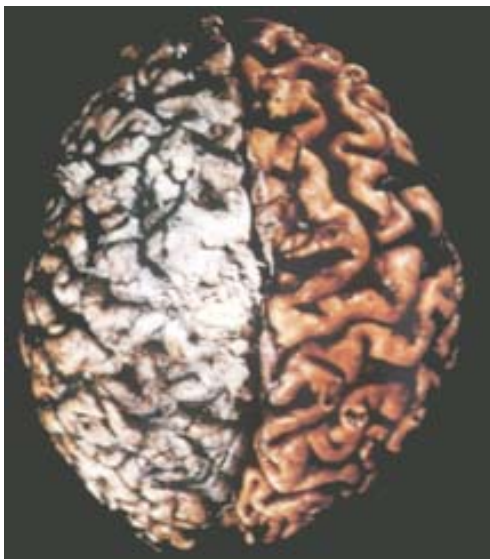
Figure 28-35 Alzheimer disease. *A*, Neuritic plaque with a rim of dystrophic neurites surrounding an amyloid core. *B*, Congo red stain of the cerebral cortex showing amyloid deposition in the blood vessels and the amyloid core of the neuritic plaque *(arrow)*. *C*, Neurofibrillary tangles *(arrowheads)* are present within the neurons (H & E). *D*, Silver stain showing a neurofibrillary tangle within the neuronal cytoplasm.
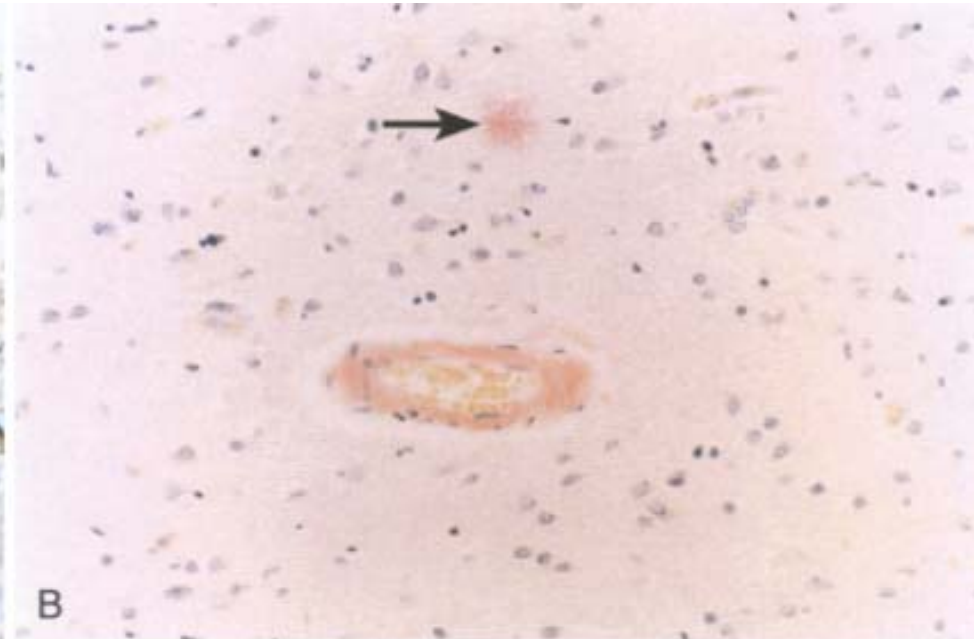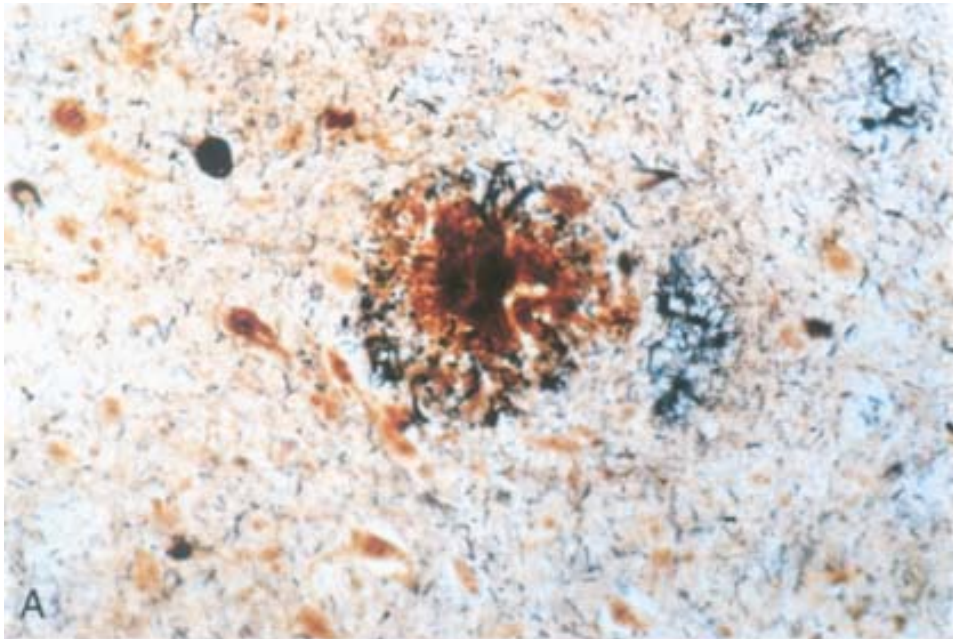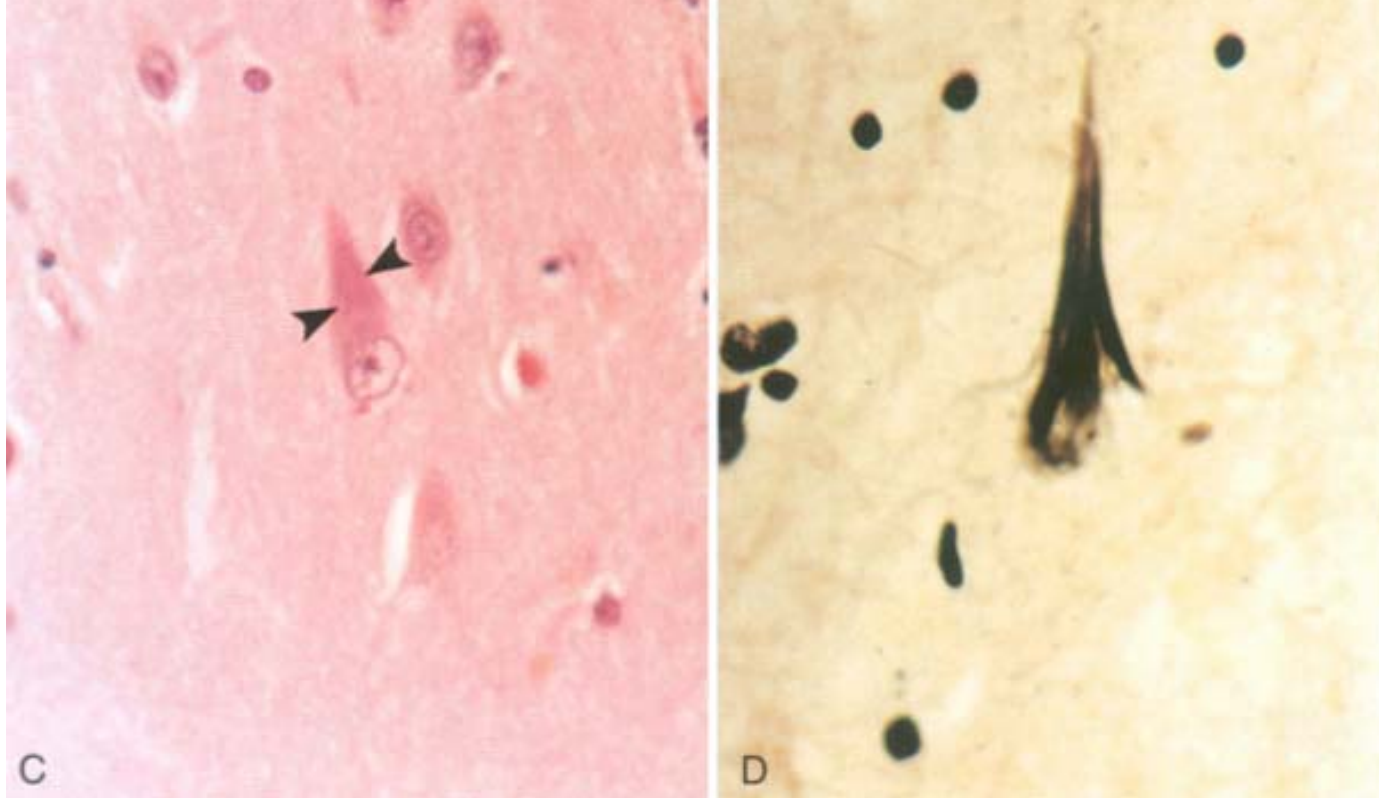
Figure 28-36 Mechanism of amyloid generation in Alzheimer disease. Amyloid precursor protein (APP) is a transmembrane protein, with potential cleavage sites for three distinct enzymes (α-, β- and γ-secretases) as shown in *A*. The Aβ domain extends from the extracellular side of the protein into the transmembrane domain. When APP is cleaved by α-secretase (*B*), subsequent cleavage by γ-secretase does not yield Aβ. In contrast, cleavage by β-secretase followed by γ-secretase (*C*) results in production of Aβ, which can then aggregate and form fibrils. In either pathway, intramembranous cleavage by γ-secretase follows cleavage at a site located closer to the N-terminus of the protein.

Figure labels:
- Amyloid precursor protein
- Cleavage sites for:
  - β-Secretase
  - α-Secretase
  - γ-Secretase
- Aβ peptide
- A
- COOH
- Soluble fragment
- α-Secretase cleavage
- γ-Secretase cleavage
- B
- COOH
- Soluble fragment
- β-Secretase cleavage
- Aβ peptide
- γ-Secretase cleavage
- C
- COOH
- Aβ Aggregates
- Amyloid fibrils
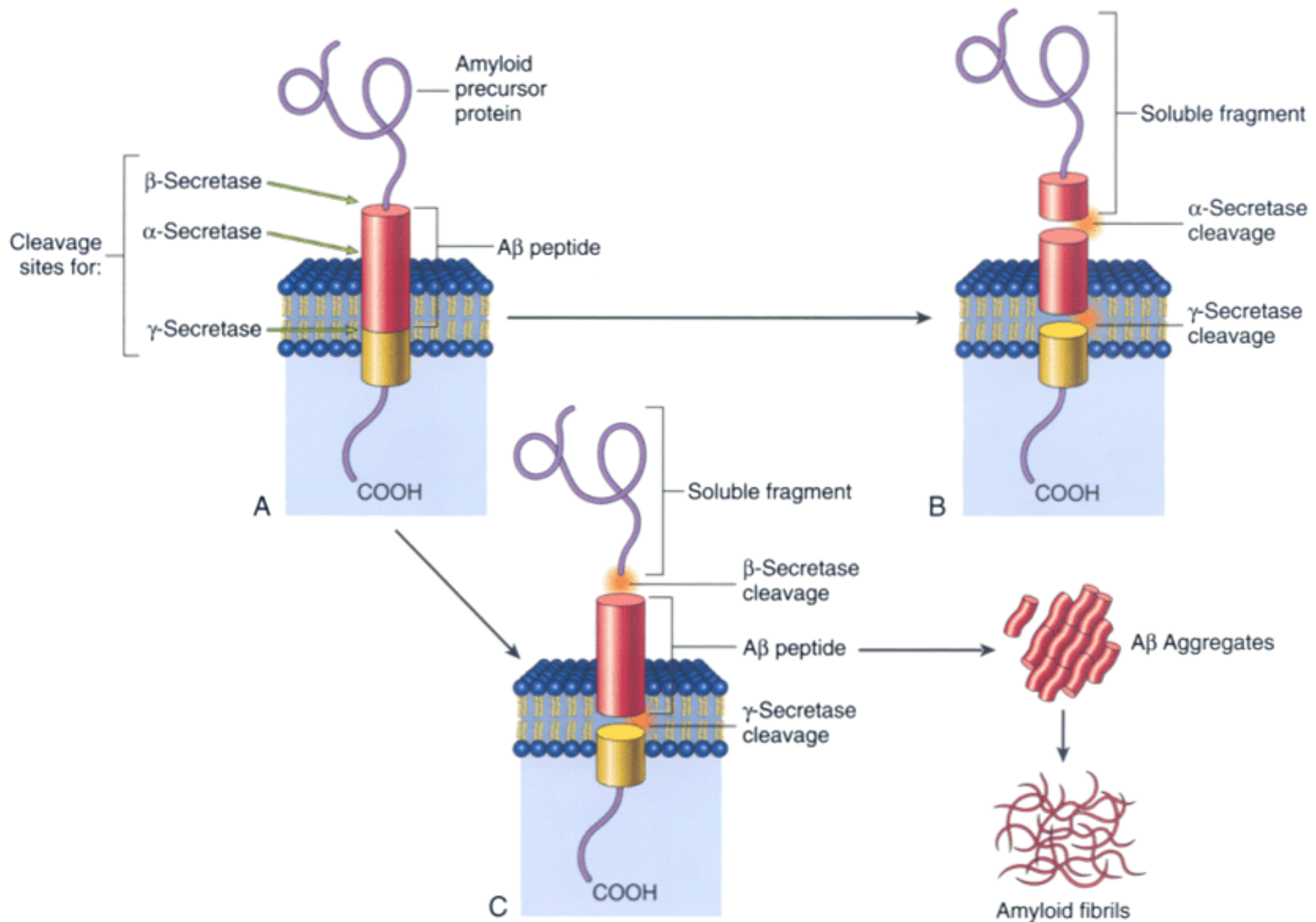
TABLE 28-2 -- Genetics of Alzheimer Disease

Chromosome	Gene	Mutations/Alleles	Consequences
21	Amyloid precursor protein (APP)	• Single missense mutations	• Early-onset FAD

		•• Double missense mutation	•• Increased Aβ production
		•• Trisomy 21 (gene dosage effect)	
14	Presenilin-1 (*PS1*)	• Missense mutations	• Early-onset FAD
		•• Splice site mutations	•• Increased Aβ production
1	Presenilin-2 (*PS2*)	• Missense mutations	• Early-onset FAD
			•• Increased Aβ production
19	Apolipoprotein E (*ApoE*)	• Allele epsilon4	• Increased *risk* of development of AD
			•• Decreased age at onset of AD

AD, Alzheimer disease; FAD, familial Alzheimer disease.

How Aβ is related to the neurodegeneration of AD, how it is linked to the other pathologic features of AD such as tangles and abnormal hyperphosphorylation of tau, and what controls the stereotypic pattern of involvement of brain regions and the pattern of progression all remain open questions. There are various lines of evidence indicating that the small aggregates of Aβ as well as larger fibrils are directly neurotoxic and can elicit various cellular responses, including oxidative damage and alterations in calcium homeostasis. In addition, the reactions of other cell types in the brain influence the disease. There is evidence that the inflammatory response that accompanies Aβ deposition may have both protective effects (through assisting clearance of the aggregated peptide) and injurious effects.[153] [154] [155] [156]

Clinical Features.

The progression of Alzheimer disease is slow but relentless, with a symptomatic course often running more than 10 years. Initial symptoms are forgetfulness and other memory disturbances; with progression of the disease, other symptoms emerge, including language deficits, loss of mathematical skills, and loss of learned motor skills. In the final stages of Alzheimer disease, patients may become incontinent, mute, and unable to walk. Intercurrent disease, often pneumonia, is usually the terminal event in these individuals. While biomarkers for AD are still unavailable, there are indicators that structural imaging can suggest which individuals are at increased risk of progressing from a mild memory disturbance to a diagnosis of probable AD.[157]

Frontotemporal Dementias

These are a group of disorders that were first gathered under a single broad term because they shared clinical features (progressive deterioration of language and changes in personality) that corresponded to degeneration and atrophy of temporal and frontal lobes. These entities have recently been better understood through a combination of immunohistochemical and biochemical studies as well as genetic insights.[158] [159]

Frontotemporal Dementia with Parkinsonism Linked to Chromosome 17 (FTD(P)-17)

As the name implies, this is a genetically determined disorder in which the clinical syndrome of a frontotemporal dementia is often accompanied by parkinsonian symptoms. In these families, the disease has been mapped to chromosome 17; in particular, it has been linked to a variety of mutations

in the *tau* gene. Tau is a microtubule binding protein that has numerous sites of potential phosphorylation and exists in six splice forms as the result of alternative splicing of exons 2, 3 and 10.[160] The protein contains either three or four copies of the microtubule binding domain depending on whether exon 10 is included (4 repeat tau) or not (3 repeat tau).

Morphology.

There is evidence of atrophy of frontal and temporal lobes in various combinations and to various degrees. The pattern of atrophy can often be predicted in part by the clinical symptomatology. The atrophic regions of cortex are marked by neuronal loss and gliosis as well as the presence of taucontaining neurofibrillary tangles. These tangles may contain either 4 repeat tau or a mixture of 3 and 4 repeat tau, depending on the underlying genetic basis for the disease. Nigral degeneration may also occur. Inclusions can also be found in glial cells in some forms of the disease.

Pathogenesis and Molecular Genetics.

The study of families with frontotemporal dementia led to the recognition that in some, but not all, pedigrees, there is linkage to mutations in the *tau* gene. The mutations fall into several broad categories: coding region mutations and intronic mutations that affect the splicing of exon 10.[161] The intronic mutations result in increased production of 4 repeat forms of tau. Coding region mutations appear to have several different consequences, including alterations in the interaction of tau with microtubules (mutations in exon 10 will change this interaction only for 4 repeat tau) and altering the intrinsic tendency to aggregate.

Pick Disease

Pick disease (lobar atrophy) is a rare, distinct, progressive dementia characterized clinically by early onset of behavioral changes together with alterations in personality (frontal lobe signs) and language disturbances (temporal lobe signs).[162] While most cases of Pick disease are sporadic, there have been some familial forms identified and linked to mutations in *tau*.

Morphology.

The brain invariably shows a pronounced, frequently asymmetric, atrophy of the frontal and temporal lobes with conspicuous sparing of the posterior two thirds of the superior temporal gyrus and only rare involvement of either the parietal or occipital lobe. The atrophy can be severe, reducing the gyri to a thin wafer ("knife-edge" appearance). This pattern of **lobar atrophy** is often prominent enough to distinguish Pick disease from Alzheimer disease on macroscopic examination. In addition to the localized cortical atrophy, there may also be bilateral atrophy of the caudate nucleus and putamen.

On microscopic examination, neuronal loss is most severe in the outer three layers of the cortex. Some of the surviving neurons show a characteristic swelling (**Pick cells**) or contain **Pick bodies,** which are cytoplasmic, round to oval, filamentous inclusions that are only weakly basophilic but stain strongly with silver methods. Ultrastructurally, these are composed of straight filaments, vesiculated endoplasmic reticulum, and paired helical filaments that are immunocytochemically similar to those found in Alzheimer disease and contain 3 repeat tau. Unlike the neurofibrillary tangles of Alzheimer disease, Pick bodies do not survive the death of their host neuron and do not remain as markers of the disease.

Progressive Supranuclear Palsy (PSP)

This is an illness characterized clinically by truncal rigidity with dysequilibrium and nuchal dystonia; pseudobulbar palsy and abnormal speech; ocular disturbances, including vertical gaze palsy progressing to difficulty with all eye movements; and mild progressive dementia in most patients. The onset of the disease is usually between the fifth and seventh decades, and males are affected approximately twice as frequently as are females. The disease is often fatal within 5 to 7 years of onset.

Morphology.

There is widespread neuronal loss in the globus pallidus, subthalamic nucleus, substantia nigra, colliculi, periaqueductal gray matter, and dentate nucleus of the cerebellum. Globose neurofibrillary tangles are found in these affected regions, in neurons as well as in glia. Ultrastructural analysis reveals 15-nm straight filaments that are composed of 4 repeat tau.

Mutations in *tau* have not been found in PSP. Analysis of the *tau* gene has shown that there is an extended haplotype (a series of polymorphic markers spread out along the gene that are in complete linkage disequilibrium; that is, recombination events do not appear to occur between the sites). Of the two haplotypes, one of them is strongly overrepresented in PSP patients.[163] How this haplotype influences the risk of PSP is unknown.

Corticobasal Degeneration (CBD)

This is a disease of the elderly, with considerable clinical and neuropathologic heterogeneity. The extrapyramidal signs and symptoms result in this disorder's also being grouped with syndromes of basal ganglia dysfunction.

Morphology.

On macroscopic examination, there is cortical atrophy, mainly of the motor, premotor, and anterior parietal lobes. The regions of cortex show severe loss of neurons, gliosis, and *"ballooned" neurons* (neuronal achromasia) that can be highlighted with immunocytochemical methods for phosphorylated neurofilaments. Tau immunoreactivity has been found in astrocytes ("tufted astrocytes"), oligodendrocytes ("coiled bodies"), basal ganglionic neurons, and, variably, cortical neurons.[164] [165] Clusters of tau-positive processes around an astrocyte ("astrocytic plaques") and the presence of tau-positive threads in gray and white matter may be the most specific pathologic findings of CBD.[166] The substantia nigra and locus ceruleus show loss of pigmented neurons, neuronal achromasia, and tangles. Similar to

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PSP, the tau deposits in CBD contain predominantly 4 repeat tau. Recently proposed consensus diagnostic criteria for CBD focus on the presence of tau-positive inclusions in neurons and glia of the cortex and striatum, including astrocytic plaques, associated with neuronal loss from substantia nigra and cortex.[167]

Clinical Features.

The disease is characterized by extrapyramidal rigidity, asymmetric motor disturbances (jerking movements of limbs: "alien hand"), and sensory cortical dysfunction (apraxias, disorders of language); cognitive decline occurs, and may be prominent in some cases.[168] [169] The same extended *tau* haplotype is linked to CBD as to PSP.[170] Although tau deposits are a hallmark of CBD, it is rare to find CBD pathology in individuals with mutations in the *tau* gene.[171]

Frontotemporal Dementias Without Tau Pathology

Some cases with clinical and pathologic findings involving these brain regions do not show evidence of Tau deposition. Some cases with this pattern are found in association with motor neuron disease (see below); in this setting, Tau-negative, ubiquitin-positive inclusions can be found in superficial cortical layers in temporal and frontal lobe and in the dentate gyrus. This pattern of pathology is termed *motor neuron disease inclusion dementia*. It has also been described in the absence of ALS-like pathology. Other cases show no specific inclusions but rather have cortical atrophy and some thalamic gliosis. This pattern of injury has been termed dementia lacking distinctive histology (DLDH). [172] With time and increased biochemical and molecular investigations, these unusual entities are likely to be reclassified.

Vascular Dementia

It is now clear from autopsy studies of individuals who were carefully studied during life that various types of vascular injury to the brain can result in dementia.[173] Some individuals with a rapidly progressive cognitive decline have vasculitis (discussed above) and will often show improvement with treatment. Among the irreversible disorders, several specific entities have been identified, which can be separated in part by their clinical course (typically a stepwise progression rather than a gradual decline) and imaging features. Various etiologies include small areas of infarction (granular atrophy from cortical microinfarcts, multiple lacunar infarcts, cortical laminar necrosis associated with reduced perfusion/oxygenation) and diffuse white matter injury (Binswanger disease, CADASIL). Additionally, dementia has been associated with so-called strategic infarcts, which are usually embolic and involve brain regions such as the hippocampus, dorsomedial thalamus, or frontal cortex including cingulate gyrus. Many individuals, in fact, will demonstrate a combination of pathologic changes. There is also an interaction between vascular injury and other dementing disorders, such as AD. It has been found that patients with vascular changes above a certain threshold have a lower burden of plaques and tangles for their level of cognitive impairment than do those without vascular-based cerebral pathology.[174]

DEGENERATIVE DISEASES OF BASAL GANGLIA AND BRAINSTEM

Diseases affecting these regions of the brain are frequently associated with movement disorders, including rigidity, abnormal posturing, and chorea. In general, they can be categorized as manifesting either a reduction of voluntary movement or an abundance of involuntary movement. The basal ganglia and especially the nigrostriatal pathway play an important role in the system of positive and negative regulatory synaptic pathways that serve to modulate feedback from the thalamus to the motor cortex. The most important disorders in this group are those associated with parkinsonism and Huntington chorea.

Parkinsonism

Parkinsonism is a clinical syndrome characterized by diminished facial expression, stooped posture, slowness of voluntary movement, festinating gait (progressively shortened, accelerated steps), rigidity, and a "pill-rolling" tremor. This type of motor disturbance is seen in a number of conditions that have in common damage to the nigrostriatal dopaminergic system. Parkinsonism may also be induced by drugs that affect this system, particularly dopamine antagonists and toxins. The principal diseases to be discussed here that involve the nigrostriatal system are as follows:

- Parkinson disease (PD)
- Multiple system atrophy, a disorder that may have parkinsonism as a prominent symptom (clinical presentation as striatonigral degeneration) as well as other symptoms (cerebellar ataxia and autonomic dysfunction)
- Postencephalitic parkinsonism, which was observed in the wake of the influenza pandemic that occurred between 1914 and 1918 and is now vanishingly rare
- Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), which are movement disorders that may also exhibit cognitive impairment; they share some pathologic and genetic features with each other and with other tauopathies (see the discussion above in the section on frontotemporal dementias).

Parkinson Disease

This diagnosis is made in patients with progressive parkinsonism in the absence of a toxic or other known underlying etiology. Familial forms with autosomal-dominant or autosomal-recessive inheritance exist. Although these make up a limited number of cases, they have contributed to our understanding of the pathogenesis of the disease. In addition to the movement disorder, there are other, less well-characterized changes in mental function, which may include dementia, in a subset of individuals with PD.

Morphology.

On pathologic examination, the typical macroscopic findings are **pallor of the substantia nigra** (Fig. 28-37) and locus ceruleus. On microscopic examination, there is loss of the pigmented, catecholaminergic neurons in these regions associated with gliosis. Lewy bodies (Fig. 28-37*C*) may be found in some of the remaining neurons.

Figure 28-37 Parkinson disease (PD). *A*, Normal substantia nigra. *B*, Depigmented substantia nigra in idiopathic PD. *C*, Lewy bodies in a substantia nigra neuron stain bright pink. *(C, courtesy of Dr. R. Kim, V.A. Medical Center, Long Beach, CA.)*
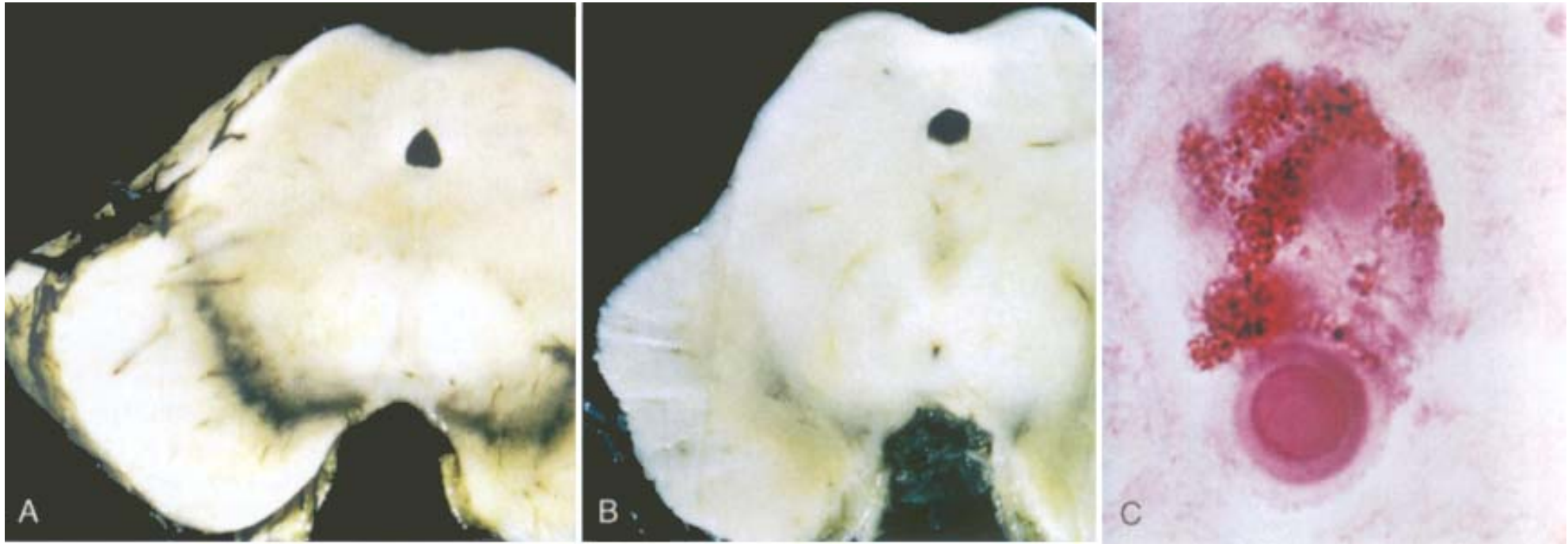
Figure 28-38 Huntington disease (HD). Normal hemisphere on the left compared with the hemisphere with HD on the right showing atrophy of the striatum and ventricular dilation. *(Courtesy of Dr. J.-P. Vonsattel, Columbia University, New York, NY.)*
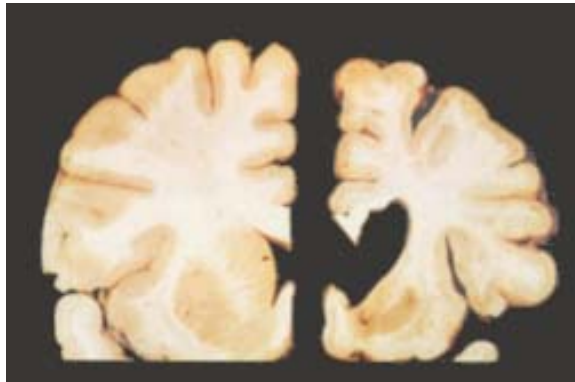
TABLE 28-3 -- Spinocerebellar Ataxias

Disease	Chromosome	Gene Product	Inheritance	Mutation
SCA1	6p23	ataxin-1	AD	CAG in coding region
SCA2	12q24.1	ataxin-2	AD	CAG in coding region
SCA3	14q21	ataxin-3	AD	CAG in coding region
SCA4	16q22.1	?	AD	?
SCA5	11	?	AD	?
SCA6	19p13.1-2	α$_{1A}$ voltage-dependent calcium channel subunit	AD	CAG in coding region
SCA7	3p21.1-p12	ataxin7	AD	CAG in coding region
SCA8	13q21	?	AD	Untranslated
				CTG repeat on antisense strand
SCA10	22q13	ataxin-10	AD	Intronic
				ATTTC repeat
SCA11	15q14-21	?	AD	
SCA12	5q31	protein phosphatase 2A	AD	CAG in 5' UTR region
SCA13	19q13	?	AD	?
SCA14	19q13.4	?	AD	?
SCA15	3pter-24.2	?	AD	?
SCA16	8q22.24	?	AD	?
SCA17	6q27	TATA-binding protein	AD	CAG in coding region
FA	9q13-21	frataxin-1	AR	Intronic GAA repeat
Ataxia-telangiectasia	11q22-23	ATM	AR	Point mutations

Friedreich Ataxia

This is an autosomal-recessive progressive illness, generally beginning in the first decade of life with gait ataxia, followed by hand clumsiness and dysarthria. Deep tendon reflexes are depressed or absent, but an extensor plantar reflex is typically present. Joint position and vibratory sense are impaired, and there is sometimes loss of pain and temperature sensation and light touch. Most patients develop pes cavus and kyphoscoliosis. There is a high incidence of cardiac disease with arrhythmias and congestive heart failure. Concomitant diabetes is found in about 10% of patients. Most patients become wheelchair-bound within about 5 years of onset; the cause of death is intercurrent pulmonary infections and cardiac disease.

The gene for Friedreich ataxia has been mapped to chromosome 9q13, and in most cases, there is a GAA trinucleotide repeat expansion in the first intron of a gene encoding a protein named *frataxin*.[218] Affected individuals inherit abnormal forms of the *frataxin* gene from both parents and have extremely low levels of the protein. In some cases of Friedreich ataxia,

one of the mutant alleles harbors a missense or nonsense mutation. Frataxin undergoes processing and ends up in the inner mitochondrial membrane, where it has been suggested to play a role in regulation of iron levels.[219] [220] Because of the need for this metal in many of the complexes of the oxidative phosphorylation chain, mutations in frataxin have been suggested to result in generalized mitochondrial dysfunction. Thus, Friedreich ataxia shares biologic features with other spinocerebellar ataxias (anatomic distribution of pathology, trinucleotide repeat expansion) and the mitochondrial encephalopathies.

Morphology.

The spinal cord shows loss of axons and gliosis in the posterior columns, the distal portions of corticospinal tracts, and the spinocerebellar tracts. There is degeneration of neurons in the spinal cord (Clarke column), the brainstem (cranial nerve nuclei VIII, X, and XII), the cerebellum (dentate nucleus and the Purkinje cells of the superior vermis), and to some extent the Betz cells of the motor cortex. Large dorsal root ganglion neurons are also decreased in number; their large myelinated axons, traveling first in the dorsal roots and then in dorsal columns, therefore undergo secondary degeneration. The heart is enlarged and may have pericardial adhesions. Multifocal destruction of myocardial fibers with inflammation and fibrosis is detectable in about half the patients who come to autopsy examination.

Ataxia-Telangiectasia

Ataxia-telangiectasia (Chapter 7) is an autosomal-recessive disorder characterized by an ataxic-dyskinetic syndrome beginning in early childhood, caused by neuronal degeneration predominantly in the cerebellum, the subsequent development of telangiectasias in the conjunctiva and skin, and immunodeficiency. Cells from patients with the disease show increased sensitivity to x-ray-induced chromosome abnormalities; these cells continue to replicate damaged DNA

rather than stopping to allow repair or apoptosis. The ataxia-telangiectasia locus on chromosome 11q22-23 has been identified as a large gene, *ATM*, that encodes a protein with a kinase domain; the protein orchestrates the cellular response to double-stranded DNA breaks.[221] [222] The carrier frequency of ataxia-telangiectasia has been estimated at 1%; in these individuals, the mutated ataxia-telangiectasia allele may underlie an increased risk of cancer, specifically breast cancer.

Morphology.

The abnormalities are predominantly in the cerebellum, with loss of Purkinje and granule cells; there is also degeneration of the dorsal columns, spinocerebellar tracts, and anterior horn cells and a peripheral neuropathy. Telangiectatic lesions have been reported in the CNS as well as in the conjunctiva and skin of the face, neck, and arms. The nuclei of cells in many organs (e.g., Schwann cells in dorsal root ganglia and peripheral nerves, endothelial cells, pituicytes) show a bizarre enlargement of the cell nucleus to two to five times normal size and are referred to as amphicytes. The lymph nodes, thymus, and gonads are hypoplastic.

Clinical Features.

The disease relentlessly progresses to death early in the second decade. Patients first come to medical attention because of recurrent sinopulmonary infections and unsteadiness in walking. Later on, speech is noted to become dysarthric, and eye movement abnormalities develop. Many affected individuals develop lymphoid malignant disease (T-cell leukemia, T-cell lymphoma); gliomas and carcinomas have been reported in some.

DEGENERATIVE DISEASES AFFECTING MOTOR NEURONS

These are a group of inherited or sporadic diseases that, in variable degrees of severity, affect:

- *Lower motor neurons* in the anterior horns of the spinal cord
- *Lower motor neurons* in certain cranial nerve motor nuclei (V, VII, IX, XII) but not those that control eye movements (III, IV, VI)
- *Upper motor neurons* (Betz cells) in the motor cortex

The disorders occur in all age groups, and the course of the illness is extremely variable, ranging from slowly progressive or nonprogressive to rapidly progressive and fatal in a period of months or a few years. Denervation of muscles from loss of lower motor neurons and their axons results in muscular atrophy, weakness, and fasciculations; the corresponding histologic changes in nerve and muscle are discussed in Chapter 27 . The clinical manifestations include paresis, hyperreflexia, spasticity, and extensor plantar responses (Babinski sign). Sensory systems and cognitive functions are unaffected, but types with dementia do occur.

Amyotrophic Lateral Sclerosis (Motor Neuron Disease)

Amytrophic lateral sclerosis (ALS) is characterized by neuronal muscle atrophy (amyotrophy) and hyperreflexia due to loss of lower motor neurons in the anterior horns of the spinal cord and upper motor neurons that project in corticospinal tracts, respectively.[223] The disease affects men slightly more frequently than women and becomes clinically manifest in the fifth decade or later. Five per cent to 10% of cases are familial, mostly with autosomal-dominant inheritance.[224]

Pathogenesis.

The etiology and pathogenesis of amyotrophic lateral sclerosis are unknown. For a subset of the familial cases, the genetic locus has been mapped to the copper-zinc superoxide dismutase gene (*SOD1*) on chromosome 21.[225] A wide variety of missense mutations have been identified that appear to generate an adverse gain-of-function phenotype. Among the mutations, the A4V mutation is the most common (approaching 50% of cases), is associated with a rapid course, and rarely has upper motor neuron signs.[226] [227] A recessive locus on chromosome 2 has been mapped to a gene encoding a protein termed alsin that has structural homology to proteins involved in GTPase regulation.[228] [229] Other genetic loci for ALS have been mapped but not yet cloned. There is also evidence of roles of glutamate toxicity and protein nitration in the development of ALS pathology.[224] The basis for the selective involvement of motor neurons remains uncertain.

Morphology.

On macroscopic examination, the anterior roots of the spinal cord are thin; the precentral gyrus may be atrophic in especially severe cases. Microscopic examination demonstrates a reduction in the number of anterior horn neurons throughout the length of the spinal cord with associated reactive gliosis and loss of anterior root myelinated fibers. Similar findings are found with involvement of the hypoglossal, ambiguus, and motor trigeminal cranial nerve nuclei. Remaining neurons often contain Bunina bodies: PAS-positive cytoplasmic inclusions that appear to be remnant of autophagic vacuoles. Skeletal muscles innervated by the degenerated lower motor neurons show neurogenic atrophy. Destruction of the upper motor neurons leads to degeneration of myelin in the corticospinal tracts, resulting in pale staining that is particularly evident at the lower segmental levels but traceable throughout the corticospinal system with special studies (Fig. 28-39).

Clinical Features.

Early symptoms include asymmetric weakness of the hands, manifested as dropping objects and difficulty in performing fine motor tasks, and cramping and

Figure 28-39 Amyotrophic lateral sclerosis. Spinal cord showing loss of myelinated fibers (lack of stain) in corticospinal tracts. The anterior roots are smaller than the posterior roots.
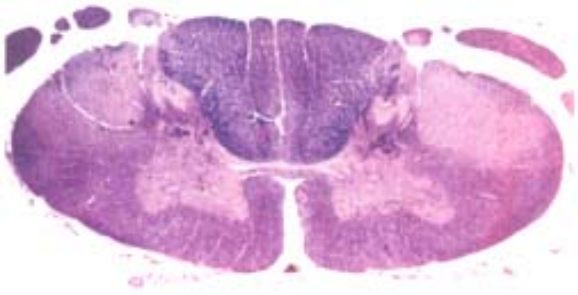
Figure 28-40 Metachromatic leukodystrophy. Demyelination is extensive. The subcortical fibers in the cerebral hemisphere are spared (Luxol fast blue PAS stain for myelin).
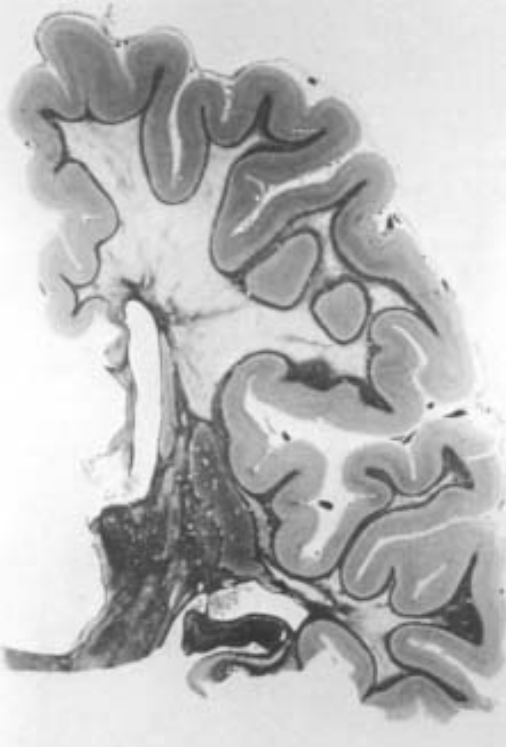
Figure 28-41 Alcoholic cerebellar degeneration. The anterior portion of the vermis *(upper portion of figure)* is atrophic with widened spaces between the folia.
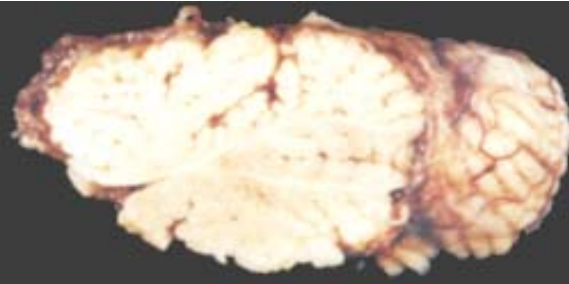
Figure 28-42 Well-differentiated astrocytoma. *A*, The right frontal tumor has expanded gyri, which led to flattening *(arrows)*. *B*, Expanded white matter of the left cerebral hemisphere and thickened corpus callosum and fornices.
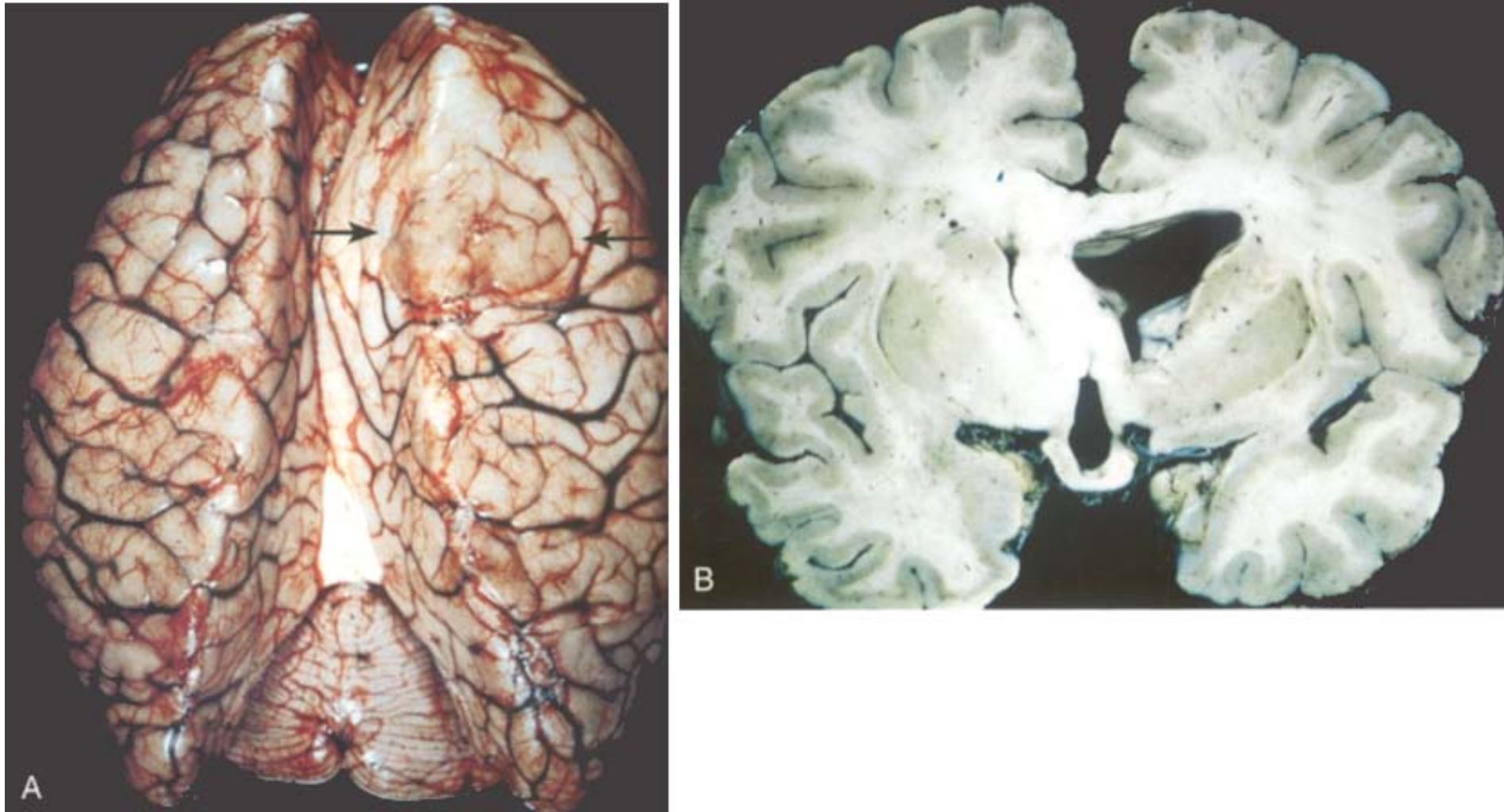
Figure 28-43 *A*, Computed tomographic (CT) scan of a large tumor in the cerebral hemisphere showing signal enhancement with contrast material and pronounced peritumoral edema. *B*, Glioblastoma multiforme appearing as a necrotic, hemorrhagic, infiltrating mass.
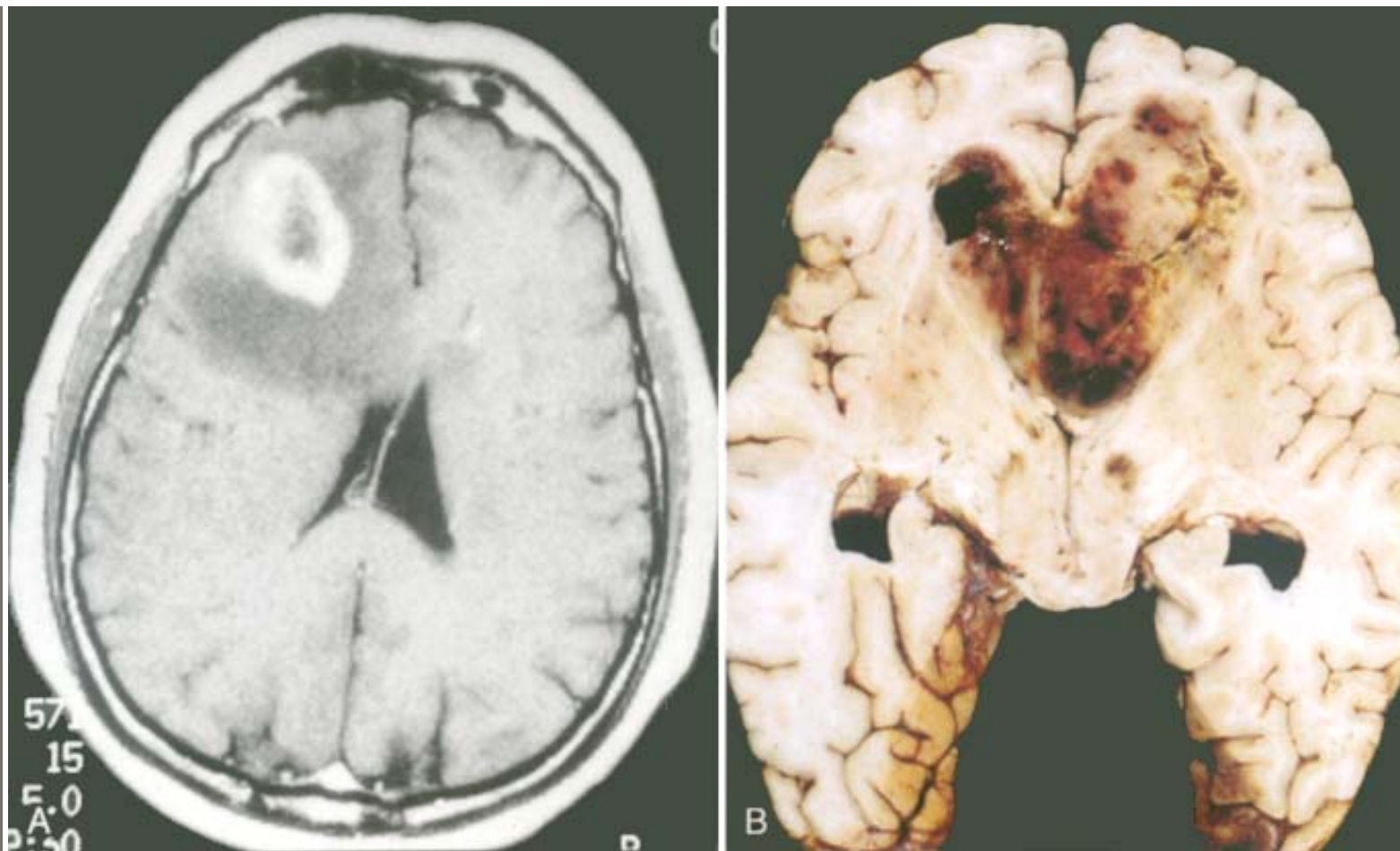
Figure 28-44 Glioblastoma. Foci of necrosis with pseudopalisading of malignant nuclei.
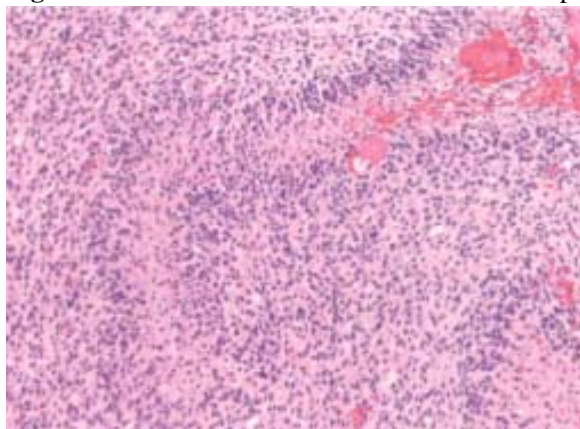
Figure 28-45 Pilocytic astrocytoma in the cerebellum with a nodule of tumor in a cyst.
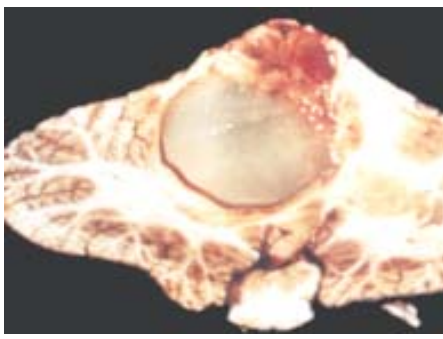
Figure 28-46 Ependymoma. *A*, Tumor growing into the fourth ventricle, distorting, compressing, and infiltrating surrounding structures. *B*, Microscopic appearance of ependymoma.
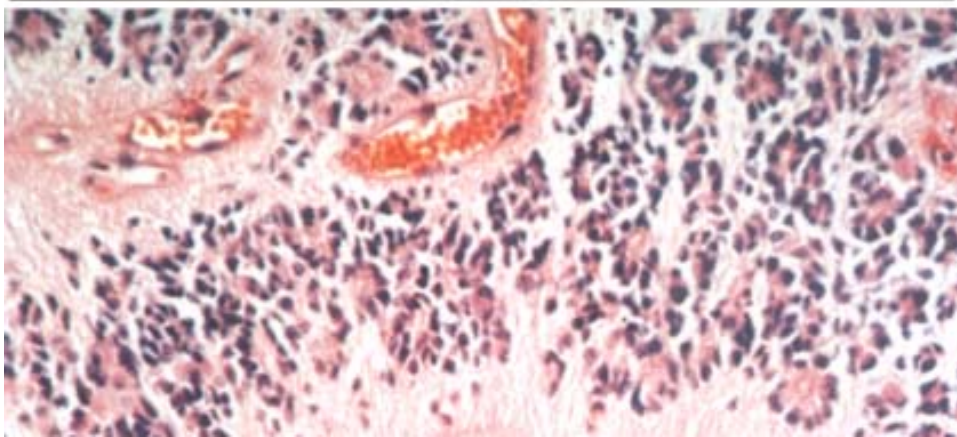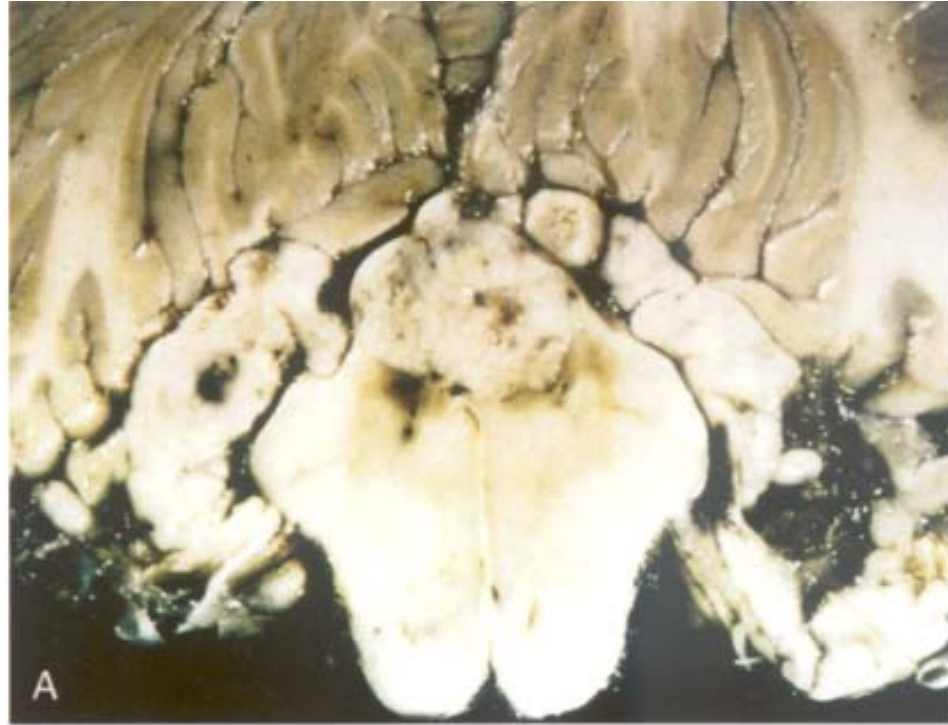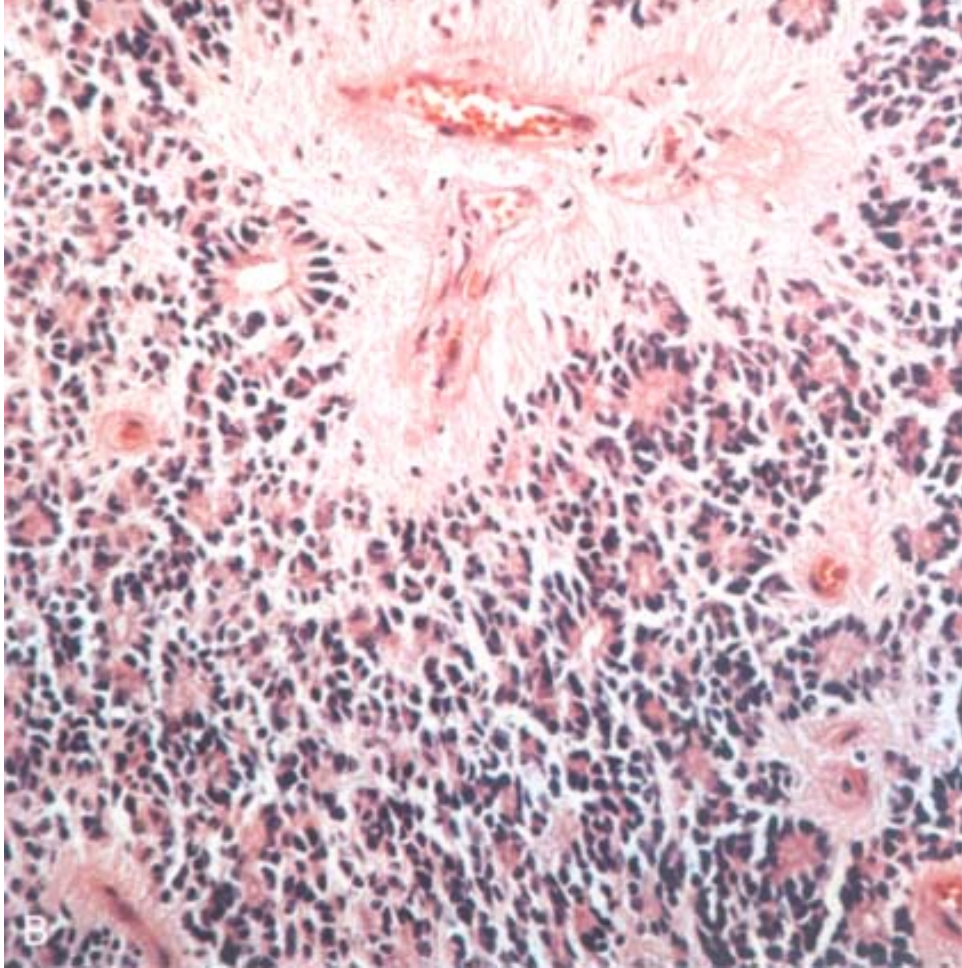
Figure 28-47 Medulloblastoma. *A*, CT scan showing a contrast-enhancing midline lesion in the posterior fossa. *B*, Sagittal section of brain showing medulloblastoma destroying the superior midline cerebellum. *C*, Microscopic appearance of medulloblastoma.
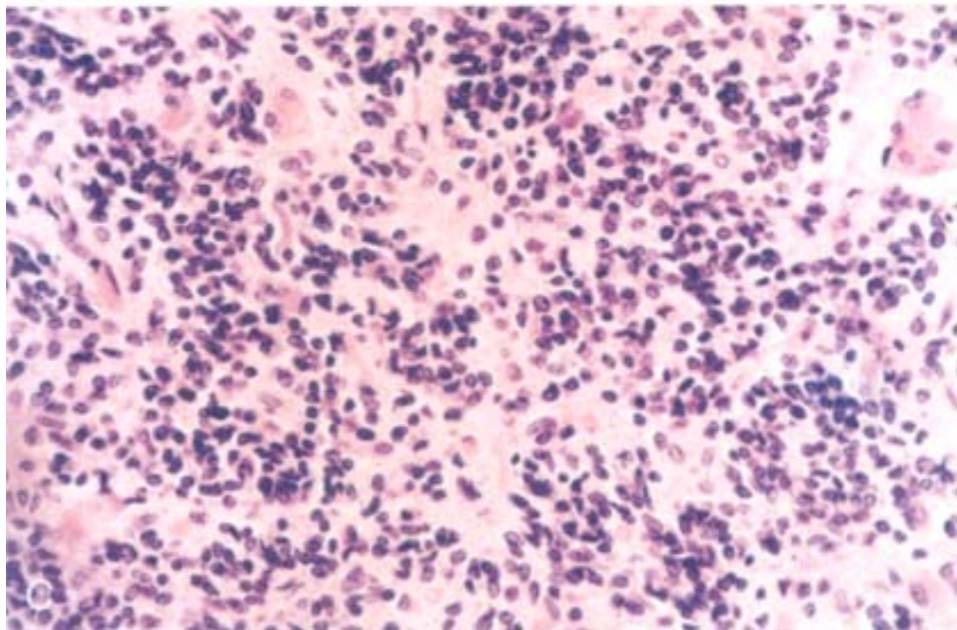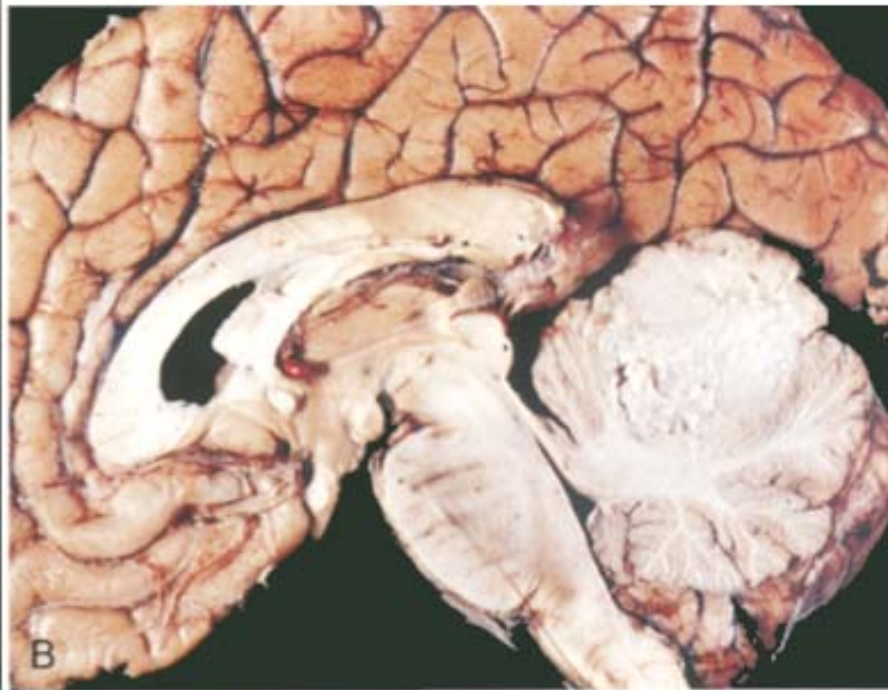
Figure 28-48 *A*, Parasagittal multilobular meningioma attached to the dura with compression of underlying brain. *B*, Meningioma with a whorled pattern of cell growth and psammoma bodies.
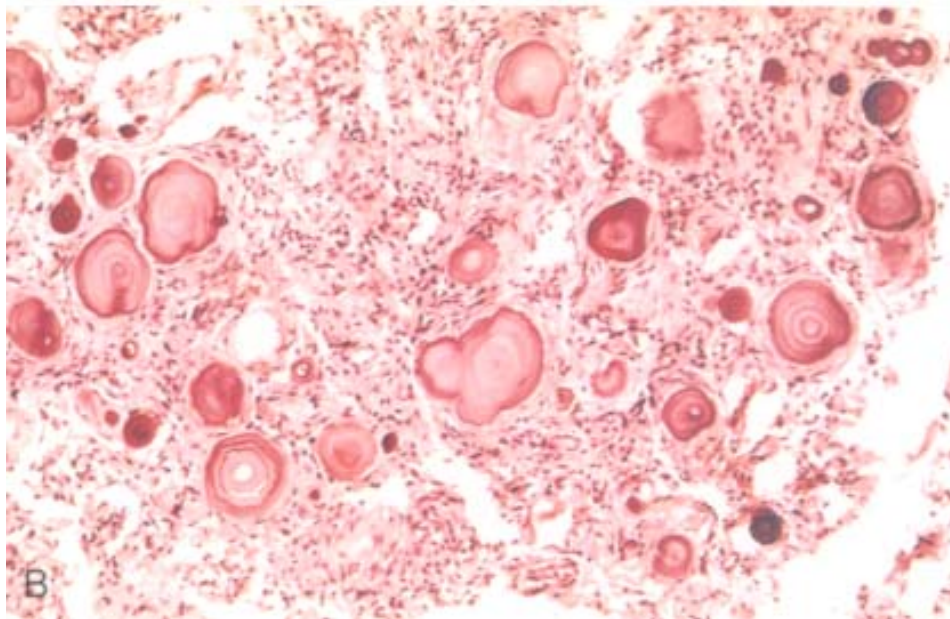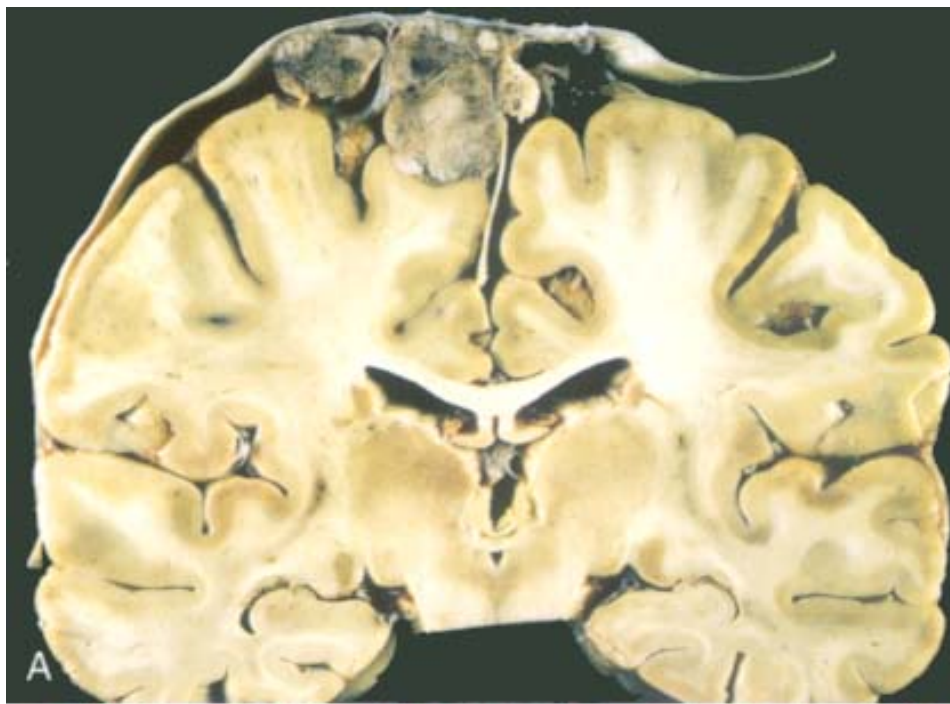
TABLE 28-4 -- Paraneoplastic Syndromes

Syndrome	Target	Tumor	Antigen
Subacute cerebellar degeneration	Purkinje cells	Hodgkin lymphoma	Tr

		Breast, GYN	Yo
		SCLC, neuroblastoma	Hu
Limbic encephalitis; brainstem encephalitis	Various neurons in mesial temporal lobe, brainstem	SCLC, neuroblastoma	Hu
		Testicular, others	Ma
Subacute sensory neuropathy	Dorsal root ganglion neurons	SCLC, neuroblastoma	Hu
Opsoclonus myoclonus	Unknown (presumed brain stem)	Neuroblastoma, Breast	Ri
Retinal degeneration	Photoreceptors	SCLC	Recoverin
Stiff-man syndrome	Spinal interneurons	Breast	Amphiphysin
Lambert-Eaton myasthenic syndrome	Presynaptic terminals at neuromuscular junction	SCLC	Presynaptic calcium channel
SCLC, Small cell lung carcinoma.			

The major underlying mechanism of these diseases involves the systemic development of an immune response against tumor antigens that can cross-react with antigens in the central or peripheral nervous systems.[280] [281] The relationship among the underlying malignant process, the clinical features, and the antigens underlying the syndrome are complex. Some tumor types are associated with multiple types of autoantibodies, and the same antibodies can be present in different clinical syndromes. What allows these antibodies access to the nervous system and how this immune response to intracellular proteins (for the most part) elicits disease remain unanswered questions. There may also be a component of T cell-mediated neuronal injury in some settings.[282]

PERIPHERAL NERVE SHEATH TUMORS

These tumors arise from cells of the peripheral nerve, including Schwann cells, perineurial cells, and fibroblasts. Many express Schwann cell characteristics, including the presence of S-100 antigen as well as the potential for melanocytic differentiation. As nerves exit the brain and spinal cord, there is a transition between myelination by oligodendrocytes and myelination by Schwann cells. This occurs within several millimeters of the substance of the brain; thus, peripheral nerve tumors can arise within the dura and may cause changes in adjacent brain or spinal cord. Tumors of comparable histogenesis and biologic behavior also arise along the peripheral course of nerves.

Schwannoma

These benign tumors arise from the neural crest-derived Schwann cell and are associated with neurofibromatosis type 2. Symptoms are referable to local compression of the involved nerve or to compression of adjacent structures (such as brain stem or spinal cord). Sporadic schwannomas are associated with mutations in the *NF2* gene on chromosome 22; there is usually absence of the *NF2* gene product by Western blotting or immunostaining, even if there is no evidence of a mutation in the gene.[283]

Morphology.

Schwannomas are well-circumscribed, encapsulated masses that are attached to the nerve but can be separated from it (Fig. 28-49*A*). Tumors form firm, gray masses but may also have areas of cystic and xanthomatous change. On microscopic examination, tumors show a mixture of two growth patterns (Fig. 28-49*B*). In the **Antoni A** pattern of growth, elongated cells with cytoplasmic processes are arranged in fascicles in areas of moderate to high cellularity with little stromal matrix; the "nuclear-free zones" of processes that lie between the regions of nuclear palisading are termed Verocay bodies. In the **Antoni B** pattern of growth, the tumor is less densely cellular with a loose meshwork of cells along with microcysts and myxoid changes. In both areas, the cytology of the individual cells is similar, with elongated cell shape and regular oval nuclei. Electron microscopy shows basement membrane deposits encasing single cells and long-spacing collagen. Because the lesion displaces the nerve of origin as it grows, silver stains or immunostains for neurofilament proteins demonstrate that

axons are largely excluded from the tumor, although they may become entrapped in the capsule. The Schwann cell origin of these tumors is borne out by their S-100 immunoreactivity. A variety of degenerative changes may be found in schwannomas, including nuclear pleomorphism, xanthomatous change, and vascular hyalinization. Malignant change is extremely rare in schwannomas, although local recurrence can follow incomplete resection.

Clinical Features.

Within the cranial vault, the most common location of schwannomas is in the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve (Fig. 28-49). Patients often present with tinnitus and hearing loss, and the tumor is often referred to as an acoustic neuroma, although it is more accurately called a vestibular schwannoma. Elsewhere within the dura, sensory nerves are preferentially involved, including branches of the trigeminal nerve and dorsal roots. When extradural, schwannomas are most commonly found in association with large nerve trunks, where motor and sensory modalities are intermixed.

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Figure 28-49 Schwannoma. *A*, Bilateral eighth nerve schwannomas. *(Courtesy of Dr. K.M. Earle.) B*, Tumor showing cellular areas (Antoni A), including Verocay bodies *(far right)*, as well as looser, myxoid regions (Antoni B).
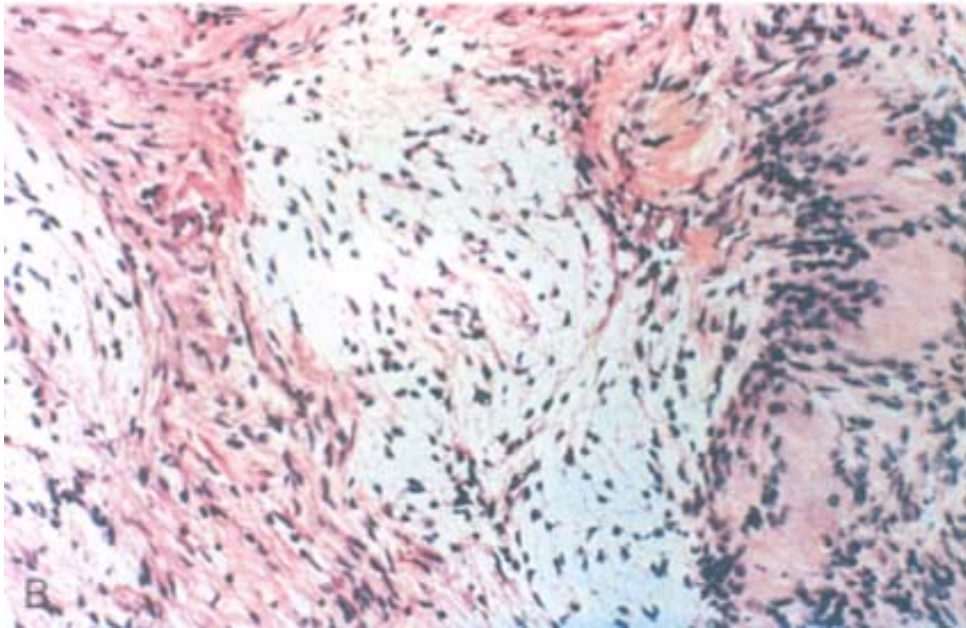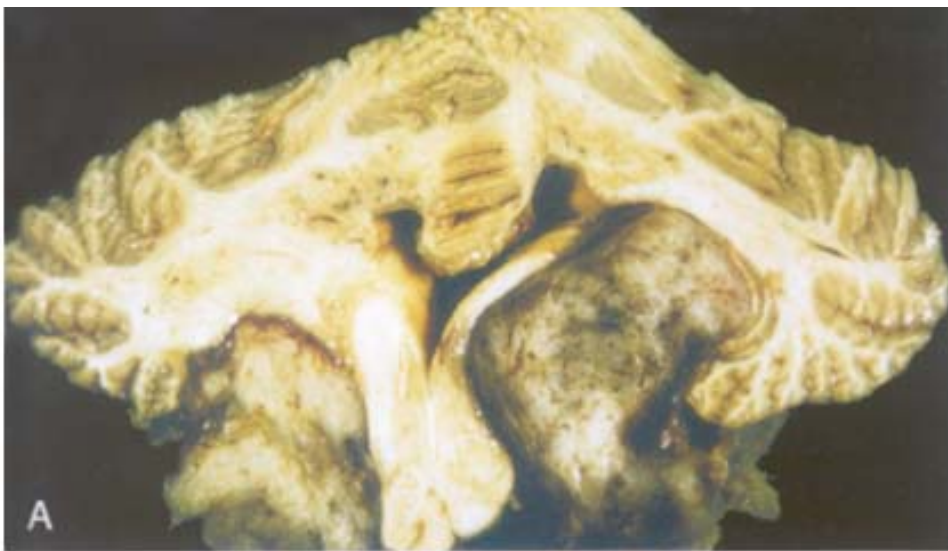
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Chapter 29 - The Eye

Robert Folberg MD

Although this chapter comes at the end of the book, it is not least important. Vision is a major quality-of-life issue for individuals. In the mid-1960s and again in the mid-1970s, the Gallup Organization polled Americans and asked the following question: "Which disease do you fear most?" Before the public awareness of AIDS and Alzheimer disease, the most feared disease among Americans was cancer. The second most feared disease was blindness. So great is the fear of blindness that even today, patients often tell their physicians, "Doctor, I'd rather be dead than be blind!"

In general, diseases that produce loss of vision do not attract as much of our attention as do many of the conditions described in this book that are life-threatening. Typically, loss of vision is enacted in the theater of the mundane. Age-related macular degeneration (ARMD) is the most common cause of irreversible visual loss in the United States. ARMD is not life-threatening and most patients do not even suffer from a total loss of vision—an immersion into total darkness. The pathology is quantitatively and qualitatively unspectacular: Small scars develop in the macula. But consider the effect of these tiny scars perhaps in a retired schoolteacher with ARMD. The small macular scars make it impossible for her to see anything clearly in the central portion of her vision. She looks directly at her life-long companion, her spouse, and cannot see his face. She cannot read a book or newspaper or look up telephone numbers. She, who raised children, had a career, and was the model of independence, can no longer drive a car and must ask people to take her where she wishes to go: true, her life is not threatened by the small scars in the macula of her
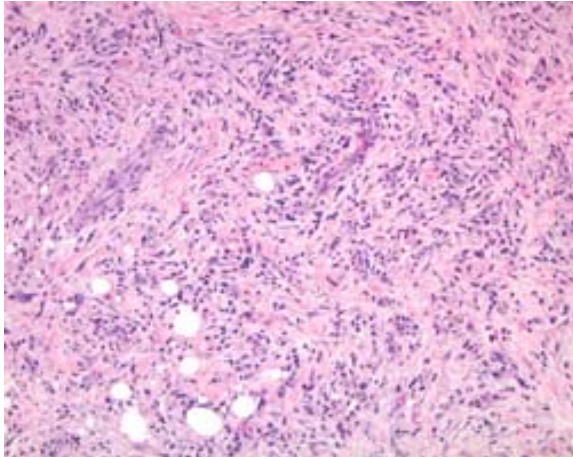
Figure 29-1 Anatomy of the eye.

Retina

Choroid

Sclera

Conjunctiva

Zonule

Posterior chamber

Optic nerve

Central artery and vein

Lens

Pupil

Anterior chamber

Cornea

Descemet membrane

Iris

Trabecular meshwork

Schlemm canal

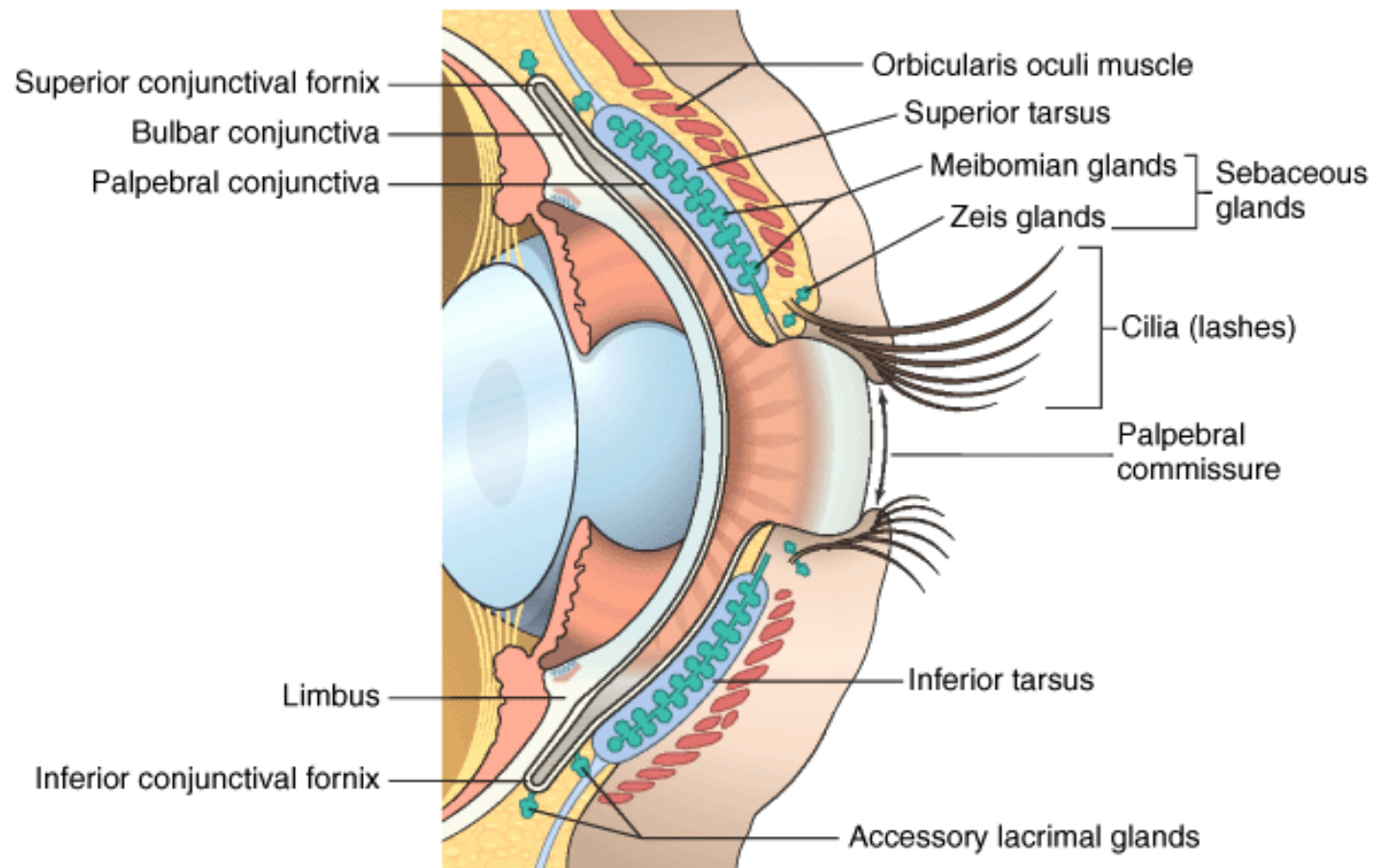Pars plicata

Pars plana

Ciliary body
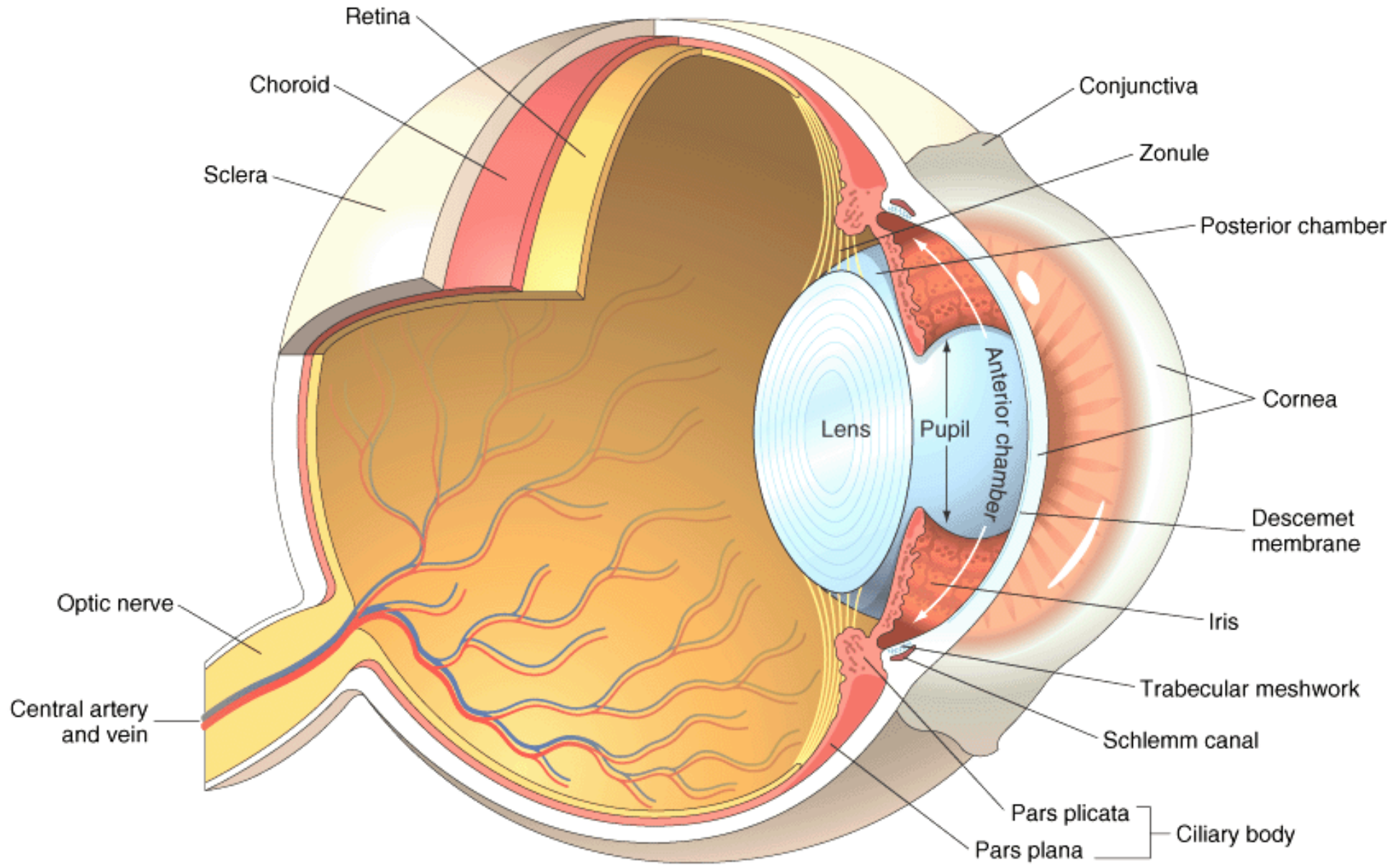
Figure 29-2 The extraocular muscles are greatly distended in this postmortem dissection of tissues from a patient with thyroid (Graves) ophthalmopathy. Note that the tendons of the muscles are spared involvement. *(Courtesy of Dr. Ralph C. Eagle Jr, Wills Eye Hospital, Philadelphia, PA.)*

Figure 29-3 In idiopathic orbital inflammation (orbital inflammatory pseudotumor), the orbital fat is replaced by fibrosis. Note the chronic inflammation, accompanied in this case by eosinophils.

Figure 29-4 Anatomy of the conjunctiva and eyelids.

Superior conjunctival fornix
Bulbar conjunctiva
Palpebral conjunctiva

Orbicularis oculi muscle
Superior tarsus
Meibomian glands ⎤ Sebaceous
Zeis glands ⎦ glands

Cilia (lashes)

Palpebral commissure

Limbus

Inferior tarsus

Inferior conjunctival fornix

Accessory lacrimal glands

Figure 29-5 Pagetoid spread of sebaceous carcinoma. Neoplastic cells with foamy cytoplasm are detected within the epidermis. Invasive sebaceous carcinoma was identified elsewhere in this biopsy sample.
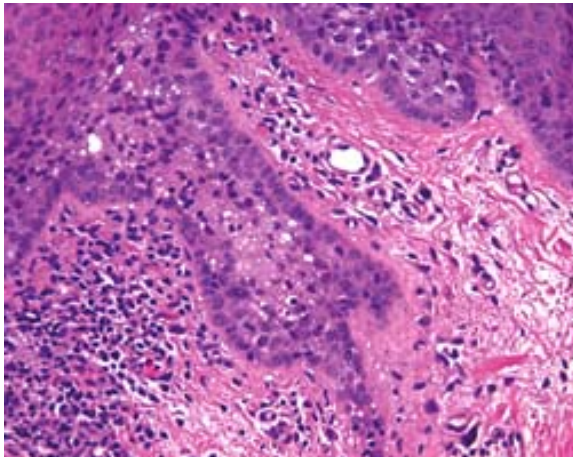
Figure 29-6 *A*, *B*, Cystic compound nevus of the conjunctiva. *(From Folberg R, Jakobiec FA, Bernardino VB, Iwamoto T: Benign conjunctival melanocytic lesions: clinicopathologic features. Ophthalmology 96:436–461, 1989.)* *C*, *D*, Conjunctival malignant melanoma. In *C*, note the deflection of the beam of the slit lamp over the surface of the lesion, indicative of invasion.
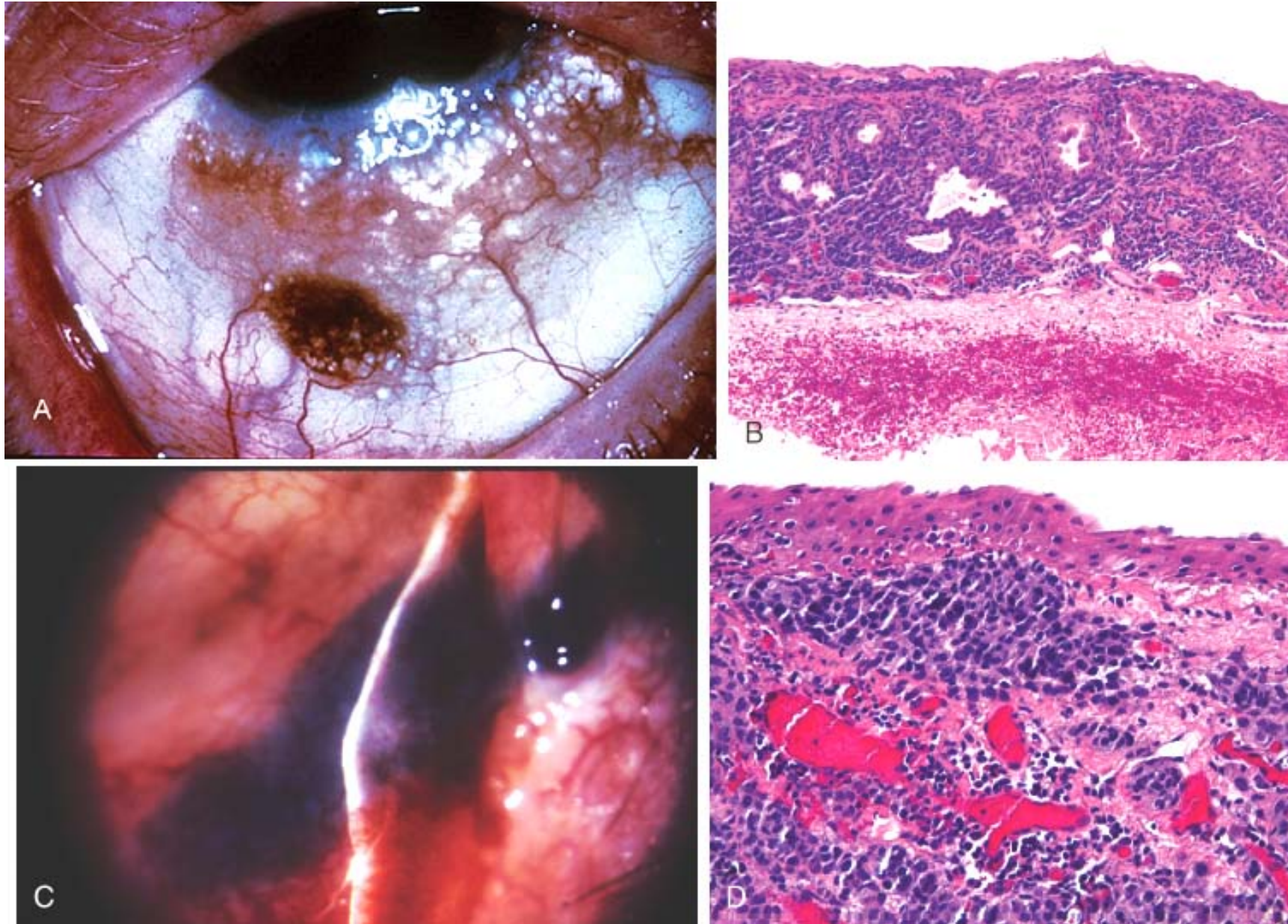
Figure 29-7 Normal corneal microarchitecture. The corneal tissue is stained by periodic acid-Schiff (PAS) to highlight basement membranes. The inset at the upper left is a high magnification of the anterior layers of the cornea: the epithelium *(e)*, Bowman's layer *(b)*, and the stroma *(s)*. A very thin PAS-positive basement membrane separates the epithelium from Bowman's layer. Note that Bowman's layer is acellular. The inset at the lower right is a high magnification of the PAS-positive Descemet membrane and the corneal endothelium. The "holes" in the stroma are artifactitious spaces between parallel collagenous stromal lamellae.
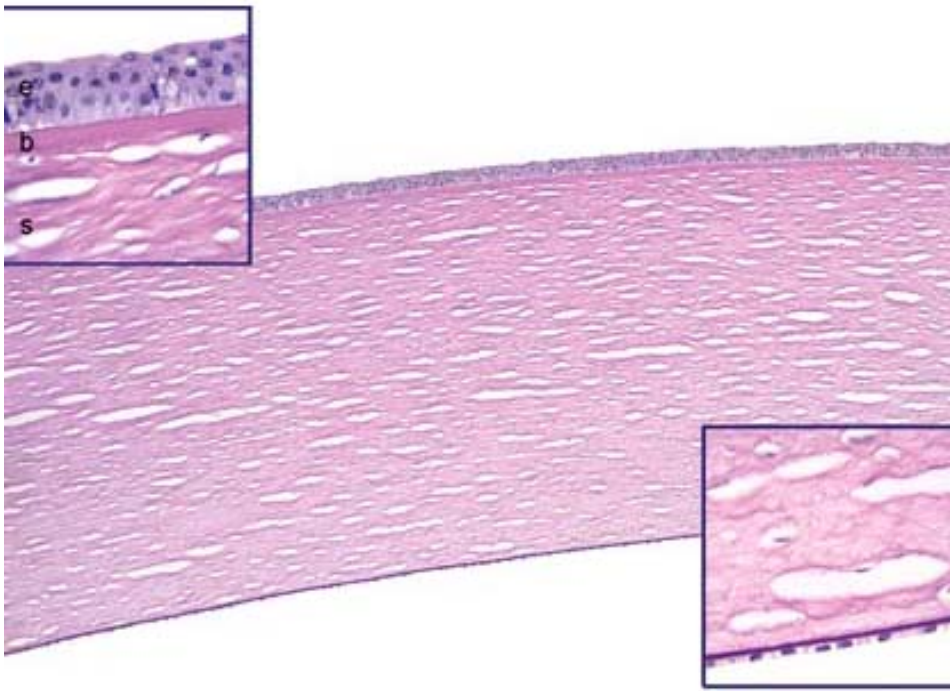
Figure 29-8 Chronic herpes simplex keratitis. The cornea is thin and scarred (note the increased number of fibroblast nuclei). Granulomatous reaction to Descemet's membrane, illustrated in this photomicrograph (*arrows*), is a histologic hallmark or chronic herpes simplex keratitis.
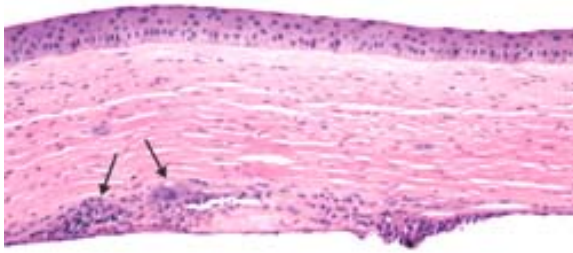
Figure 29-9 Keratoconus. This high-magnification photomicrograph captures the epithelium, Bowman's layer, and the superficial layers of the corneal stroma; the posterior layers of the stroma, Descemet's membrane, and the endothelium are not included. The tissue section is stained by periodic acid-Schiff to highlight the epithelial basement membrane (ebm), which is intact. Bowman's layer (bl), situated between the epithelial basement membrane and the stroma (s), is not a basement membrane. By tracing Bowman's layer from the right side of the photomicrograph toward the center, one notices a discontinuity in this layer, diagnostic of keratoconus. The epithelial separation just to the left of the Bowman's layer break resulted from an episode of corneal hydrops, secondary to a break in Descemet's membrane (not shown).
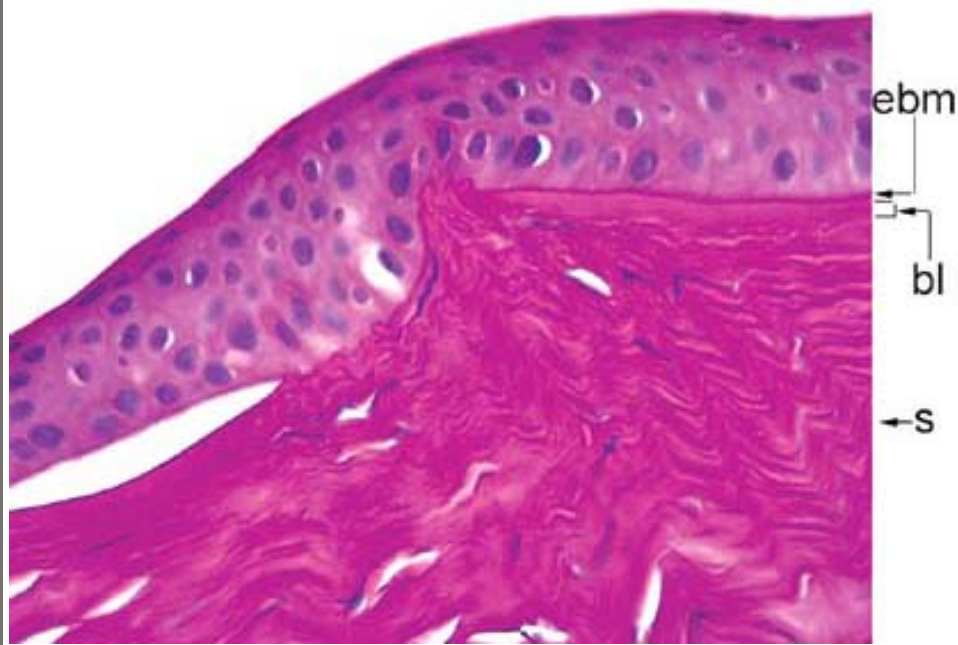
Figure 29-10 Fuchs dystrophy. This tissue section is stained by periodic acid-Schiff to highlight the Descemet's membrane, which is thick. Numerous droplike excrescences—guttata—protrude downward from Descemet's membrane. Endothelial cell nuclei are not seen. Epithelial bullae, not shown in this micrograph, were present, reflecting corneal edema.
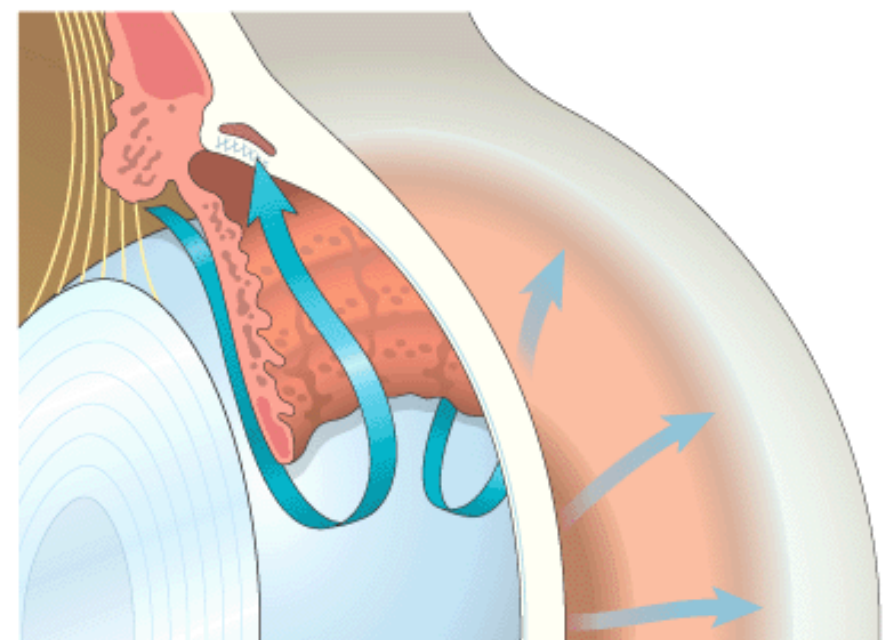

Figure 29-11 *Upper left*, The normal eye. Note that the surface of the iris is highly textured with crypts and folds. *Upper right*, The normal flow of aqueous humor. Aqueous humor, produced in the posterior chamber, flows through the pupil into the anterior chamber. The major pathway for the egress of aqueous humor is through the trabecular meshwork, into Schlemm's canal. Minor outflow pathways (uveoscleral and iris, not depicted) contribute to a limited extent to aqueous outflow. *Lower left*, Primary angle closure glaucoma. In anatomically predisposed eyes, transient apposition of the iris at the pupillary margin to the lens blocks the passage of aqueous humor from the posterior chamber to the anterior chamber. Pressure builds in the posterior chamber, bowing the iris forward (iris bombé) and occluding the trabecular meshwork. *Lower right*, A neovascular membrane has grown over the surface of the iris, smoothing the iris folds and crypts. Myofibroblasts within the neovascular membrane cause the membrane to contract and to become apposed to the trabecular meshwork (peripheral anterior synechiae). Outflow of aqueous humor is blocked, and the intraocular pressure becomes elevated.
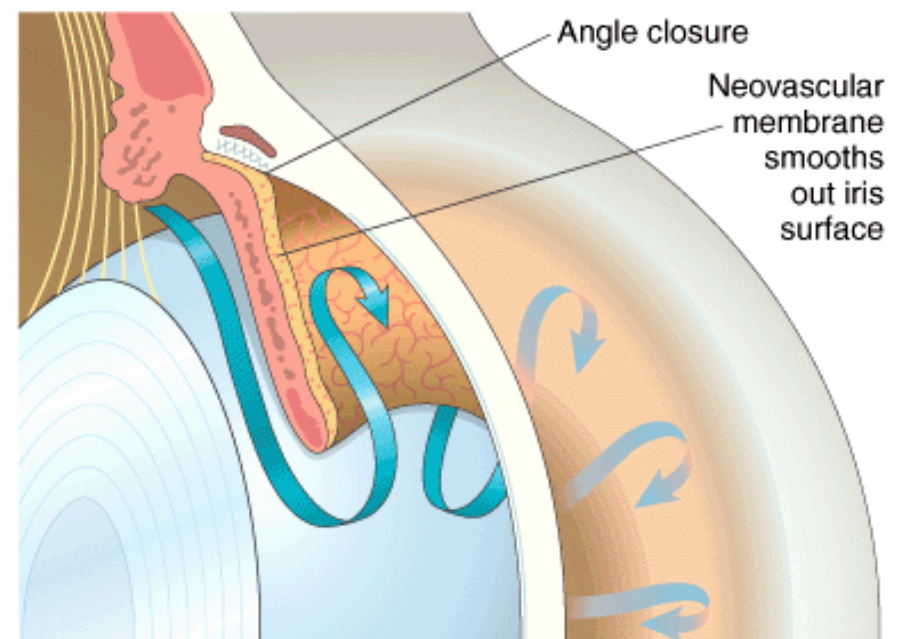
ANTERIOR AND POSTERIOR CHAMBERS

Ciliary body
Angle
Posterior chamber
Iris
Lens
Pupil
Anterior chamber
Schlemm's canal
Trabecular meshwork
Cornea
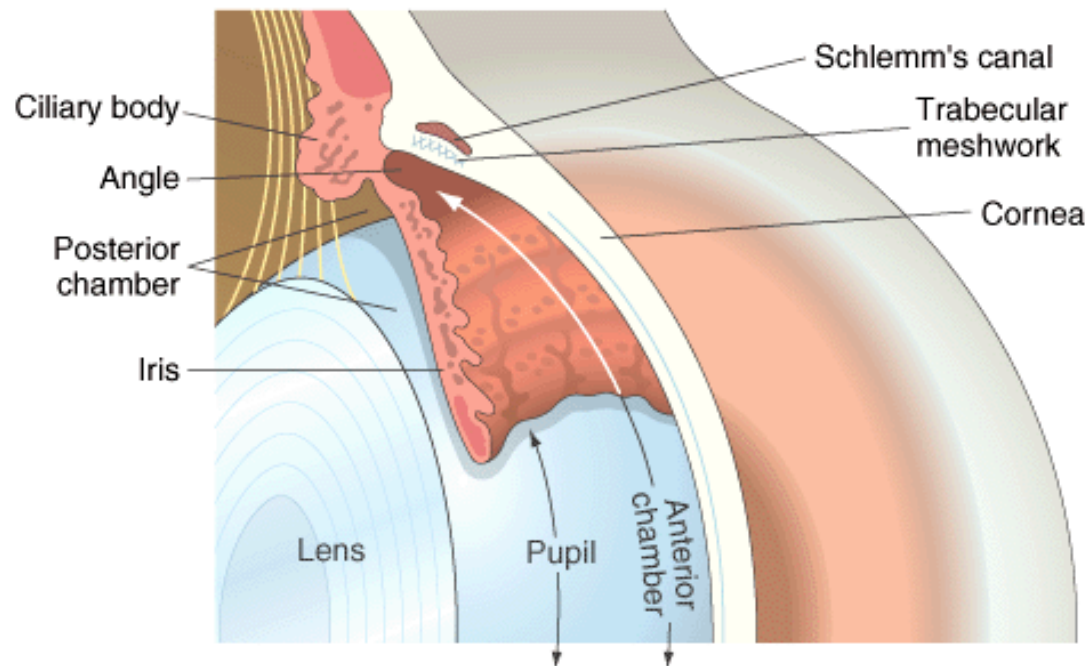
MAJOR AQUEOUS OUTFLOW PATHWAY

PRIMARY ANGLE CLOSURE GLAUCOMA

Obstructed flow leads to increased posterior chamber pressure
Angle closure
Iris bows forward (iris bombé)
Pupillary block

NEOVASCULAR GLAUCOMA
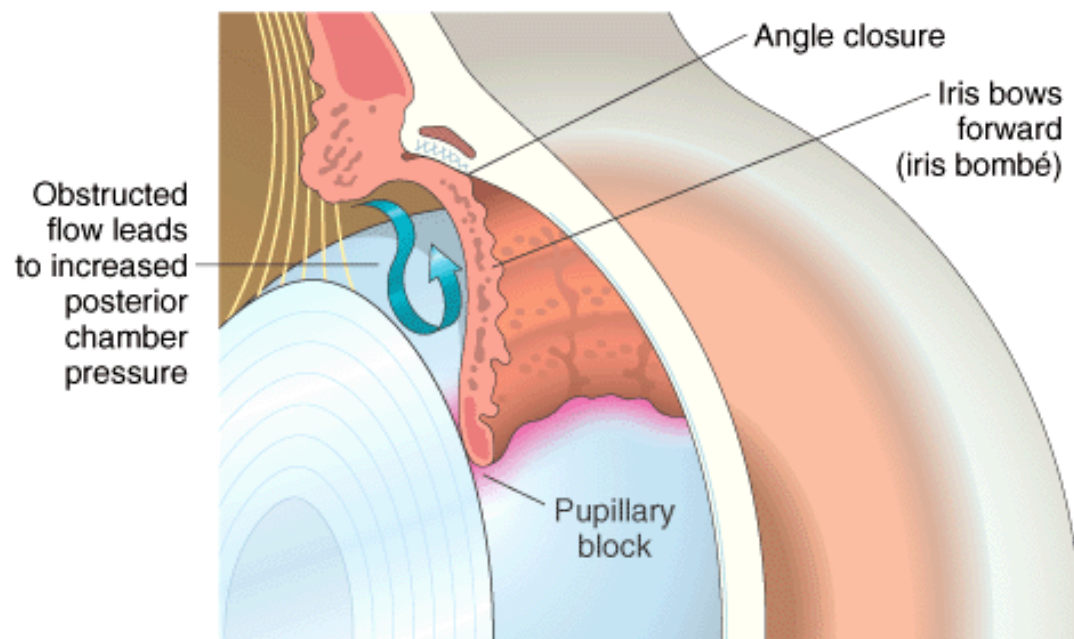
Angle closure
Neovascular membrane smooths out iris surface

Figure 29-12 Sequelae of anterior segment inflammation. This eye was removed for complications of chronic corneal inflammation (which cannot be discerned at this magnification). The exudate (e) present in the anterior chamber would have been visualized at the slit lamp as an optical "flare." The iris is adherent focally to the cornea, obstructing the trabecular meshwork (anterior synechia, *arrow*), and adheres to the lens (posterior synechiae, *arrowheads*). An anterior subcapsular cataract (asc) has formed. The radial folds in the lens are artifacts.
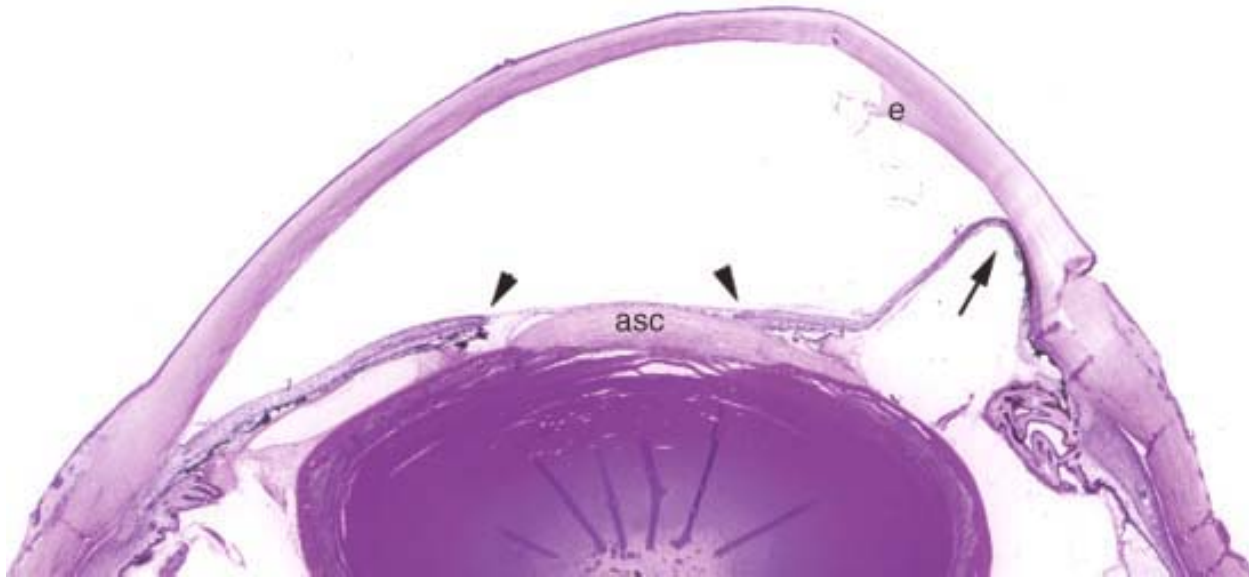
Figure 29-13 Exogenous panophthalmitis. This eye was removed after a foreign body injury. Note the suppurative inflammation behind the lens and drawn up to the right of the lens to the cornea, the site of the wound. The central portion of the vitreous humor was extracted surgically (by vitrectomy). Note the adhesions to the surface of the eye at the eight o'clock position, indicating that the intraocular inflammation has spread through the sclera into the orbit: panophthalmitis. *(From Folberg R: The Eye. In Spencer WH (ed.) Ophthalmic Pathology—An Atlas and Textbook (4th Edition). Philadelphia, WB Saunders, 1985.)*
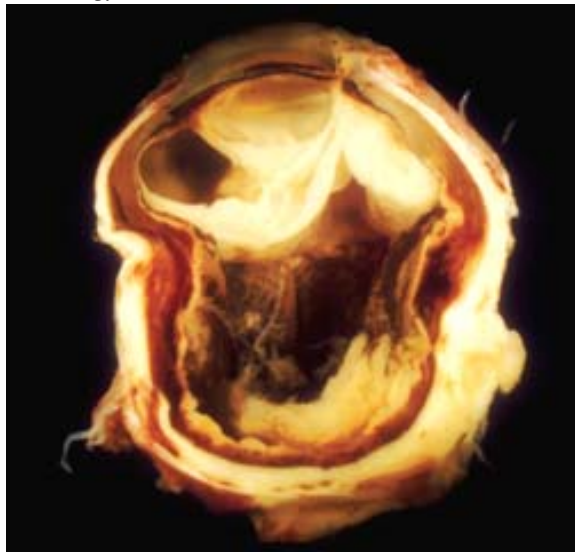
Figure 29-14 Sympathetic ophthalmia. The granulomatous inflammation depicted here was identified diffusely throughout the uvea. The uveal granulomas may contain melanin pigment

and may be accompanied by eosinophils.
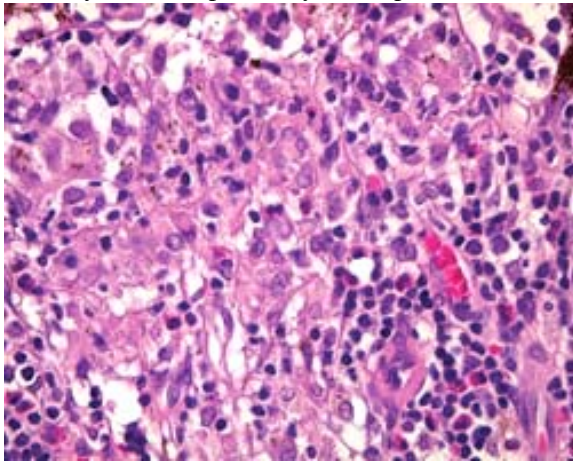
Figure 29-15 Uveal melanoma. *A*, Fundus photograph from a patient with a relatively flat pigmented lesion of the choroid near the optic disc. *B*, Fundus photograph of the same patient several years later; the tumor has grown and has ruptured through Bruch's membrane. *C*, Gross photograph of a choroidal melanoma that has ruptured Bruch's membrane. The overlying retina is detached. *D*, Epithelioid melanoma cells are associated with an adverse outcome. *E*, Patterns rich in laminin (that are periodic acid-Schiff positive) surround aggregates of melanoma cells; these patterns form a "fluid-conducting meshwork" in uveal melanoma and are associated with an adverse outcome. *(A to C from Folberg R: Pathology of the eye—an interactive CD-ROM program. Philadelphia, Mosby, 1996; E from Maniotis AJ, Chen X, Garcia C, et al: Control of melanoma morphogenesis, endothelial survival, and perfusion by extracellular matrix. Lab Invest 82(8):1031–1043, 2002.)*
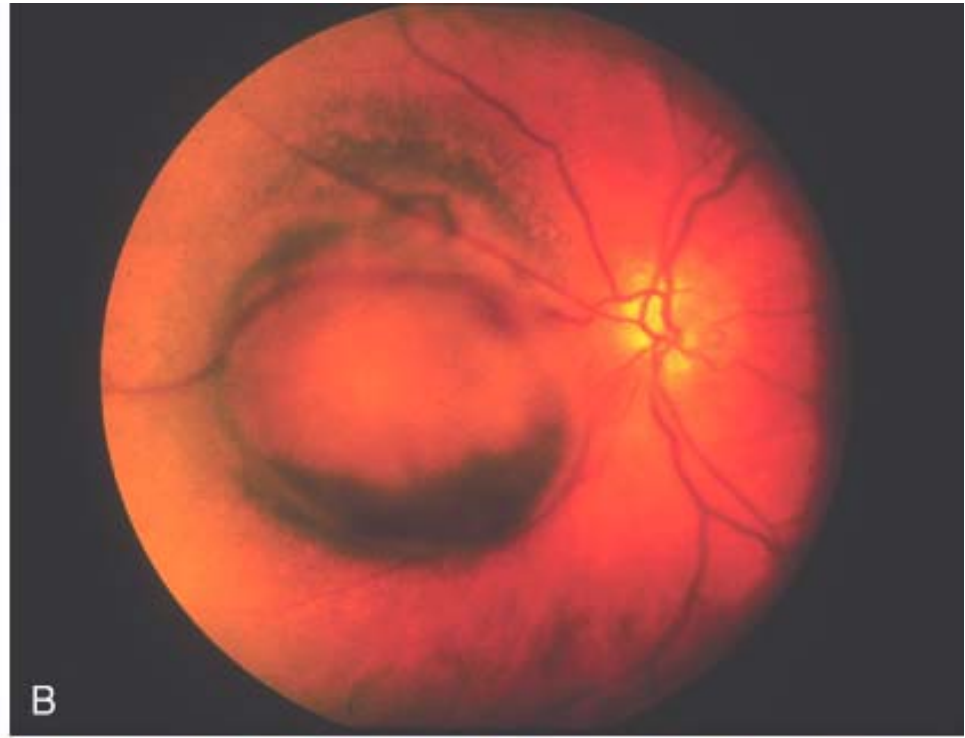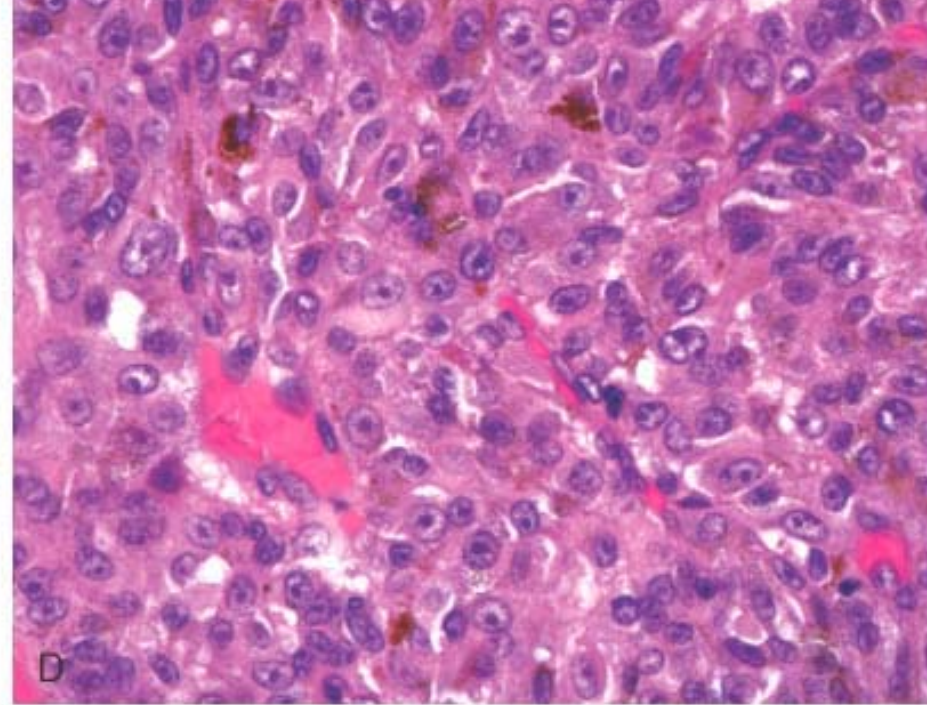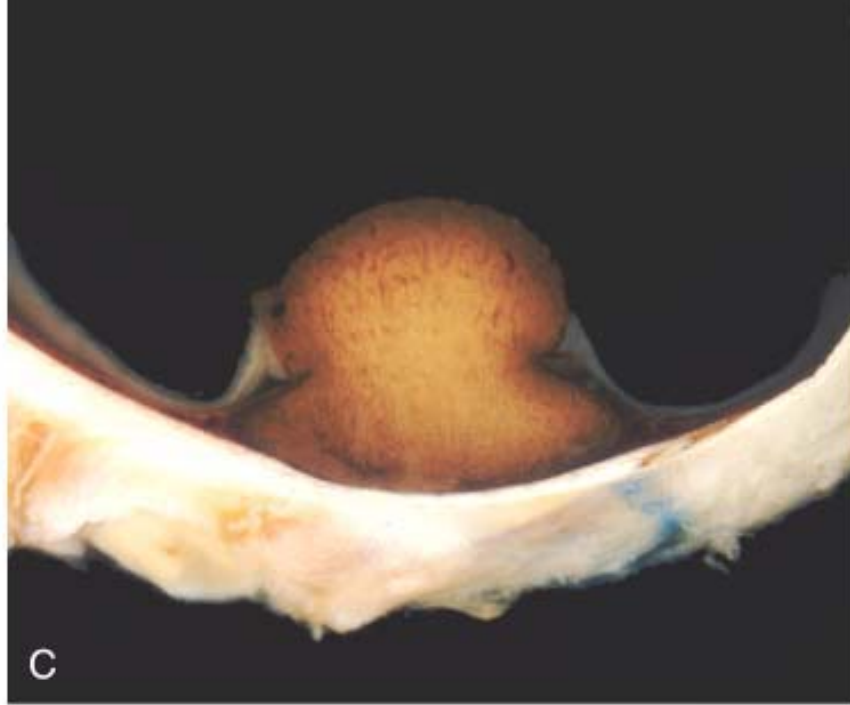
Figure 29-16 Clinicopathologic correlations of retinal hemorrhages and exudates. The location of the hemorrhage within the retina determines its appearance by ophthalmoscopy. The retinal nerve fiber layer is oriented parallel to the internal limiting membrane, and hemorrhages of this layer appear to be flame-shaped ophthalmoscopically. The deeper retinal layers

are oriented perpendicular to the internal limiting membrane and hemorrhages in this location appear as cross-sections of a cylinder or "dot" hemorrhages. Exudates that originate from leaky retinal vessels accumulate in the outer plexiform layer.
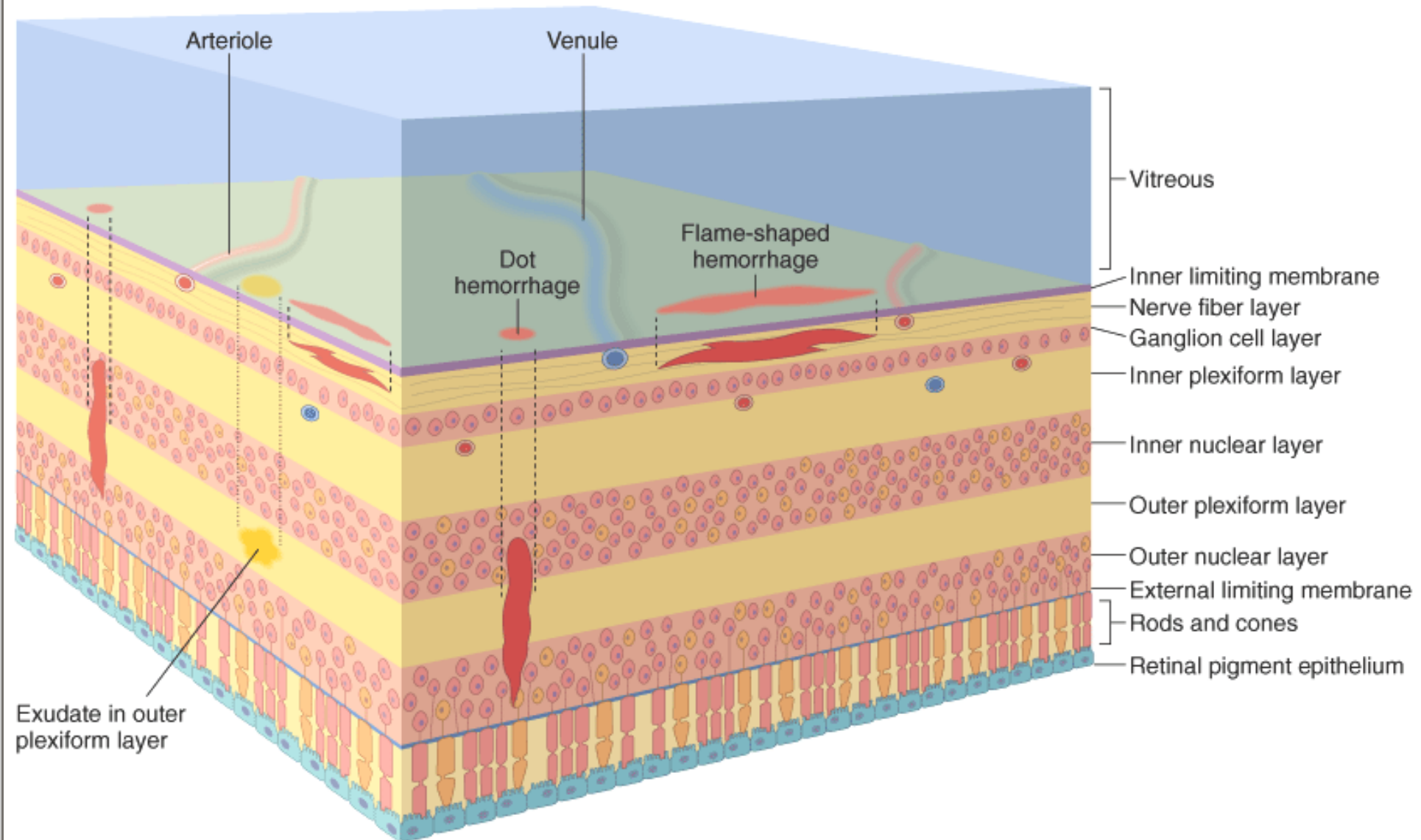
Figure 29-17 Retinal detachment is defined as the separation of the neurosensory retina from the retinal pigment epithelium. Retinal detachments are classified broadly into non-rhegmatogenous (without a retinal break) and rhegmatogenous (with a retinal break) types. *Top*, In non-rhegmatogenous retinal detachment, the subretinal space is filled with protein-rich exudate. Note in this sketch that the outer segments of the photoreceptors are missing. This indicates a chronic retinal detachment, a finding that can be seen in both non-rhegmatogenous and rhegmatogenous detachments. *Middle*, Posterior vitreous detachment involves the separation of the posterior hyaloid from the internal limiting membrane of the retina and is a normal occurrence in the aging eye. *Bottom*, If, during a posterior vitreous detachment, the posterior hyaloid does not separate cleanly from the internal limiting membrane of the retina, the vitreous humor will exert traction on the retina which will be torn at this point. Liquefied vitreous humor seeps through the retinal defect, and the retina is separated from the retinal pigment epithelium. Note in this sketch that the photoreceptor outer segments are intact, suggesting that an acute detachment is being illustrated.

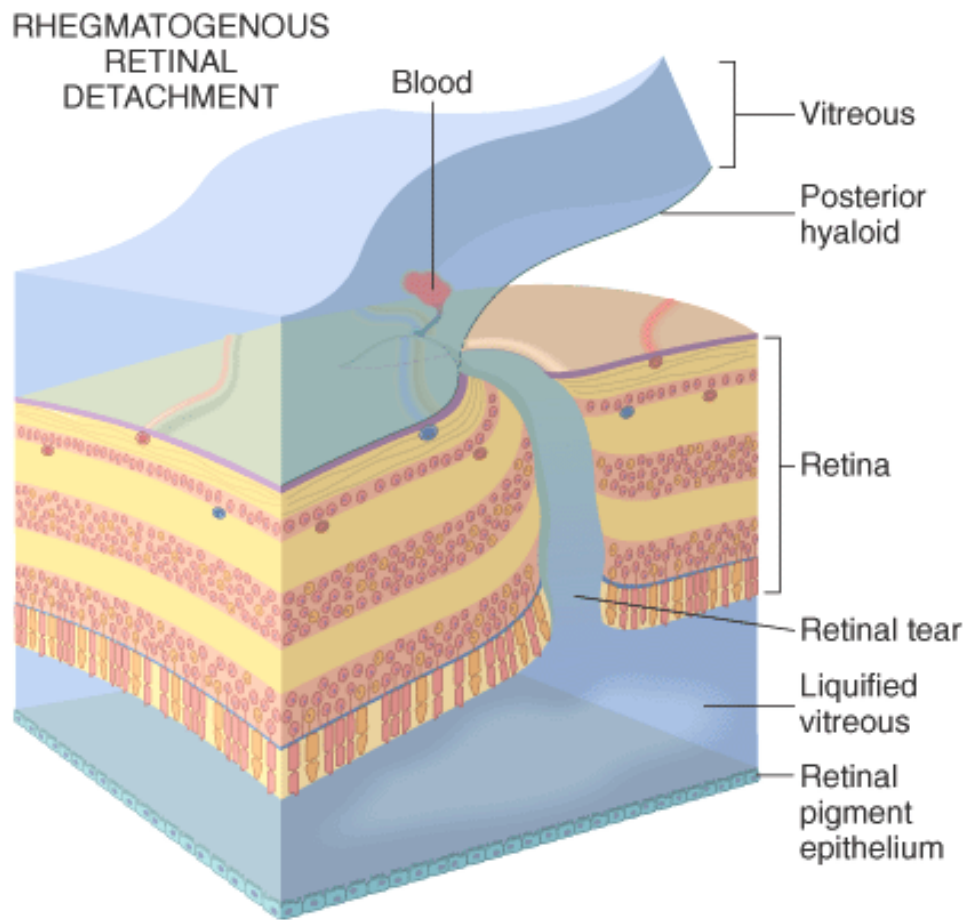NON-RHEGMATOGENOUS
RETINAL DETACHMENT

Vitreous

Retina

Protein-rich
fluid in sub-
retinal space

Retinal
pigment
epithelium

VITREOUS DETACHMENT

Vitreous

Posterior
hyaloid

Internal
limiting
membrane

RHEGMATOGENOUS RETINAL DETACHMENT

Blood

Vitreous

Posterior hyaloid

Retina

Retinal tear

Liquified vitreous

Retinal pigment epithelium
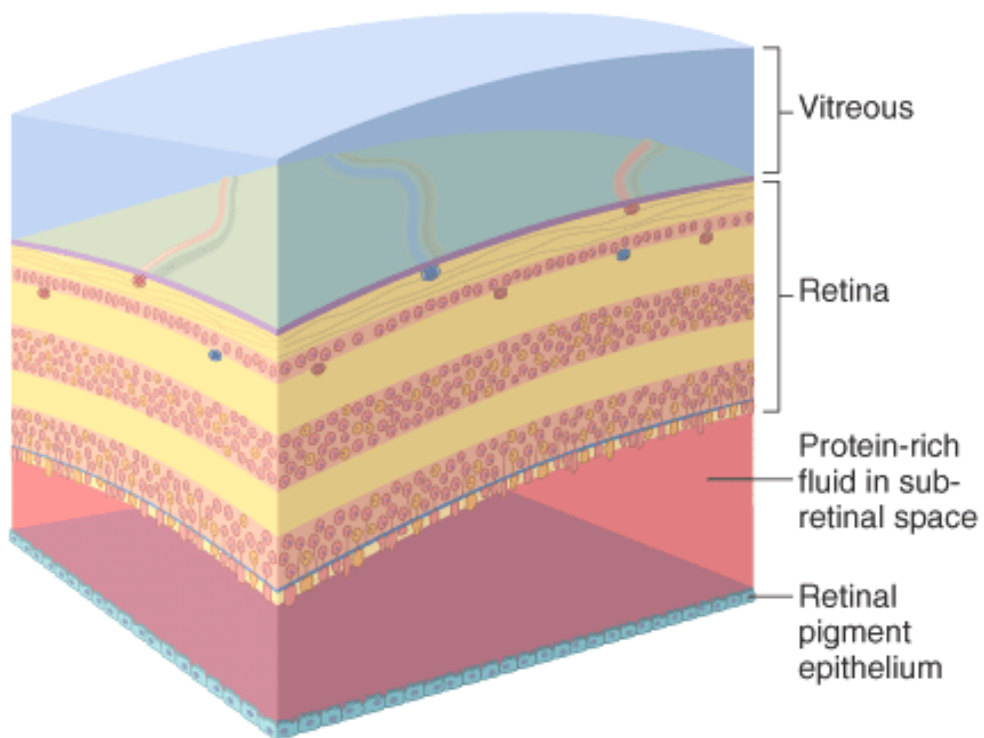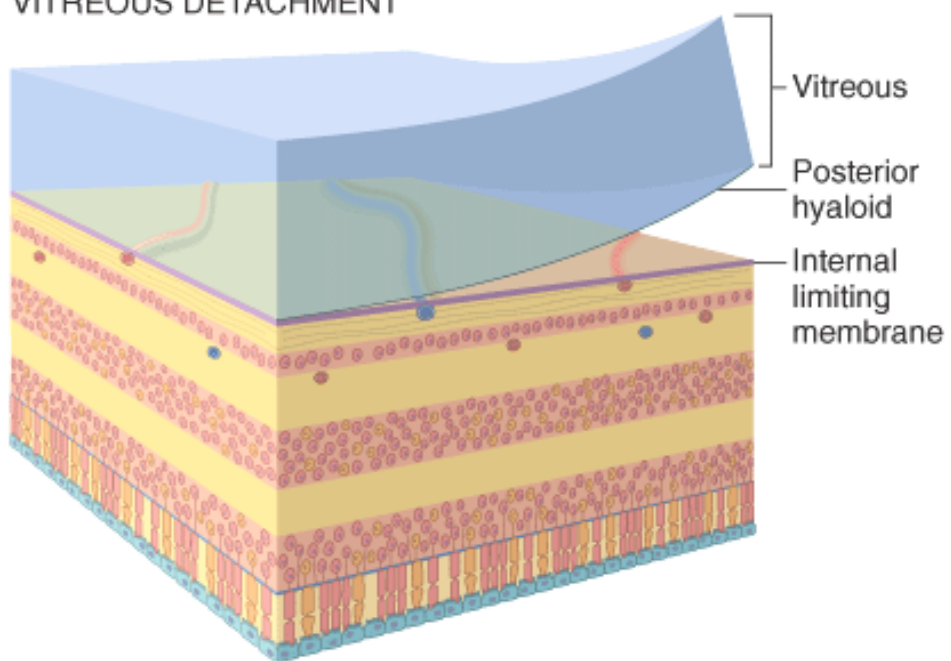
Figure 29-18 The retina in hypertension. *A*, The wall of the retinal arteriole *(arrow)* is thick. Note the exudate (e) in the retinal outer plexiform layer. *B*, The fundus in hypertension. The diameter of the arterioles is reduced, and the color of the blood column appears to be less saturated (copper wire-like). The retinal venule is compressed at a point where the artery and vein cross. If the wall of the vessel were thicker still, the degree of red color would diminish such that the vessels might appear clinically to have a "silver-wire" appearance. In this fundus photograph, note that the vein is compressed where the sclerotic arteriole crosses over it. *(B, courtesy of Dr. Thomas A. Weingeist, Department of Ophthalmology & Visual Science, University of Iowa, Iowa City, IA.)*
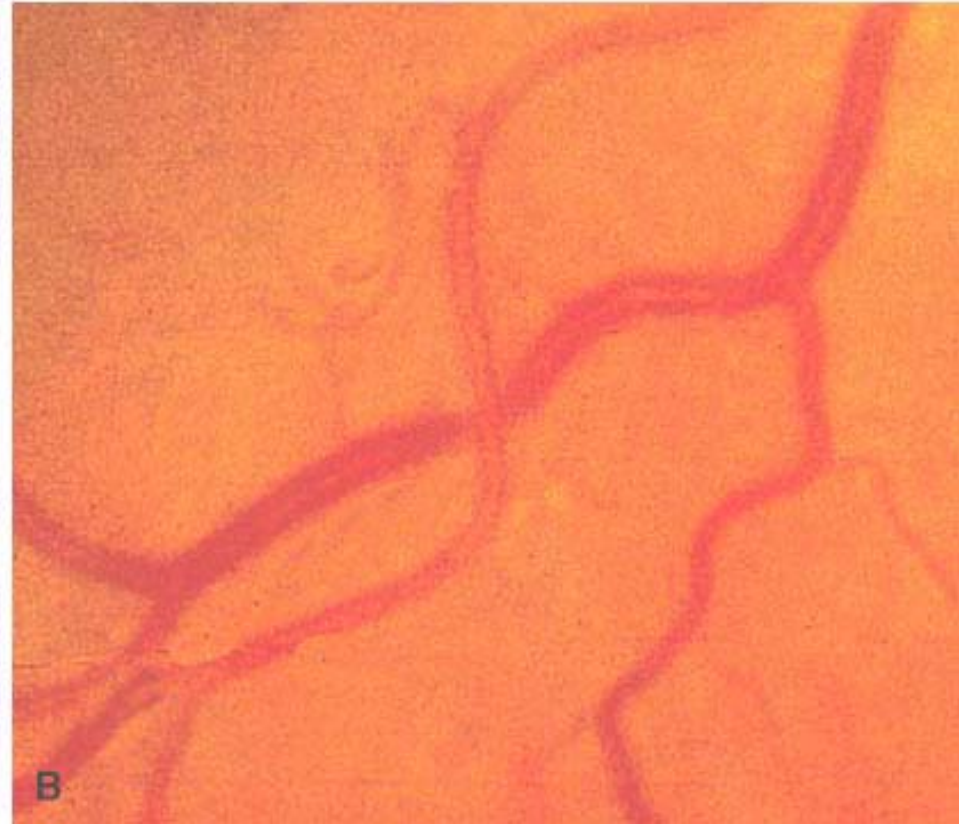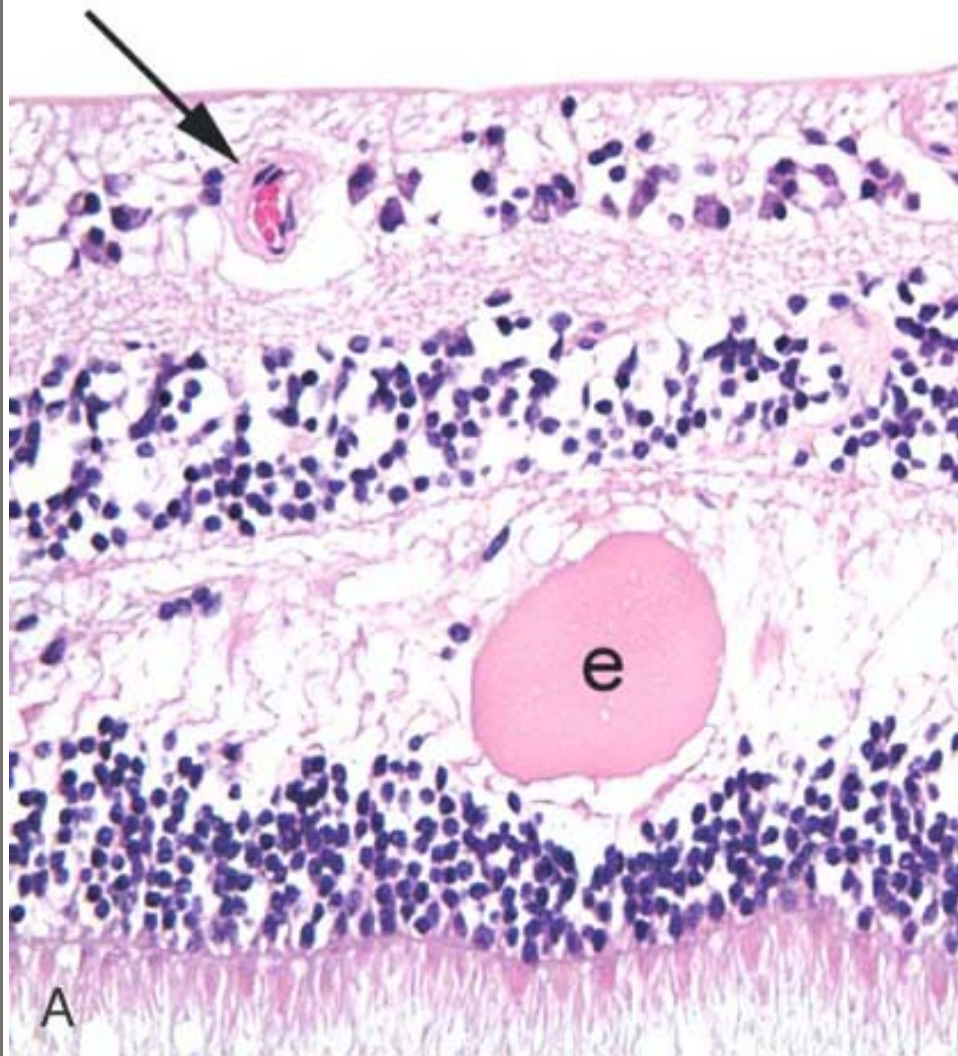
Figure 29-19 Nerve fiber layer infarct. A "cotton-wool spot" is illustrated in the inset, adjacent to a flame-shaped (nerve fiber layer) hemorrhage. The histology of a cotton-wool spot—an infarct of the nerve fiber layer of the retina—is illustrated in the photomicrograph. A focal swelling of the nerve fiber layer is occupied by numerous red to pink cytoid bodies *(arrowheads)*, bulbous ends of severed axons. Hemorrhage *(arrows)* surrounding the nerve fiber layer infarct as illustrated here is a variable and inconsistent finding. *(The fundus photo courtesy of Dr. Thomas A. Weingeist, Department of Ophthalmology & Visual Science, University of Iowa, Iowa City, IA.)*
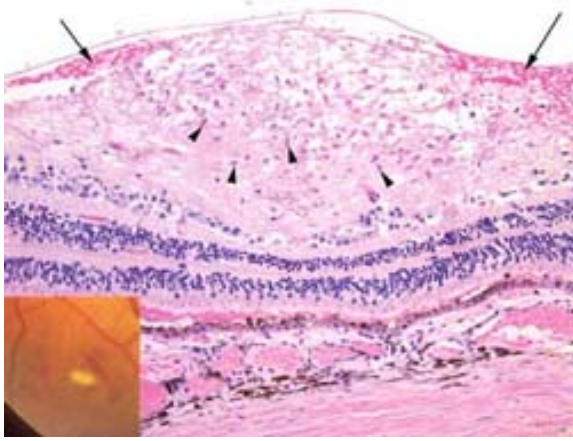
Figure 29-20 The ciliary body in chronic diabetes mellitus, periodic acid-Schiff stain. Note the massive thickening of the basement membrane of the ciliary body epithelia, reminiscent of changes in the mesangium of the renal glomerulus.
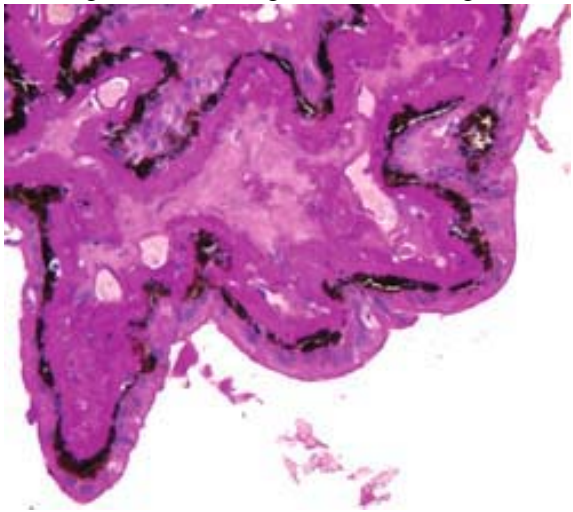

Figure 29-21 The retina in diabetes mellitus. *A*, Note the tangle of abnormal vessels just beneath the internal limiting membrane of the retina on the right half of the photomicrograph *(between arrows)*. This is an example of intraretinal angiogenesis known as intraretinal microangiopathy (IRMA). Note the retinal hemorrhage in the outer plexiform layer in the left half of this photomicrograph. Ophthalmoscopically, this outer retinal layer hemorrhage would appear as a "dot" hemorrhage. Finally, note that there are only two well-defined layers of retinal nuclei: the outer nuclear layer and the inner nuclear layer. The ganglion cell layer is absent, and the nerve fiber layer—the axons of the ganglion cells—is also absent. The rarefied space beneath internal limiting membrane to the left of the focus of IRMA consists largely of elements of retinal glial (Müller) cells. Absence of the ganglion cell and nerve fiber layers is a hallmark of glaucoma. The chronic diabetes mellitus in this patient was complicated by the development of iris neovascularization and secondary angle closure glaucoma (neovascular glaucoma). *B*, In this histologic section, stained by periodic acid-Schiff, the internal limiting membrane is noted by the long, thick arrows and the posterior hyaloid of the vitreous by the thin, short arrows. Note the vessels in the potential space between these two landmarks. The vessels to the left of the short arrow are invested with a fibrous-glial stroma and would appear ophthalmoscopically as a white neovascular membrane. However, the thin-walled vessel to the right of the short arrow is not invested with a connective tissue stroma and would appear ophthalmoscopically as merely a very thin vessel. A posterior vitreous detachment in an eye such as this might exert traction on these new vessels and precipitate a massive vitreous hemorrhage. *C*, Ophthalmoscopic view of retinal neovascularization (known clinically as neovascularization "elsewhere" in contrast with neovascularization of the optic disc). Note the blush of thin-walled vessels that are not accompanied by a fibrous stroma (analogous to the thin walled vessel in *B*). Even without a connective tissue stroma, this qualifies clinically as a neovascular membrane and is reminiscent of the appearance of experimental angiogenesis on a chick chorioallantoic membrane.
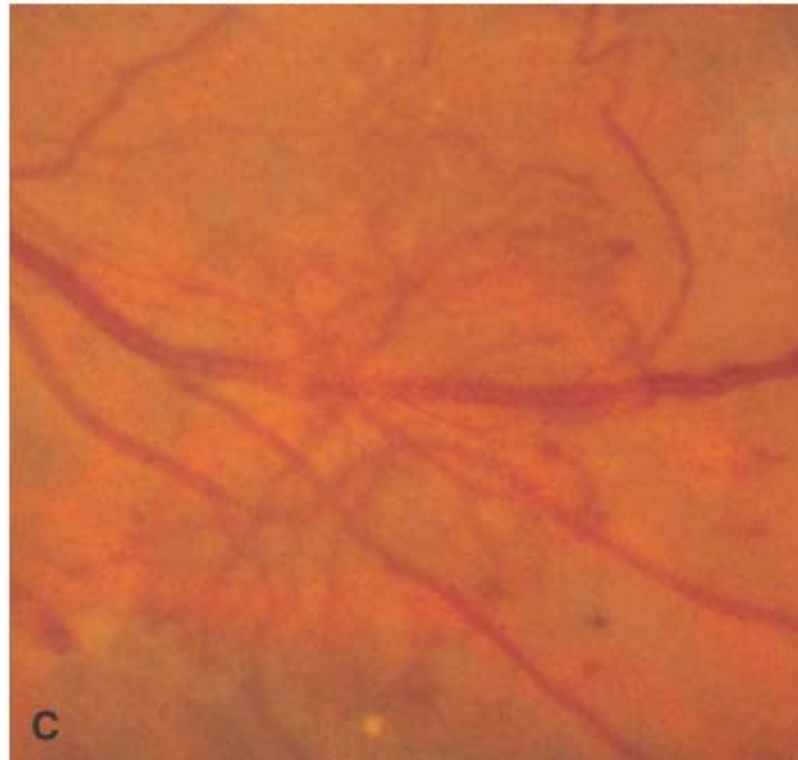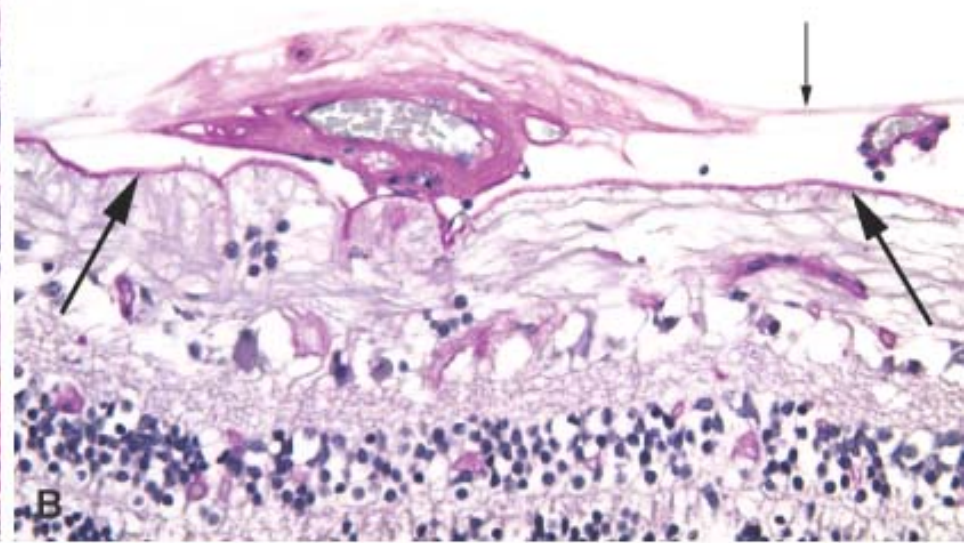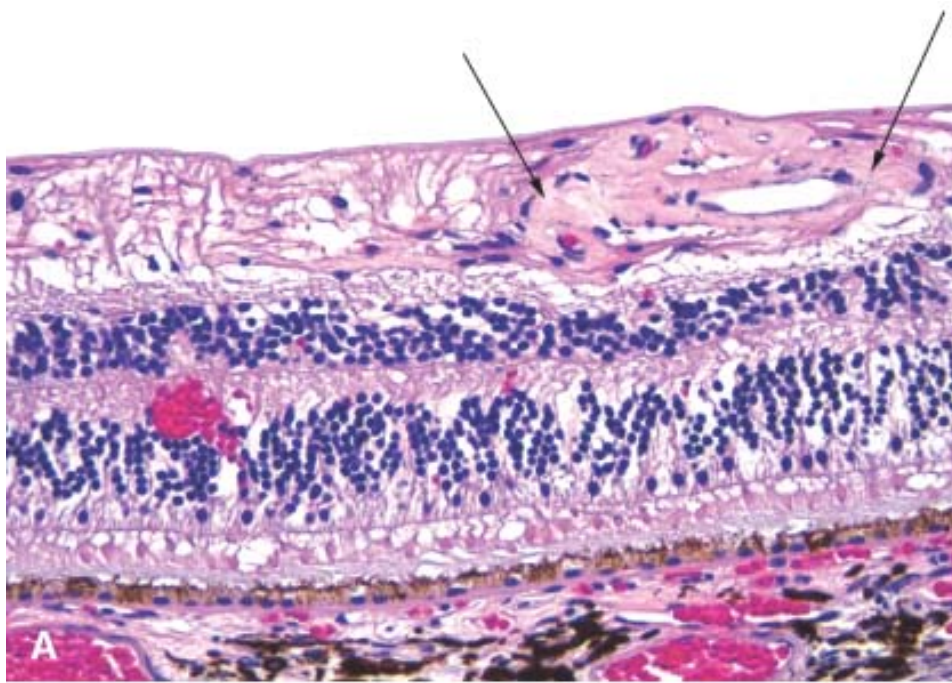
Figure 29-22 The cherry-red spot in Tay-Sachs disease. *A*, Fundus photograph of the cherry-red spot in Tay-Sachs disease. *B*, Photomicrograph of the macula in a patient with Tay-

Sachs disease, stained with periodic acid-Schiff to highlight the accumulation of ganglioside material in the retinal ganglion cells. The presence of ganglion cells filled with gangliosides outside the fovea blocks the transmission of the normal orange-red color of the choroid, but absence of ganglion cells within the fovea (to the right of the vertical bar) permits the normal orange-red color to be visualized, accounting for the so-called cherry-red spot. *(A courtesy of Dr. Thomas A. Weingeist, Department of Ophthalmology & Visual Science, University of Iowa, Iowa City, IA; B originates from the teaching collection of the Armed Forces Institute of Pathology.)*
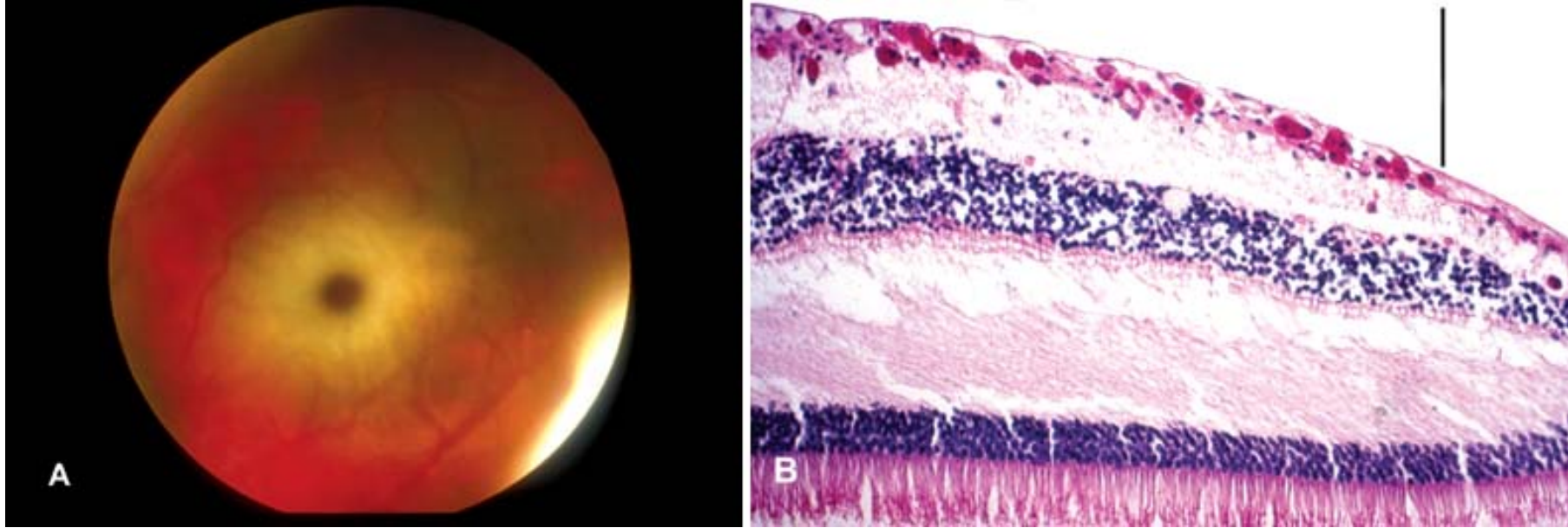

Figure 29-23 Age-related macular degeneration. A neovascular membrane is positioned between the retinal pigment epithelium (RPE) and Bruch's membrane (BM). Note the blue discoloration of Bruch's membrane to the right of the label, indicating focal calcification.
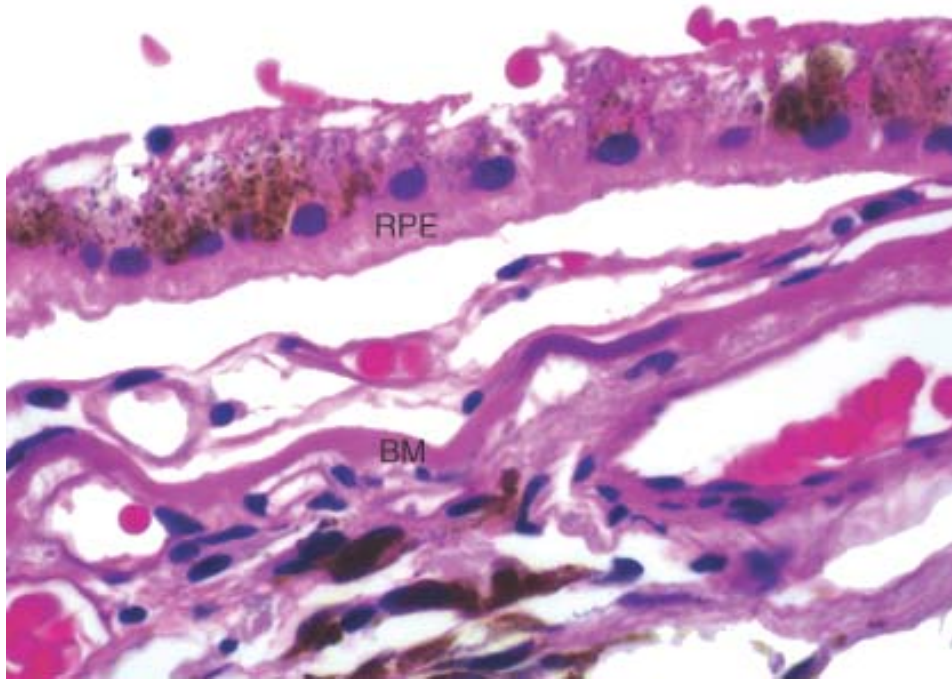
Figure 29-24 Retinoblastoma. *A*, Gross photograph of retinoblastoma. *B*, Tumor cells appear viable when in proximity to blood vessels, but necrosis is seen as the distance from the vessel increases. Dystrophic calcification *(dark arrow)* is present in the zones of tumor necrosis. Flexner-Wintersteiner rosettes—arrangements of a single layer of tumor cells around an apparent "lumen"—are seen throughout the tumor, and one such rosette is indicated by the white arrow.
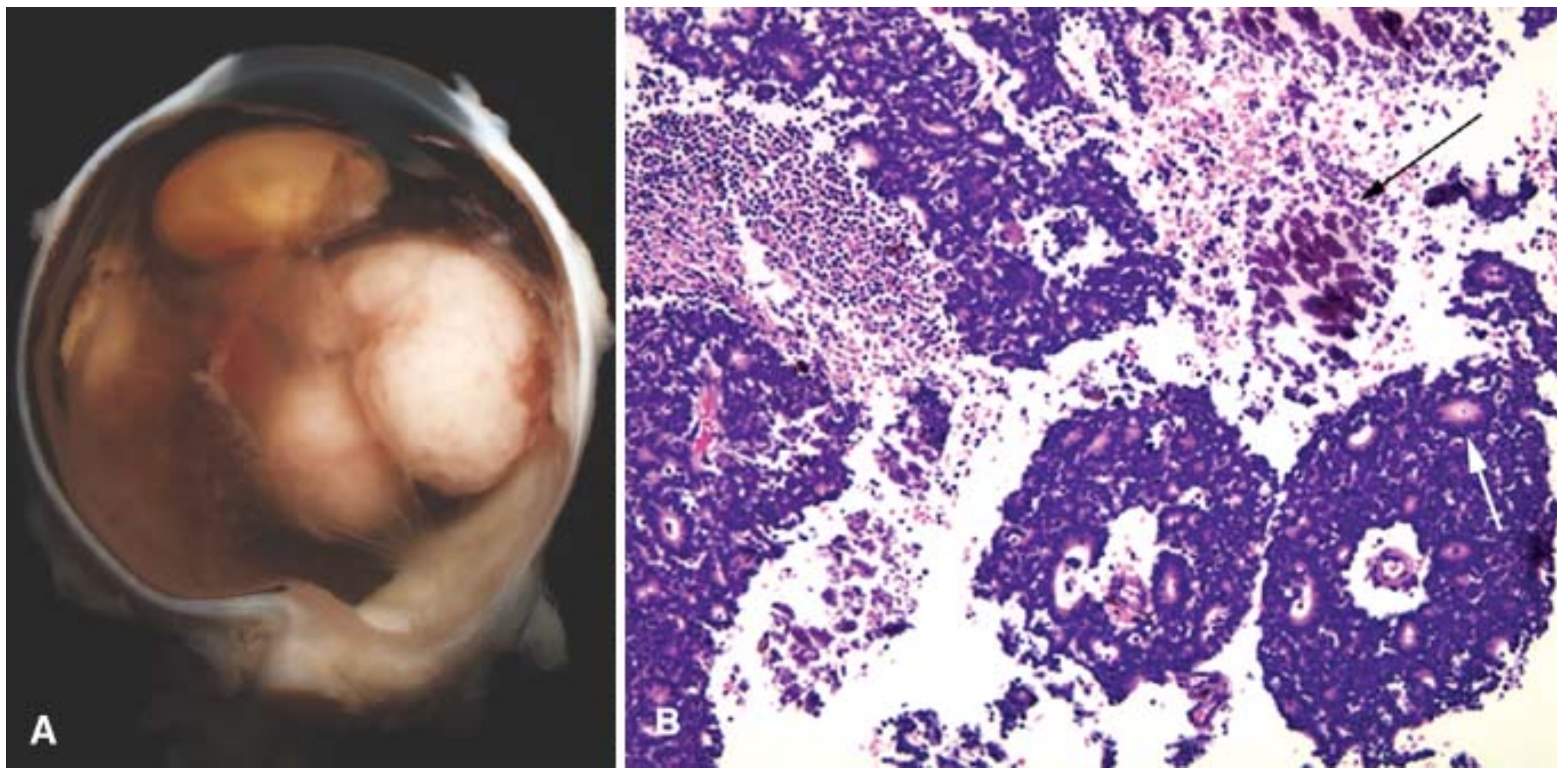
Figure 29-25 The optic nerve in anterior ischemic optic neuropathy (AION) and papilledema. *A*, In the relatively acute phases of AION, the optic nerve may be swollen, but it is relatively pale because of decreased perfusion. *B*, In papilledema secondary to increased intracranial pressure, the optic nerve is typically swollen and hyperemic. *C*, Normally, the termination of Bruch's membrane *(arrowhead)* is aligned with the beginning of the neurosensory retina, as indicated by the presence of stratified nuclei *(arrow)*, but in papilledema, the optic nerve is swollen, and the retina is displaced laterally. This is the histologic explanation for the blurred margins of the optic nerve head seen clinically in this condition. *(A and B courtesy of Dr. Sohan S. Hayreh, Department of Ophthalmology & Visual Science, University of Iowa, Iowa City, IA; C originates from the teaching collection of the Armed Forces Institute of Pathology.)*
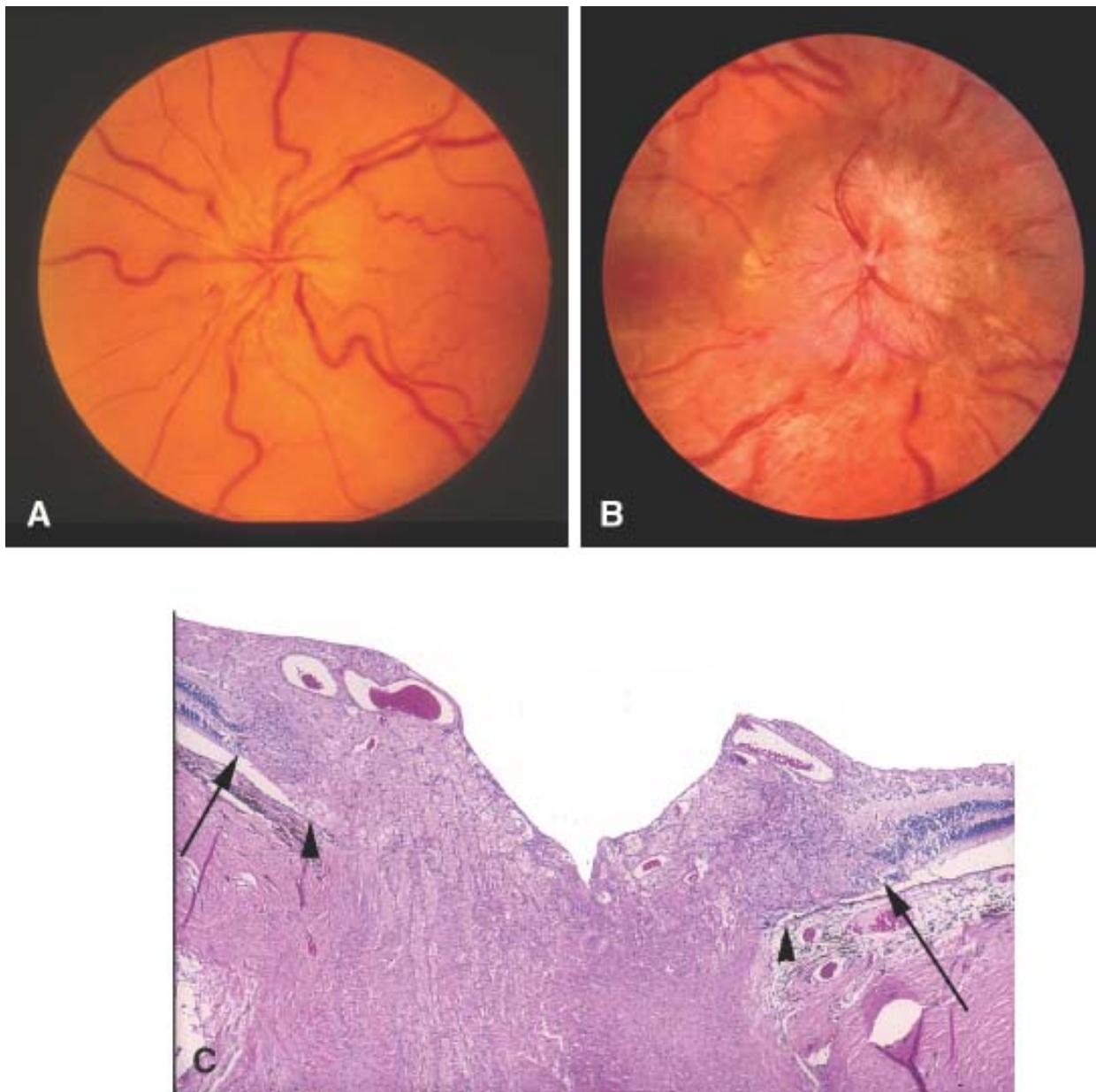
Figure 29-26 The retina and optic nerve in glaucoma. *A*, The normal retina is illustrated in the left panel, and the retina in long-standing glaucoma is in the right panel. Both pictures were taken at the same magnification. Note that the full thickness of the glaucomatous retina is captured (right), whereas only a portion of the normal retina (left) can be seen—a reflection of the thinning of the retina in glaucoma. In the glaucomatous retina, the areas corresponding to the nerve fiber layer (NFL) and ganglion cell layer (GC) are atrophic; the inner plexiform layer (IPL) is labeled for a point of reference. *B*, Glaucomatous optic nerve cupping results, in part, from loss of retinal ganglion cells, the axons of which populate the optic nerve. *C*, The arrows point to the dura of the optic nerve. Notice the wide subdural space, a result of atrophy of the substance of the optic nerve. The degree of cupping on the surface of the nerve is striking in this eye, which was removed because of complications of long-standing glaucoma.

A

B