Central nervous system

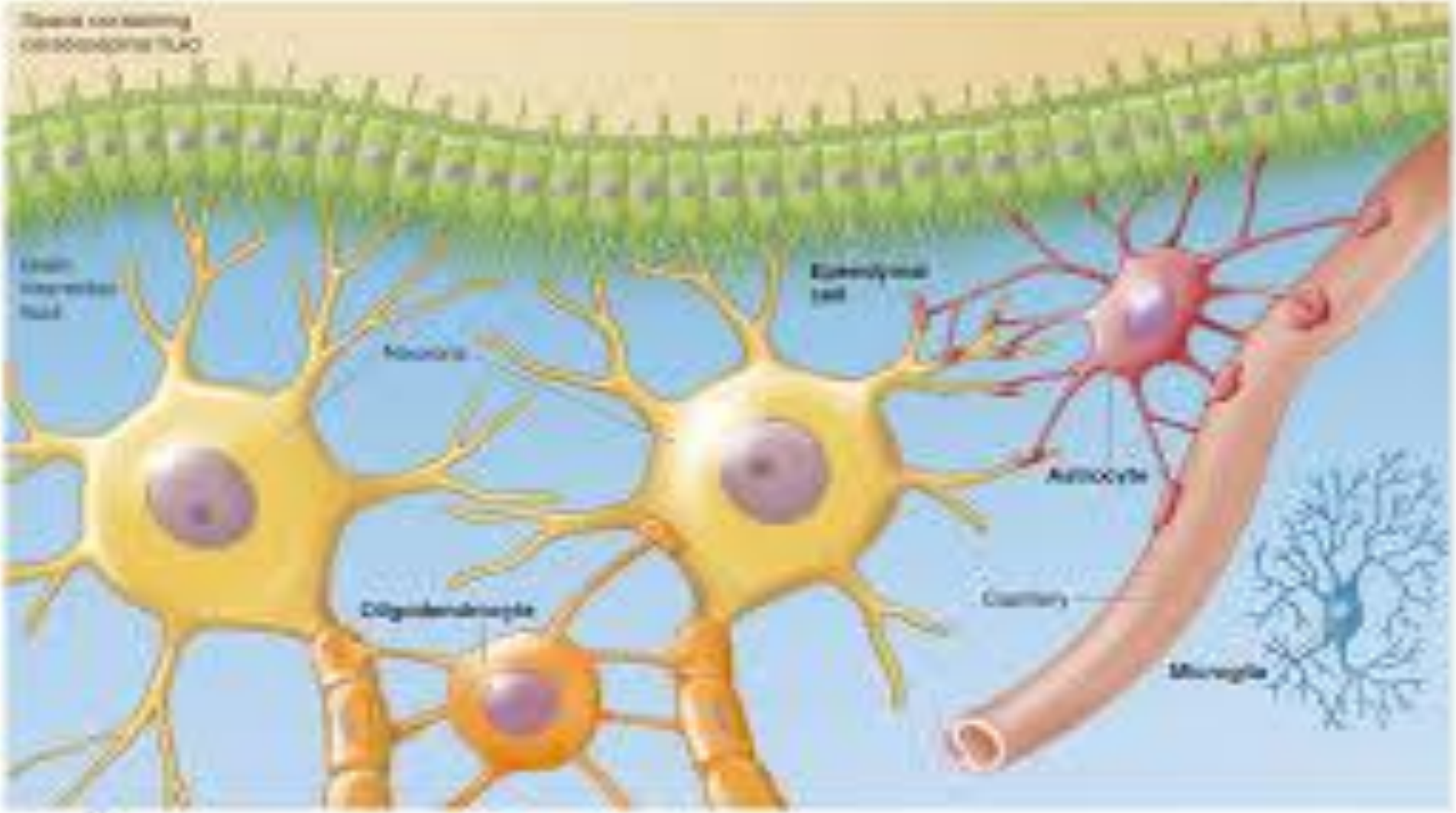
- Glia :

1. Supporting function to neurons and their processes
2. Primary role in repair
3. Fluid balance
4. Energy metabolism

- Astrocytes : have round to oval nucleus, finely stippled chromatine and branching cytoplasm processes, contain glial fibrillary acidic protien; their functions:

1. support, blood brain barrier, detoxifiers.
2. Repair and scar formation.

GLIAL CELLS


Ependymal cell
Neuron
Astrocyte
Oligodendrocyte
Capillary
Microglia

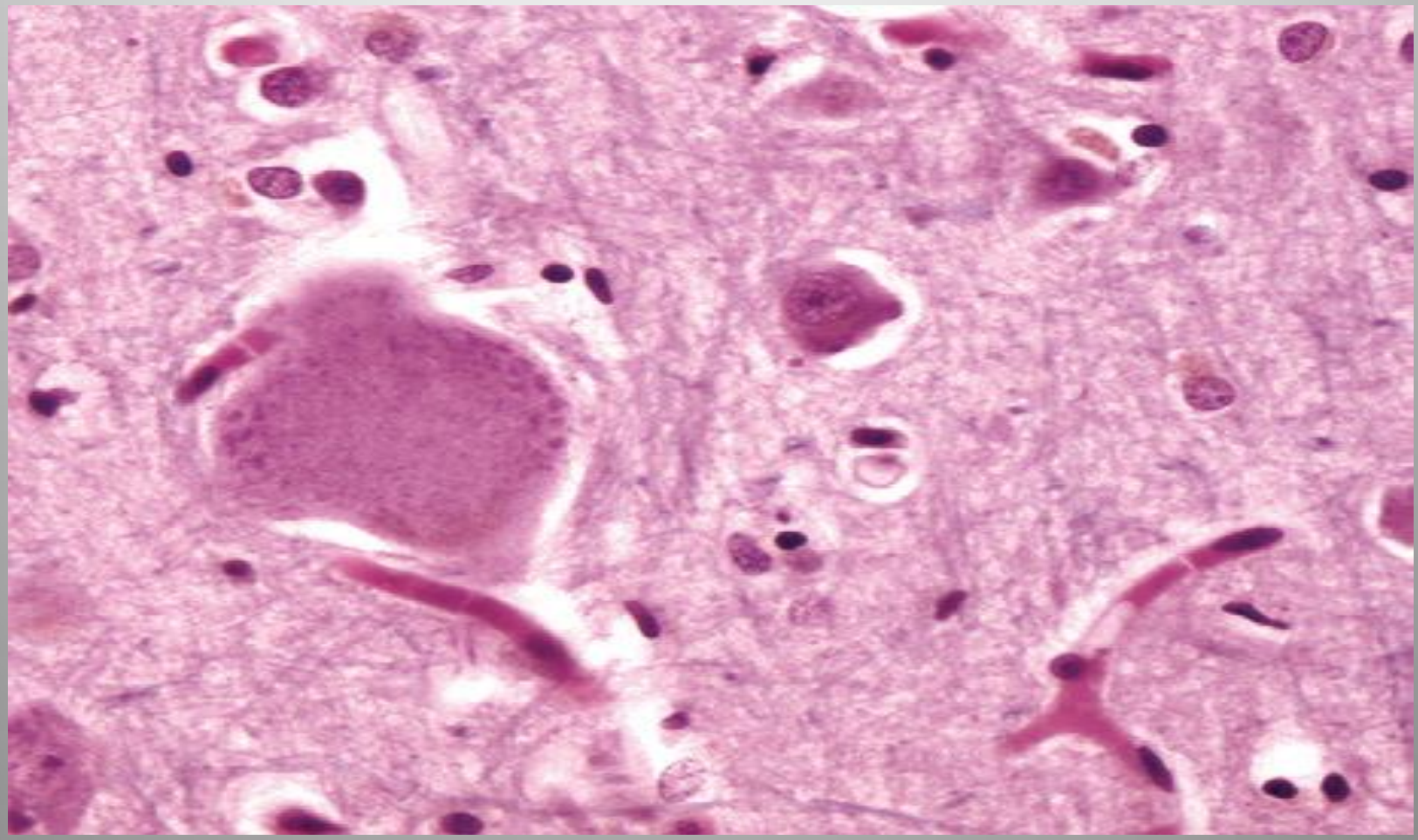
Normal cells and their reactions to injury

Neurons :

Vary in structure, functional interconnections, and biochemical properties. Pathological changes are as follow:

1. Axonal reaction : after injury the cytoplasm becomes pale and swollen.
2. Acute cell injury (red neuron): intense eosinophilia of perinuclear cytoplasm and pyknosis of nucleus e.g. anoxia and ischemia.
3. Atrophy and degeneration : characteristics of slowly progressive neurological diseases and system degeneration.
4. Intraneuronal deposit: occur in aging (lipofuscin), storage disease , viral diseases (inclusion bodies) , degenerative diseases (neurofibirillary tangles in Alzheimer disease and Lewy bodies in parkinson disease.)

axonal injury there can be swelling of the cell body



Oligodendrocytes : have lymphocytes sized nucleus with dense chromatin and little cytoplasm. They produce and maintain CNS myelin.

Ependyma : single layer of cuboidal cells that line the ventricular system and rest on subependymal glia. After injury form ependymal granulation.

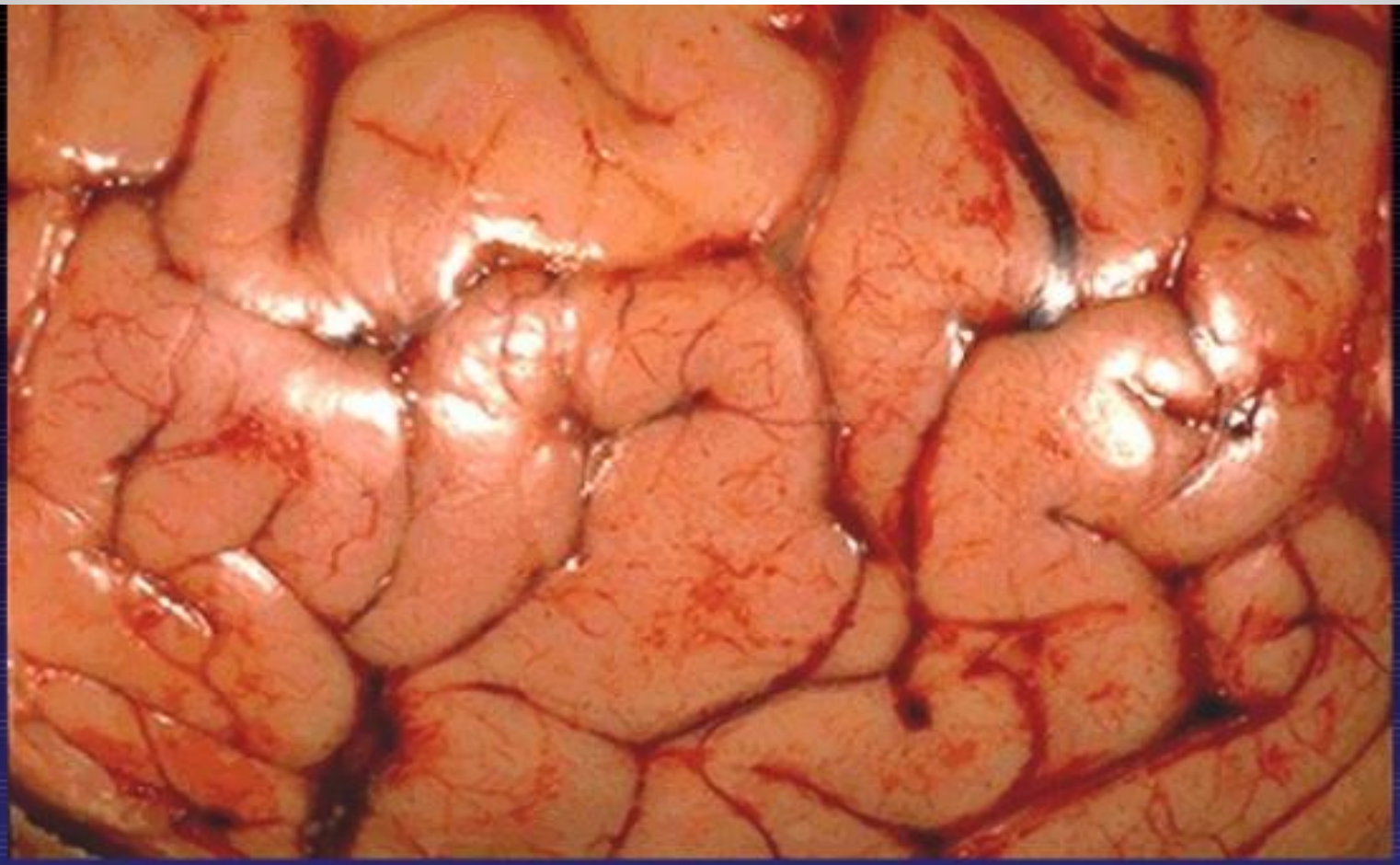
Microglia : bone marrow derived, CD3 and CD4 mononuclear cells, contain bean shape nucleus and little cytoplasm. They respond to injury by forming aggregates about small foci of tissue necrosis (microglioal nodules).

Cerebral edema

- **Cerebral edema ;accumulation of excess fluid within the brain parenchymal is of two principal :**
- ***Vasogenic edema* is caused by blood-brain barrier disruption and increased vascular permeability, allowing fluid to shift from the intravascular compartment to the intercellular spaces of the brain. (maligency)**
- ***Cytotoxic edema* is an increase in intracellular fluid secondary to neuronal, glial, or endothelial cell membrane injury, as in**

hypoxic/ischemic insult or with metabolic damage.

- **Interstitial edema (hydrocephalic edema) occurs especially around the lateral ventricles when an increase in intravascular pressure causes an abnormal flow of fluid from the intraventricular CSF across the ependymal lining to the periventricular white matter. 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.**



Gross: The surface of the brain with cerebral edema demonstrates widened gyri with a flattened surface. The sulci are narrowed.

HYDROCEPHALUS

- . *Hydrocephalus* refers to the accumulation of excessive CSF within the ventricular system . Most cases occur as a consequence of impaired flow and resorption of CSF; within the ventricles expands them and can elevate the intracranial pressure.

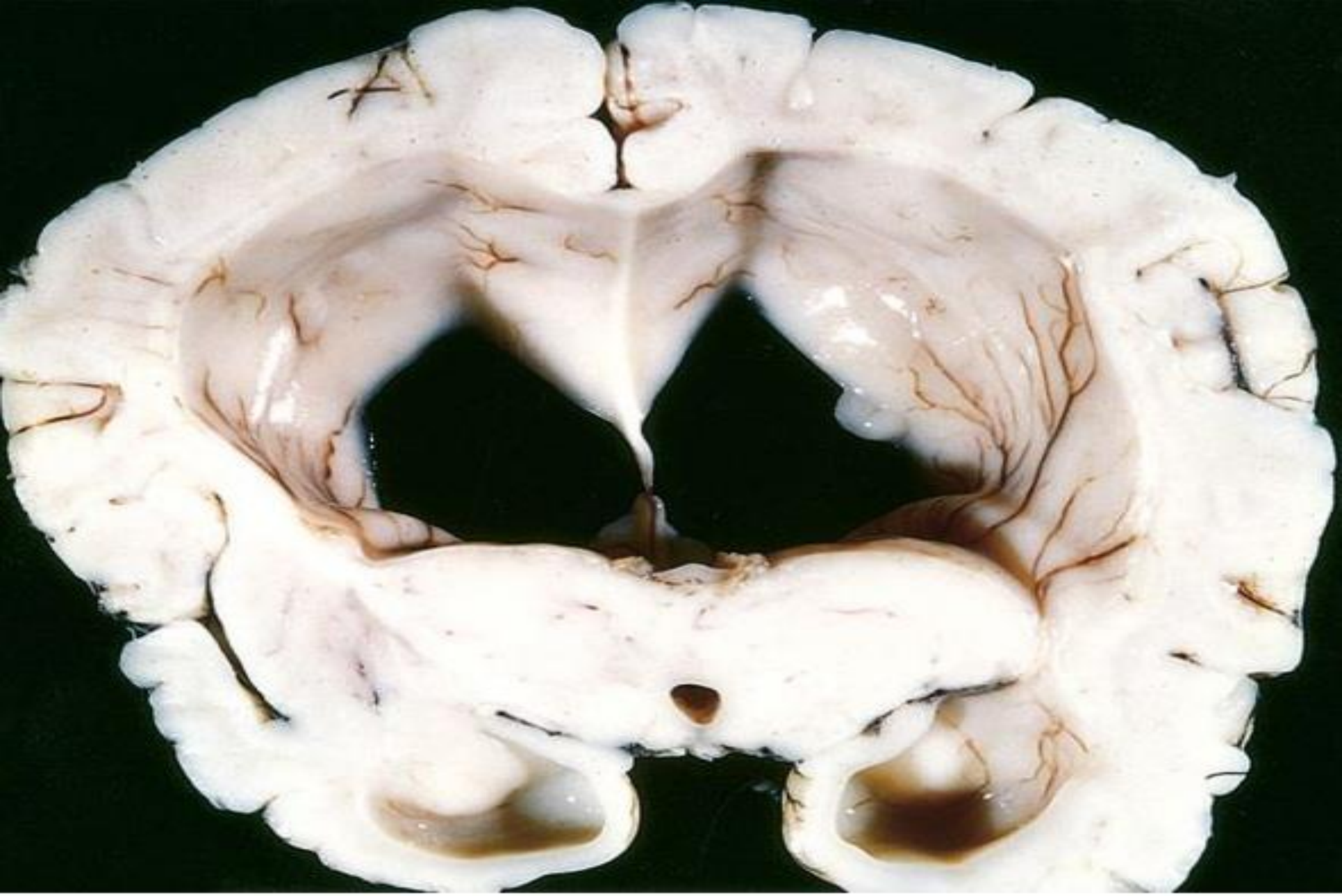


FIGURE 28-2 Hydrocephalus. Dilated lateral ventricles seen in a coronal section through the midthalamus.

RAISED INTRACRANIAL PRESSURE AND HERNIATION

- **When the volume of the brain increases beyond the limit permitted by compression of veins and displacement of CSF, the pressure within the skull will increase. Most cases are associated with a mass effect, either diffuse, as in generalized brain edema. If the expansion is sufficiently sever, a *herniation syndrome* may occur**
- - **_Subfalcine (cingulate) herniation_ occurs when unilateral or asymmetric expansion of a cerebral hemisphere displaces the cingulate gyrus under the falx cerebri. This may lead to 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.**
- ***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**

The most common causes of a brain herniation include:

..head injury leading to a subdural hematoma (when blood collects on the brain's surface beneath the skull) or swelling (cerebral edema)

..stroke

..brain hemorrhage (bleeding in the brain)

…brain tumor

Complications of brain herniation includ

respiratory or cardiac arrest

, brain death

permanent brain damage

coma

death

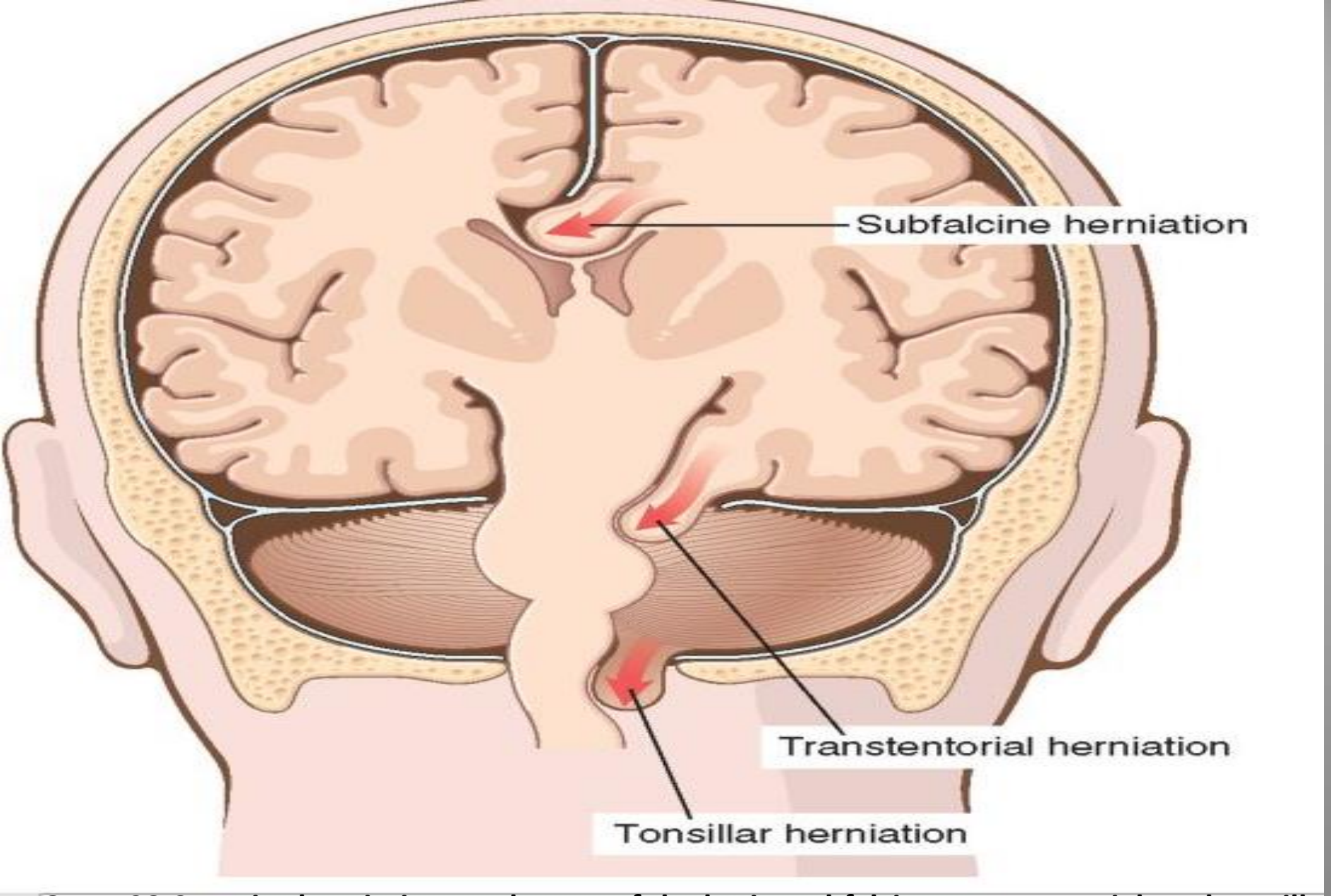


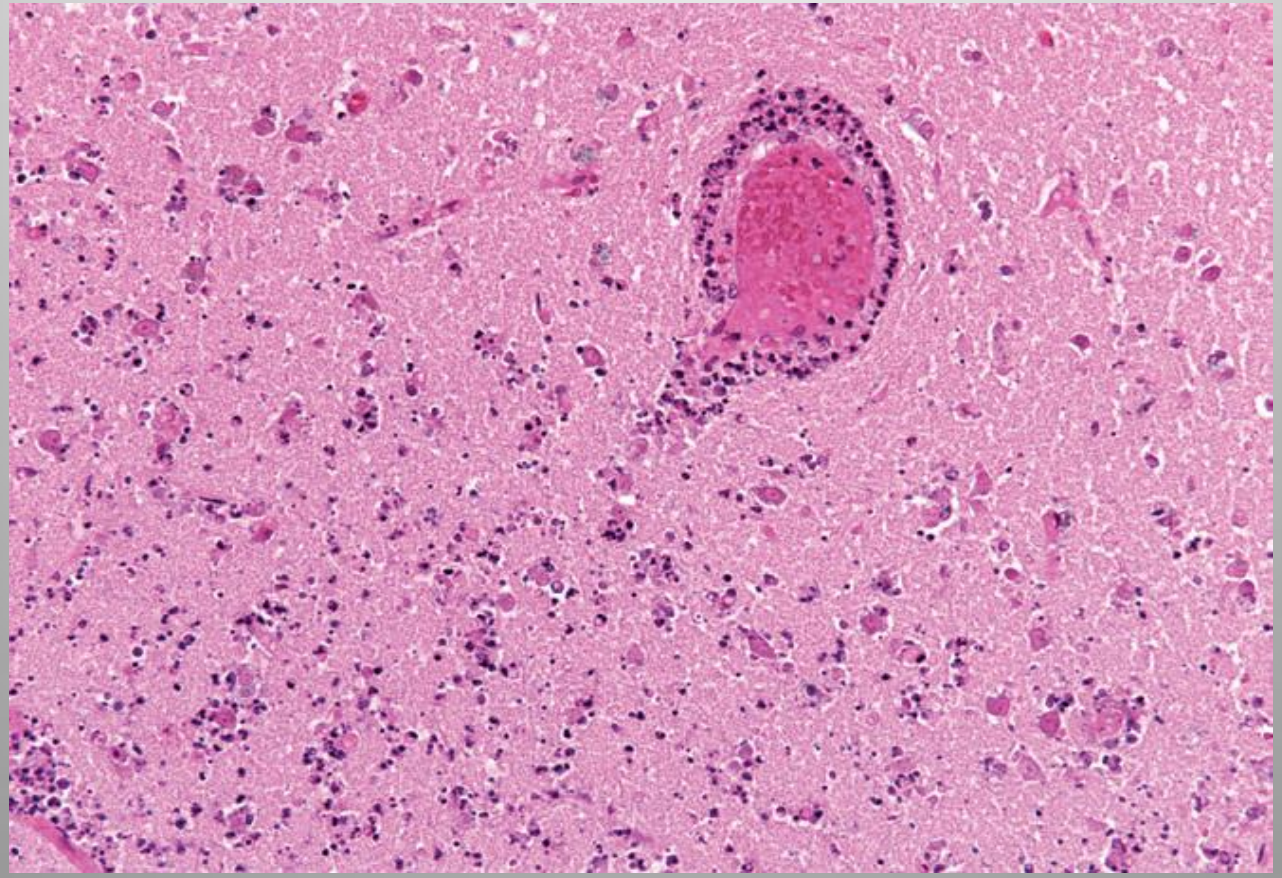
FIGURE 28-3 Major herniation syndromes of the brain: subfalcine, transtentorial, and tonsillar.

Cerebrovascular Diseases

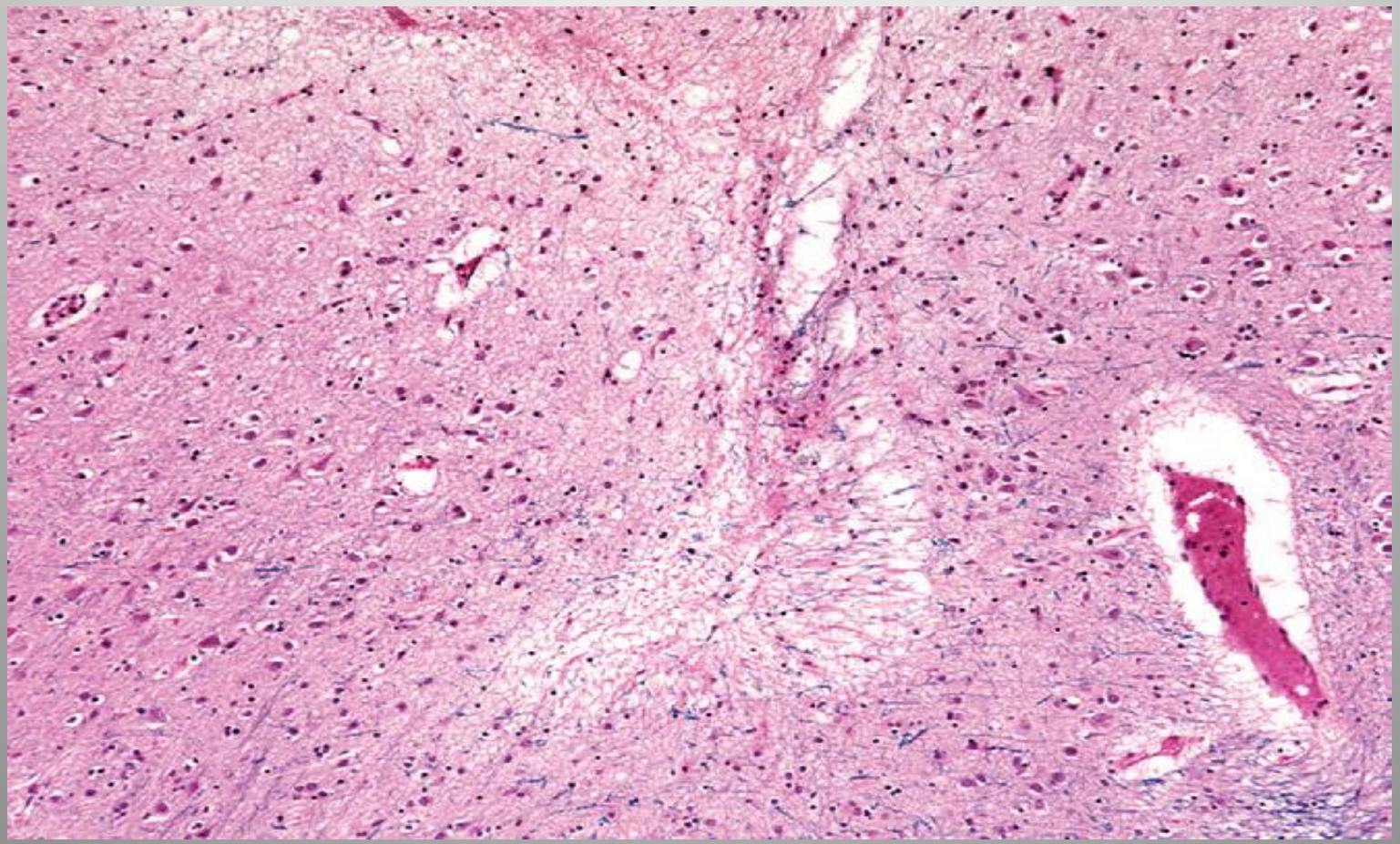
- **Cerebrovascular disease is the third leading cause of death (after heart disease and cancer) in the United States; it is also the most prevalent neurologic disorder in terms of both morbidity and mortality. Cerebrovascular diseases include the expected three major categories, thrombosis, embolism, and hemorrhage. "Stroke" is the clinical designation that applies to all these conditions, cerebrovascular disease as two processes:**
  - **Hypoxia, ischemia, and infarction resulting from impairment of blood supply and oxygenation of CNS tissue**
  - **Hemorrhage resulting from rupture of CNS vessels**

The most common cerebrovascular disorders are global ischemia, embolism, hypertensive intraparenchymal hemorrhage, and ruptured aneurysm.

Infiltration of a cerebral infarction



Old intracortical
infarcts are seen as areas of tissue loss with a modest amount of residual gliosis.



When blood flow to a portion of the brain is reduced, the survival of the tissue at risk depends on the presence of collateral circulation, the duration of ischemia, and the magnitude and rapidity of the reduction of flow. These factors determine, in turn, the precise anatomic site and size of the lesion and, consequently, the clinical deficit. Two principal types of acute ischemic injury are recognized:

- ***Global cerebral ischemia*** **(ischemic/hypoxic encephalopathy) occurs when there is a generalized reduction of cerebral perfusion, as in cardiac arrest, shock, and severe hypotension.**
- ***Focal cerebral ischemia*** **follows reduction or cessation of blood flow to a localized area of the brain due to large-vessel disease (such as embolic or thrombotic arterial occlusion, often in a setting of atherosclerosis) or to small-vessel disease (such as vasculitis or occlusion secondary to arteriosclerotic lesions seen in hypertension).**

-]The metabolic depletion of energy associated with ischemia can result in inappropriate release of excitatory amino acid neurotransmitters such as glutamate, initiating cell damage by allowing excessive influx of calcium ions through NMDA-type glutamate receptors. This elevation of cellular calcium ions can, in turn, trigger a wide range of processes including inappropriate activation of signaling cascades, free radical generation, and mitochondrial injury. these together result in cell death, mostly through necrosis. In the region of transition between necrotic tissue and the normal brain, there is an area of “at-risk” tissue, referred to as the penumbra.

FIGURE 28-17 Lacunar infarcts in the caudate and putamen (*arrows*).

Slit Hemorrhages

- **Hypertension also gives rise to rupture of the small-caliber penetrating vessels and the development of small hemorrhages. In time these hemorrhages resorb, leaving behind a slitlike cavity *(slit hemorrhage)* surrounded by brownish discoloration; on microscopic examination, slit hemorrhages show focal tissue destruction, pigment-laden macrophages, and gliosis.**

Hypertensive Encephalopathy

- **Acute hypertensive encephalopathy is a clinicopathologic syndrome arising in an individual with malignant hypertension, and is characterized by diffuse cerebral dysfunction, including headaches, confusion, vomiting, and convulsions, sometimes leading to coma. Rapid therapeutic intervention to reduce the accompanying increased intracranial pressure is required, since the syndrome often does not remit spontaneously. At postmortem examination such individuals may show an edematous brain with or without transtentorial or tonsillar herniation. Petechiae and fibrinoid necrosis of arterioles in the gray and white matter may be seen microscopically.**

- **Individuals who, over the course of many months and years, suffer multiple, bilateral, gray matter (cortex, thalamus, basal ganglia) and white matter (centrum semiovale) infarcts may develop a distinctive clinical syndrome characterized by dementia, gait abnormalities, and pseudobulbar signs, often with superimposed focal neurologic deficits. The syndrome, generally referred to as *vascular (multi-infarct) dementia*, is caused by multifocal vascular disease of several types, including (1) cerebral atherosclerosis, (2) vessel thrombosis or embolization from carotid vessels or from the heart, and (3) cerebral arteriolar sclerosis from chronic hypertension. When the pattern of injury preferentially involves large areas of the subcortical white matter with myelin and axon loss, the disorder is referred to as *Binswanger disease*; this distribution of vascular white-matter injury must be distinguished clinically and radiologically from other diseases that affect the hemispheral white matter.**

INTRACRANIAL HEMORRHAGE

- **Hemorrhages may occur at any site within the CNS. In some instances they may be a secondary phenomenon occurring, for example, within infarcts in arterial border zones or in infarcts caused by only partial or transient vascular obstruction. Hemorrhages within the brain parenchyma and subarachnoid space, in contrast, are more often a manifestation of underlying cerebrovascular disease, although trauma may also cause hemorrhage in these sites.**

Intracerebral (Intraparenchymal) Hemorrhage

- **Spontaneous (nontraumatic) intraparenchymal hemorrhages occur most commonly in middle to late adult life, with a peak incidence at about age 60 years. Most are caused by rupture of a small intraparenchymal vessel. When the hemorrhages occur in the basal ganglia and thalamus, they are designated ganglionic hemorrhages to distinguish them from those that occur in the lobes of the cerebral hemispheres, which are called lobar hemorrhages. The two major underlying etiologies of this form of cerebrovascular disease are hypertension and cerebral amyloid angiopathy (CAA). In addition, other local and systemic factors may cause or contribute to nontraumatic hemorrhage, including systemic coagulation disorders, neoplasms, vasculitis, aneurysms, and vascular malformations.**

- ***Hypertension is the most common underlying cause of primary brain parenchymal hemorrhage*, accounting for more than 50% of clinically significant hemorrhages and for roughly 15% of deaths among individuals with chronic hypertension. Hypertension causes a number of abnormalities in vessel walls, including accelerated atherosclerosis in larger arteries; hyaline arteriolosclerosis in smaller vessels; and, in severe cases, proliferative changes and frank necrosis of arterioles. Arteriolar walls affected by hyaline change are presumably weaker than are normal vessels and are therefore more vulnerable to rupture. In some instances chronic hypertension is associated with the development of minute aneurysms, termed *Charcot-Bouchard microaneurysms*, which may be the site of rupture. Charcot-Bouchard aneurysms, not to be confused with saccular aneurysms of larger intracranial vessels, occur in vessels that are less than 300 µm in diameter, most**

- **Morphology. Hypertensive intraparenchymal hemorrhage may originate in the putamen (50% to 60% of cases), thalamus, pons, cerebellar hemispheres (rarely), and other regions of the brain . Acute hemorrhages, independent of etiology, are characterized by extravasation of blood with compression of the adjacent parenchyma. Old hemorrhages show an area of cavitary destruction of brain with a rim of brownish discoloration. On microscopic examination the early lesion consists of a central core of clotted blood surrounded by a rim of brain tissue showing anoxic neuronal and glial changes as well as edema. Eventually the edema resolves, pigment- and lipid-laden macrophages appear, and proliferation of reactive astrocytes is seen at the periphery of the lesion. The cellular events then follow the same time course that is observed after cerebral infarction.**

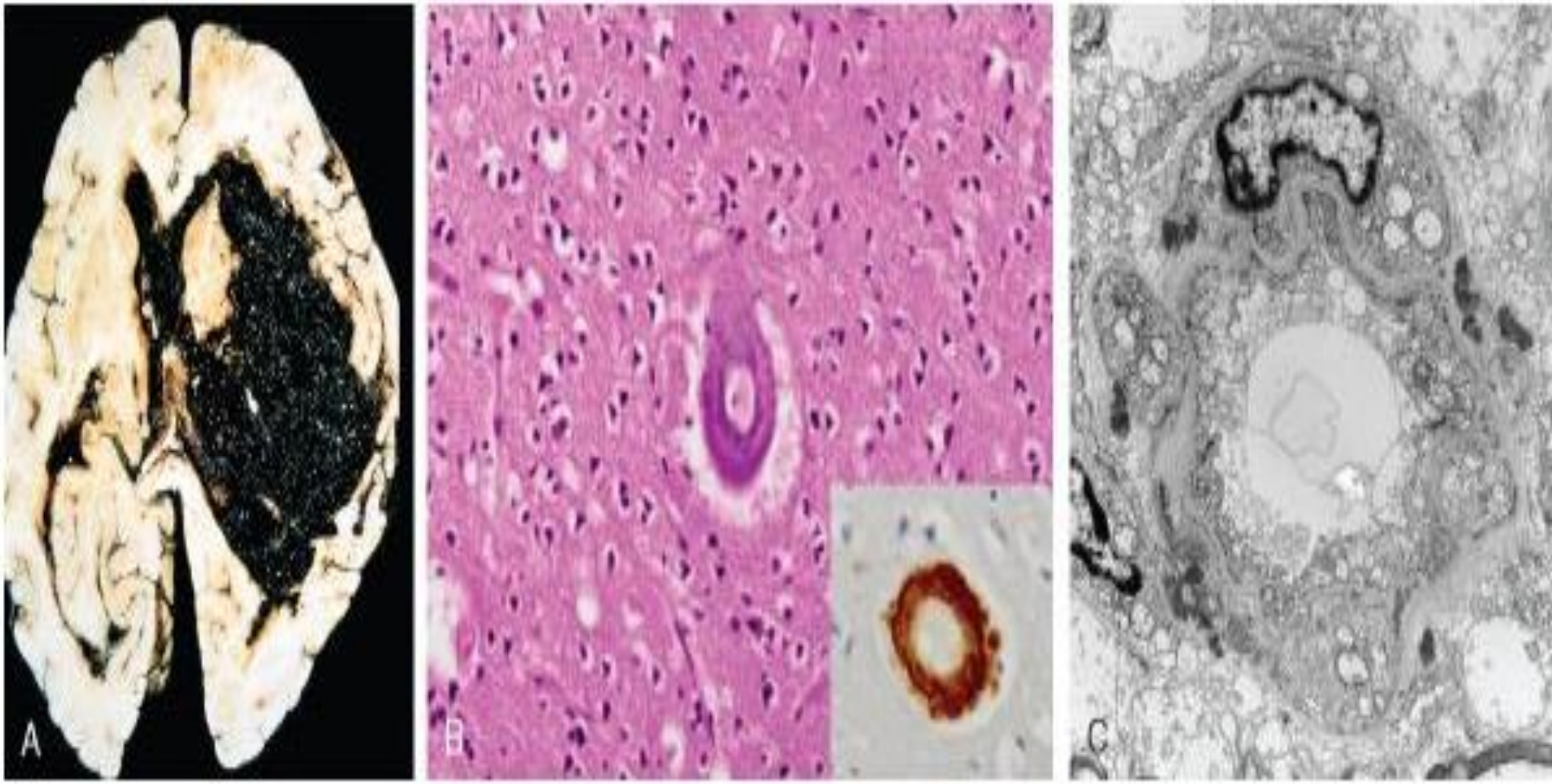


FIGURE 28-18 **A**, Massive hypertensive hemorrhage rupturing into a lateral ventricle. **B**, Amyloid deposition in a cortical arteriole in cerebral amyloid angiopathy; *inset*, Immunohistochemical staining for Aβ shows the deposited material in the vessel wall. **C**, Electron micrograph shows granular osmophilic material in a case of CADASIL.

Subarachnoid Hemorrhage and Ruptured Saccular Aneurysms

- **The most frequent cause of clinically significant subarachnoid hemorrhage is rupture of a *saccular* (*berry) aneurysm*. Subarachnoid hemorrhage may also result from extension of a traumatic hematoma, rupture of a hypertensive intracerebral hemorrhage into the ventricular system, vascular malformation, hematologic disturbances, and tumors.**
- ***Saccular aneurysm* is the most common type of intracranial aneurysm. Other aneurysm types include atherosclerotic (fusiform; mostly of the basilar artery), mycotic, traumatic, and dissecting. These latter three, like saccular aneurysms, are most often found in the anterior circulation, but differ in that they more often cause cerebral infarction rather than subarachnoid hemorrhage.**
- **Saccular aneurysms are found in about 2% of the population. About 90% of saccular aneurysms are found near major arterial branch points in the anterior circulation ,multiple aneurysms exist in 20% to 30% of cases in autopsy series.**

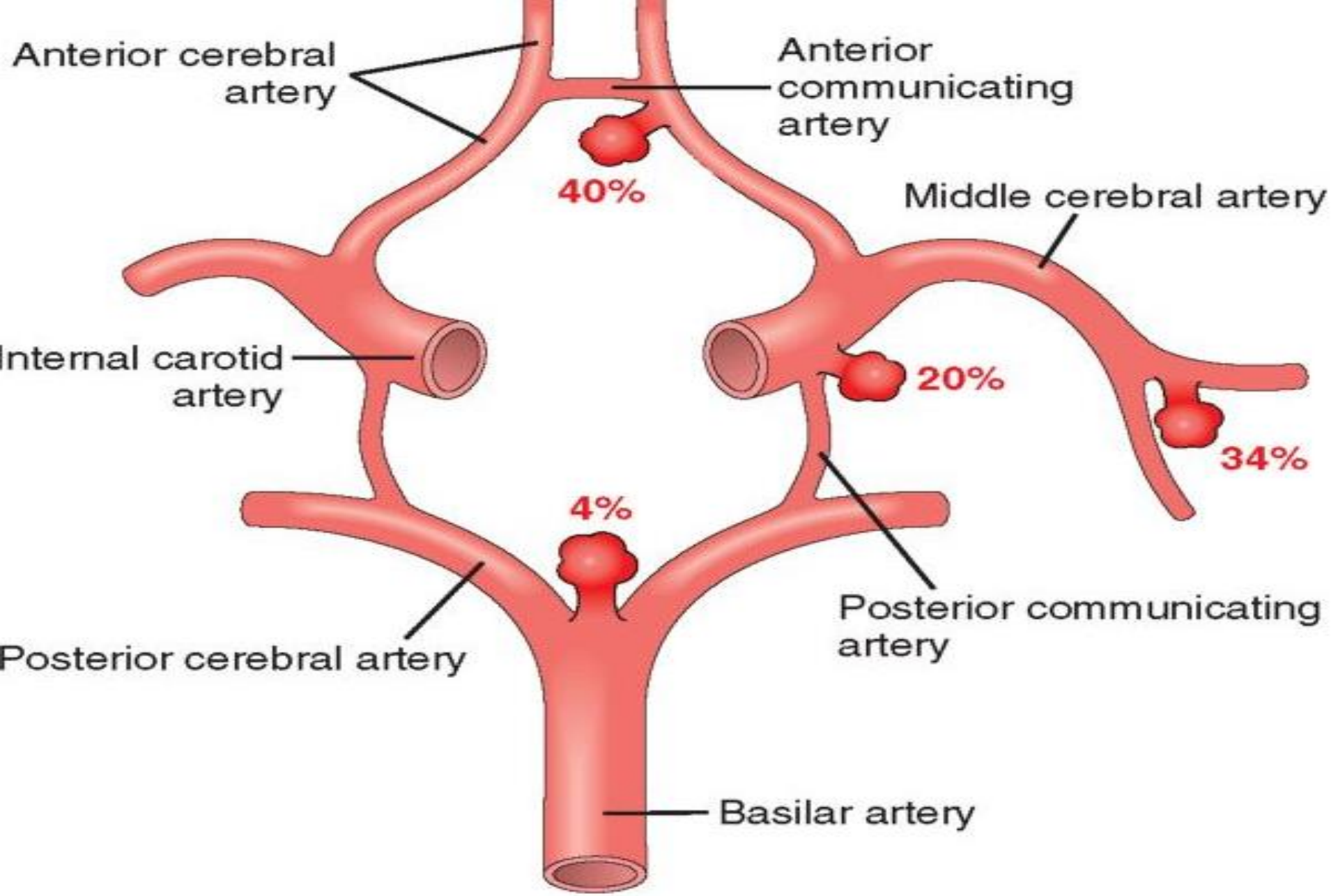
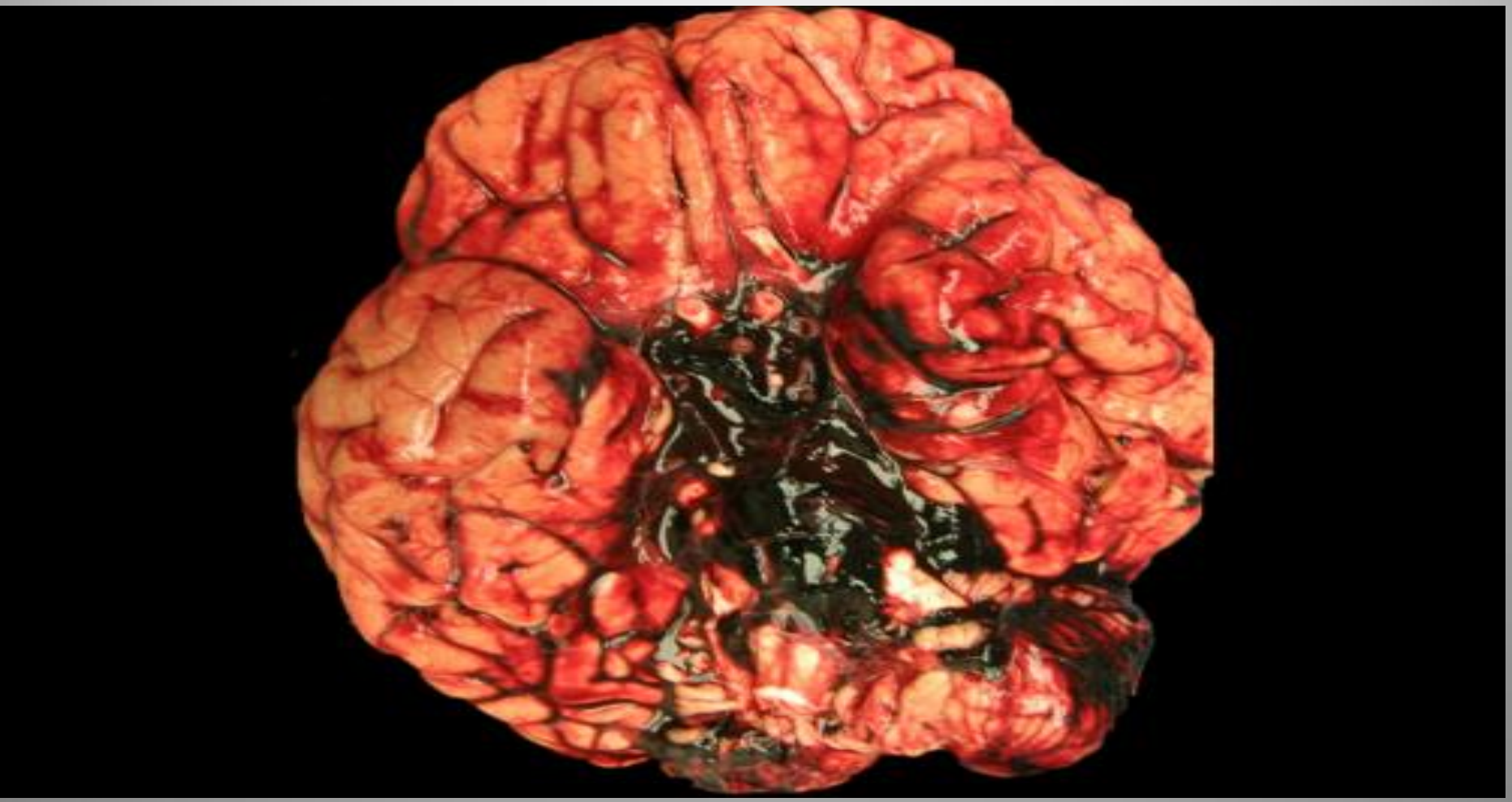


FIGURE 28-19 Common sites of saccular (berry) aneurysms in the circle of Willis

Aneurysms(Berry)



Pathogenesis of Saccular Aneurysms

- **The etiology of saccular aneurysms is unknown. Although the majority occur sporadically, genetic factors may be important in their pathogenesis, since there is an increased incidence of aneurysms in first-degree relatives of those affected. There is also an increased incidence in individuals with certain mendelian disorders (such as autosomal dominant polycystic kidney disease, Ehlers-Danlos syndrome type IV, neurofibromatosis type 1 [NF1], and Marfan syndrome), fibromuscular dysplasia of extracranial arteries, and coarctation of the aorta. The predisposing factors include cigarette smoking and hypertension (estimated to be present in about half of these patients). Although they are sometimes referred to as congenital, the aneurysms are not present at birth but develop over time because of an underlying defect in the media of the vessel.**

Morphology

- **An unruptured saccular aneurysm is a thin-walled outpouching, usually at an arterial branch point along the circle of Willis or a major vessel just beyond. Saccular aneurysms measure from a few millimeters to 2 or 3 cm in diameter and have a bright red, shiny surface and a thin, translucent wall . Atheromatous plaques, calcification, or thrombotic occlusion of the sac may be found in the wall or lumen of the aneurysm. Brownish discoloration of the adjacent brain and meninges is evidence of prior hemorrhage. The neck of the aneurysm may be either wide or narrow. Rupture usually occurs at the apex of the sac with extravasation of blood into the subarachnoid space, the substance of the brain, or both.The sac is made up of thickened hyalinized intima. The adventitia covering the sac is continuous with that of the parent artery.**

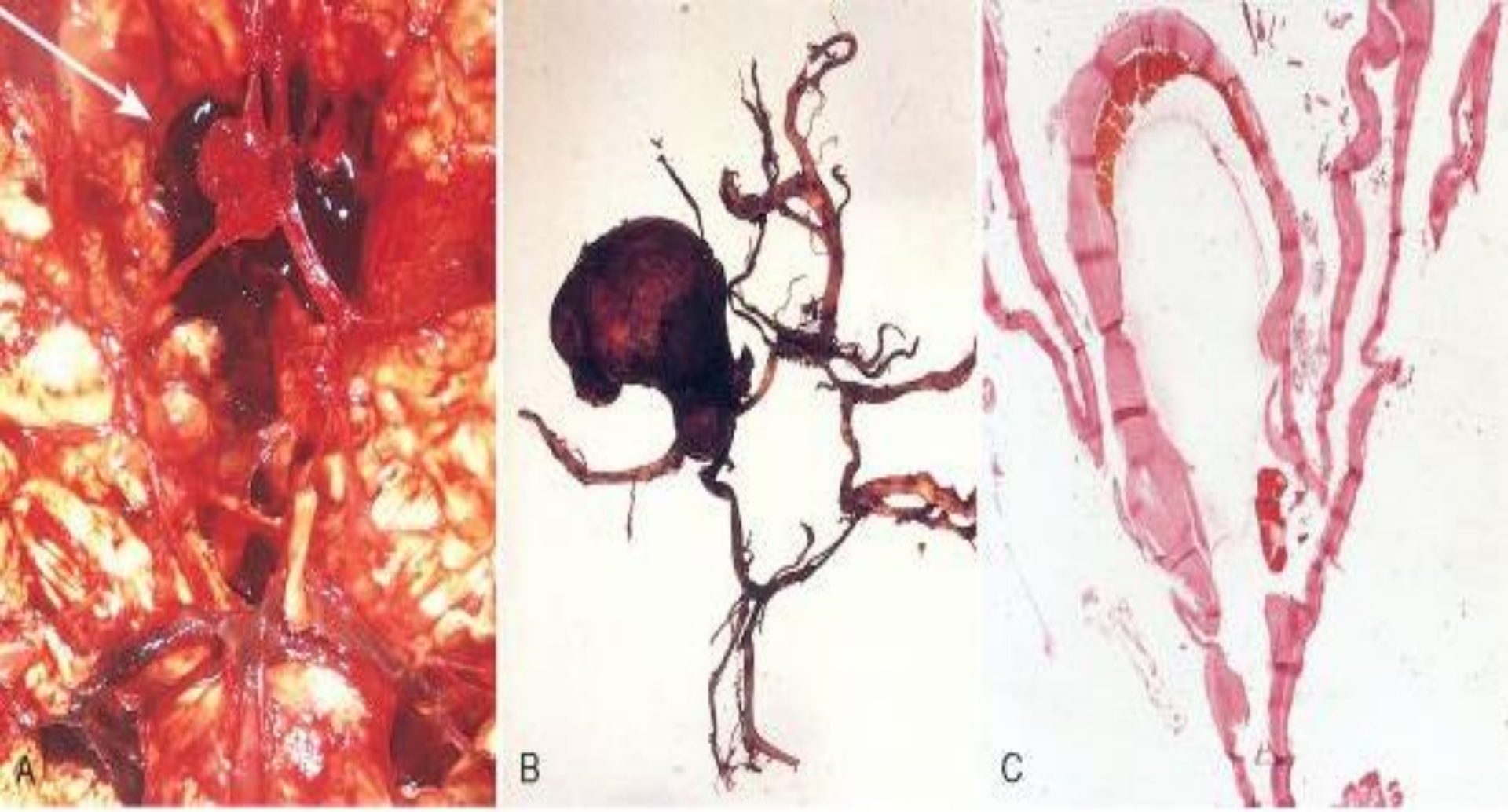


FIGURE 28-20 **A**, View of the base of the brain, dissected to show the circle of Willis with an aneurysm of the anterior cerebral artery *(arrow)*. **B**, Dissected circle of Willis to show large aneurysm. **C**, Section through a saccular aneurysm showing the hyalinized fibrous vessel wall (H&E).

Clinical features

- **Rupture of an aneurysm with clinically significant subarachnoid hemorrhage is most frequent in the fifth decade and is slightly more frequent in females. Overall, the rate of bleeding is roughly 1.3% per year, with the probability of rupture increasing with the size of the lesion. Aneurysms greater than 10 mm in diameter have a roughly 50% risk of bleeding per year. Rupture may occur at any time, but in about one third of cases it is associated with acute increases in intracranial pressure, such as with straining at stool or sexual orgasm. Blood under arterial pressure is forced into the subarachnoid space and affected individuals are stricken with a sudden, excruciating headache, rapidly losing consciousness. Between 25% and 50% of patients die with the first rupture, but patients who survive often improve and recover consciousness in minutes. Repeat bleeding is common in survivors, and it is currently not possible to predict in which patients repeat bleeding will occur. With each episode of bleeding, the prognosis is worse.**

- **In the first few days after a subarachnoid hemorrhage, regardless of the etiology, there is an increased risk of additional ischemic injury from vasospasm affecting vessels bathed in the extravasated blood. This problem is of greatest significance in cases of basal subarachnoid hemorrhage, in which vasospasm can involve major vessels of the circle of Willis. Various mediators have been proposed to have a role in this reactive process, including endothelins, nitric oxide, and arachidonic acid metabolites. In the healing phase of subarachnoid hemorrhage, meningeal fibrosis and scarring occur, sometimes leading to obstruction of CSF flow as well as interruption of the normal pathways of CSF resorption.**

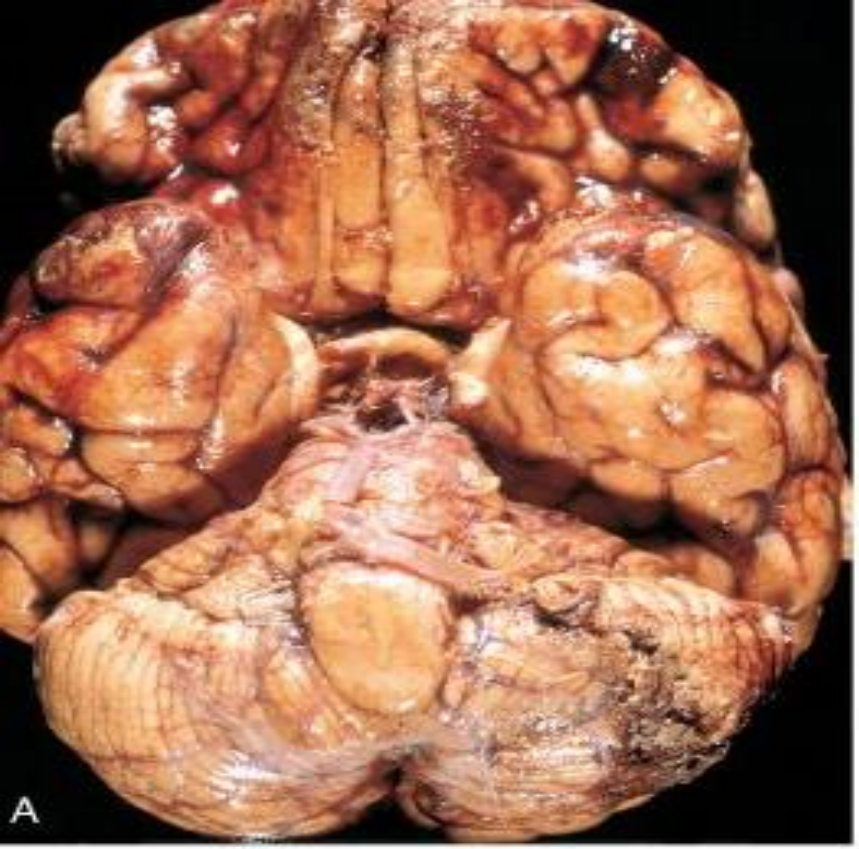
PARENCHYMAL INJURIES

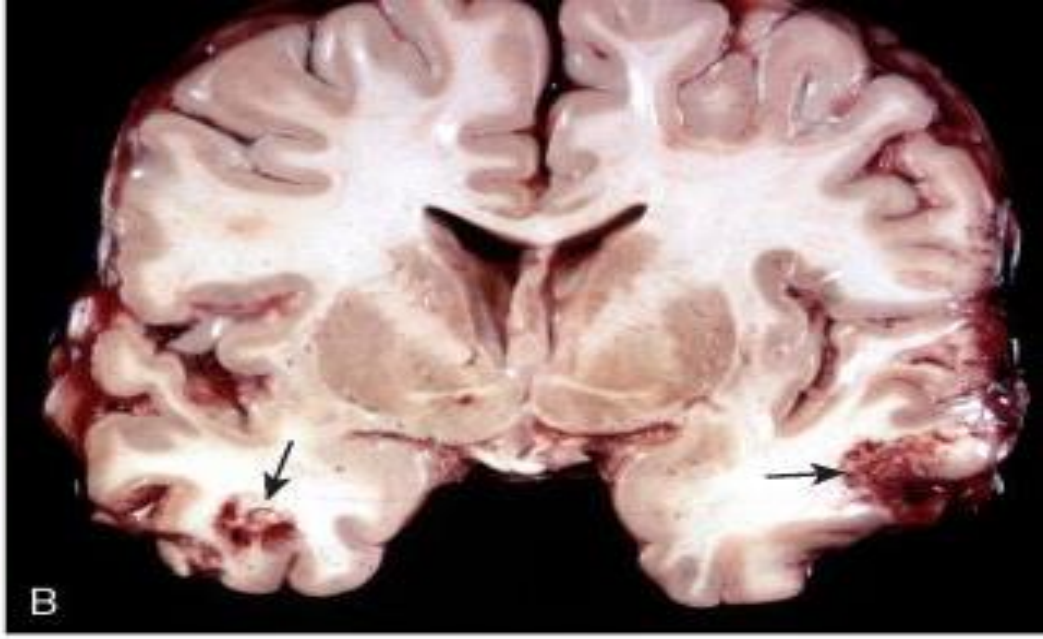
Concussion

- **Concussion is a clinical syndrome of altered consciousness secondary to head injury typically brought about by a change in the momentum of the head (when a moving head is suddenly arrested by impact on a rigid surface). The characteristic neurologic picture including loss of consciousness, temporary respiratory arrest, and loss of reflexes. Although neurologic recovery is complete, amnesia for the event persists. The pathogenesis of the sudden disruption of neurologic function is unknown; it probably involves dysregulation of the reticular activating system in the brainstem.**

Direct parenchymal injury

- ***Contusion*** **and** ***laceration*** **are lesions associated with direct parenchymal injury of the brain, either through transmission of kinetic energy to the brain and bruising analogous to what is seen in soft tissues (contusion) or by penetration of an object and tearing of tissue (laceration). As with any other organ, a blow to the surface of the brain, transmitted through the skull, leads to rapid tissue displacement, disruption of vascular channels, and subsequent hemorrhage, tissue injury, and edema . The crests of gyri are most susceptible, since this is where the direct force is greatest. The most common locations for contusions correspond to the most frequent sites of direct impact and to regions of the brain that overlie a rough and irregular inner skull surface, such as the frontal lobes along the orbital ridges and the temporal lobes. Contusions are less frequent over the occipital lobes, brainstem, and cerebellum unless these sites are adjacent to a skull fracture** ***(fracture contusions)*****.**





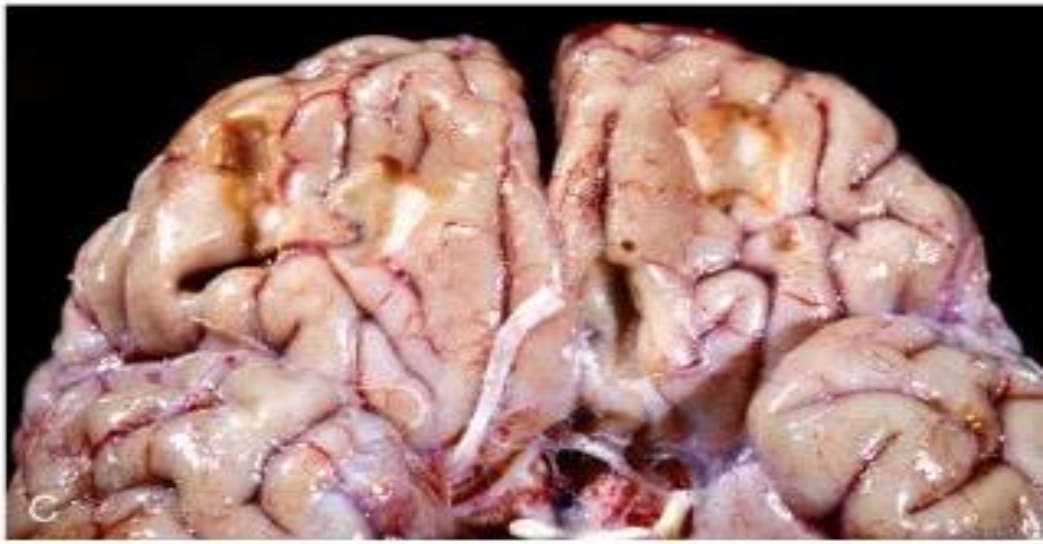


FIGURE 28-9 **A**, Multiple contusions involving the inferior surfaces of frontal lobes, anterior temporal lobes, and cerebellum. **B**, Acute contusions are present in both temporal lobes, with areas of hemorrhage and tissue disruption (*arrows*). **C**, Remote contusions are present on the inferior frontal surface of this brain, with a yellow color (associated with the term *plaque jaune*).

- **Morphology. When seen on cross-section, contusions are wedge shaped, with the broad base lying along the surface, deep to the point of impact . The histologic appearance of contusions is independent of the type of trauma. In the earliest stages, there is edema and hemorrhage, which is often pericapillary. During the next few hours, the extravasation of blood extends throughout the involved tissue, across the width of the cerebral cortex, and into the white matter and subarachnoid space. Morphologic evidence of neuronal injury (pyknosis of the nucleus, eosinophilia of the cytoplasm) takes about 24 hours to appear, although functional deficits may occur earlier. Axonal swellings develop in the vicinity of damaged neurons or at great distances away.**

- **The inflammatory response to the injured tissue follows its usual course, with the appearance of neutrophils followed by macrophages. Old traumatic lesions are depressed, retracted, yellowish brown patches involving the crests of gyri most commonly located at the sites of contrecorup lesions (inferior frontal cortex, temporal and occipital poles). The term plaque jaune is applied to these lesions . they can become epileptic foci. More extensive hemorrhagic regions of brain trauma give rise to larger cavitated lesions, which can resemble remote infarcts. In sites of old contusions, gliosis and residual hemosiderin-laden macrophages predominate.**

TRAUMATIC VASCULAR INJURY

- **Vascular injury is a frequent component of CNS trauma. It results from direct trauma and disruption of the vessel wall, and leads to hemorrhage. Depending on the anatomic position of the ruptured vessel, hemorrhage may occur in the *epidural*, *subdural*, *subarachnoid*, and *intraparenchymal* compartments, sometimes in combination . Subarachnoid and intraparenchymal hemorrhages most often occur concomitantly in the setting of brain trauma that also results in superficial contusions and lacerations. A traumatic tear of the carotid artery where it traverses the carotid sinus may lead to the formation of an arteriovenous fistula.**

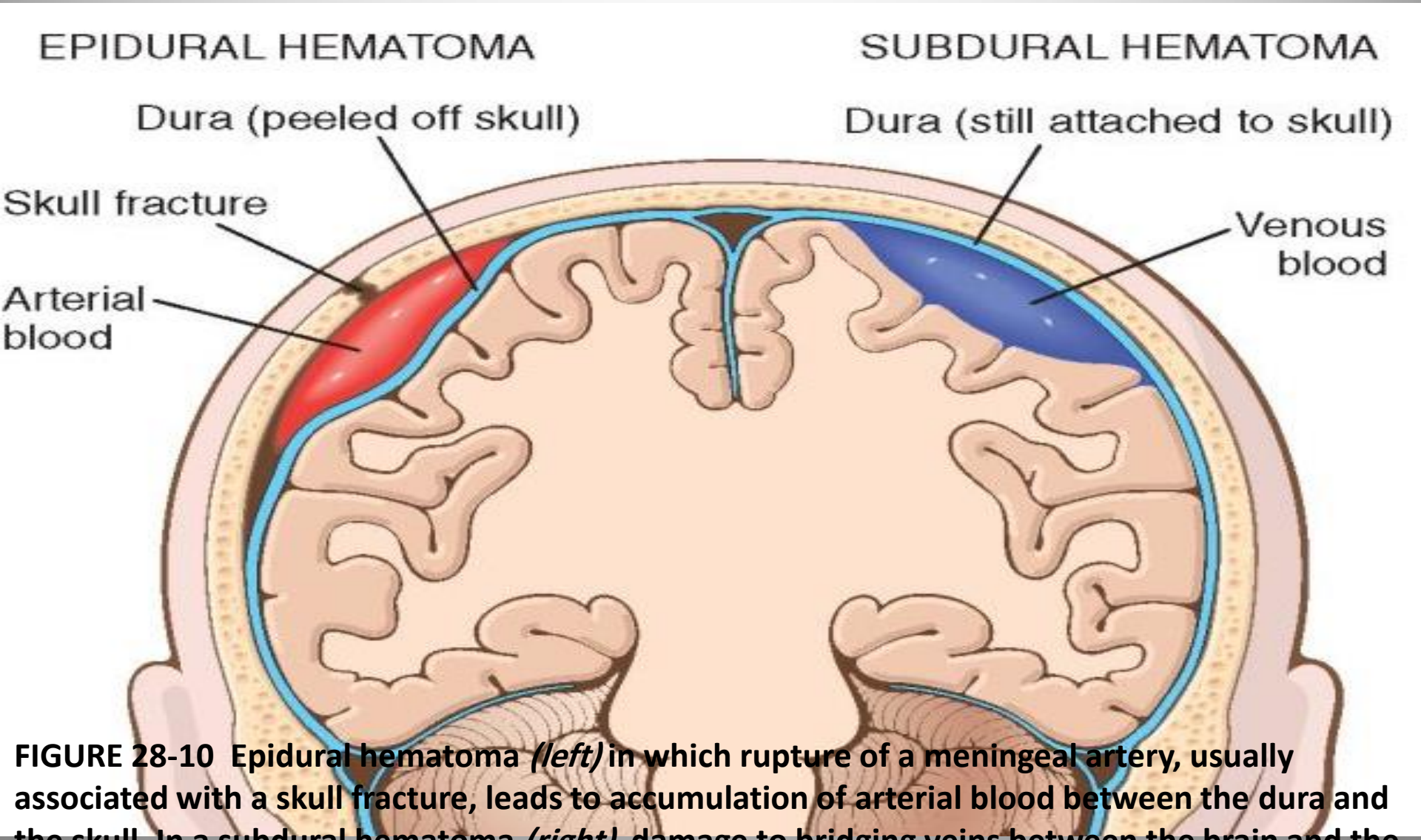
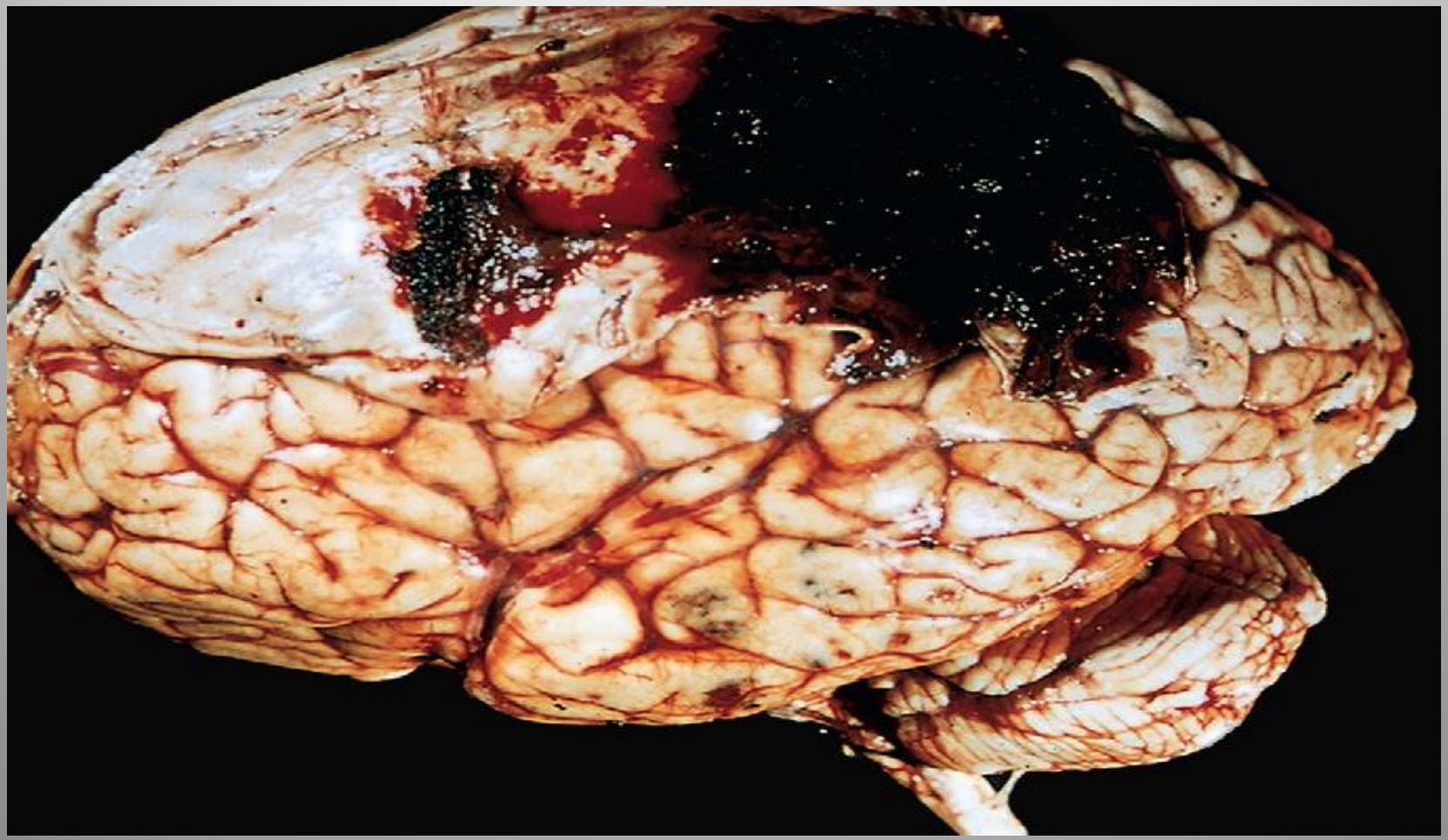


FIGURE 28-10 Epidural hematoma *(left)* in which rupture of a meningeal artery, usually associated with a skull fracture, leads to accumulation of arterial blood between the dura and the skull. In a subdural hematoma *(right)*, damage to bridging veins between the brain and the superior sagittal sinus leads to the accumulation of blood between the dura and the arachnoid.

Epidural hematoma



Epidural hematoma

- **Normally the dura is fused with the periosteum on the internal surface of the skull. Dural arteries, most importantly the middle meningeal artery, are vulnerable to injury, particularly with temporal skull fractures in which the fracture lines cross the course of the vessel. In children, in whom the skull is deformable, a temporary displacement of the skull bones leading to laceration of a vessel can occur in the absence of a skull fracture.**
- **Once a vessel has been torn, the extravasation of blood under arterial pressure can cause the dura to separate from the inner surface of the skull . The expanding hematoma has a smooth inner contour**

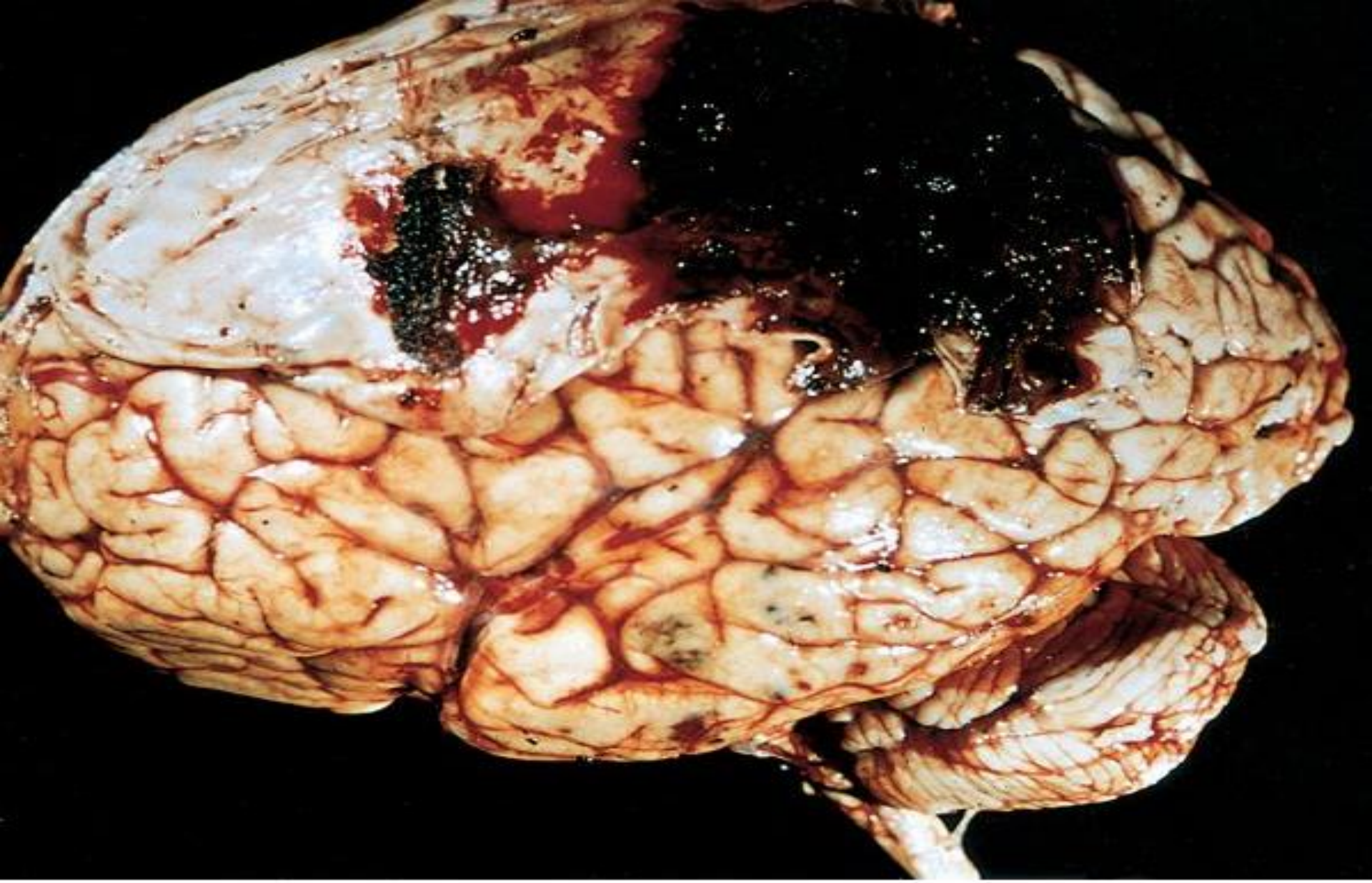


FIGURE 28-11 Epidural hematoma covering a portion of the dura. Also present are multiple small contusions in the temporal lobe. *(Courtesy of the late Dr. Raymond D. Adams, Massachusetts General Hospital, Boston, MA.)*

Subdural hematoma

Between the inner surface of the dura mater and the outer arachnoid layer of the leptomeninges lies the subdural space. *Bridging veins* travel from the convexities of the cerebral hemispheres through the subarachnoid space and the subdural space to empty into the superior sagittal sinus. Similar anatomic relationships exist with other dural sinuses. These vessels are particularly prone to tearing along their course through the subdural space and are the source of bleeding in most cases of subdural hematoma. It is thought that the brain, floating freely bathed in CSF, can move within the skull, but the venous sinuses are fixed. The displacement of the brain that occurs in trauma can tear the veins at the point where they penetrate the dura. In elderly individuals with brain atrophy, the bridging veins are stretched out and the brain has additional space for movement, hence the increased rate of subdural hematomas in these patients, even after relatively minor head trauma. Infants are also particularly susceptible to subdural hematomas because their bridging veins are thin-walled.

MORPHOLOGY

On macroscopic examination, the acute subdural hematoma appears as a collection of freshly clotted blood along the brain surface, without extension into the depths of sulci . The underlying brain is flattened and the subarachnoid space is often clear. Typically, venous bleeding is self-limited; breakdown and organization of the hematoma take place over time. This usually occurs in the following sequence:

- **Lysis of the clot (about 1 week)**
- **Growth of fibroblasts from the dural surface into the hematoma (2 weeks)**
- **Early development of hyalinized connective tissue (1 to 3 months)**

- **Typically, the organized hematoma is firmly attached by fibrous tissue only to the inner surface of the dura and is not adherent to the underlying smooth arachnoid, which does not contribute to its formation. The lesion can eventually retract as the granulation tissue matures, until there is only a thin layer of reactive connective tissue (“subdural membranes”). A common finding in subdural hematomas, however, is the occurrence of multiple episodes of repeat bleeding (chronic subdural hematomas), presumably from the thin-walled vessels of the granulation tissue. The risk of repeat bleeding is greatest in the first few months after the initial hemorrhage**

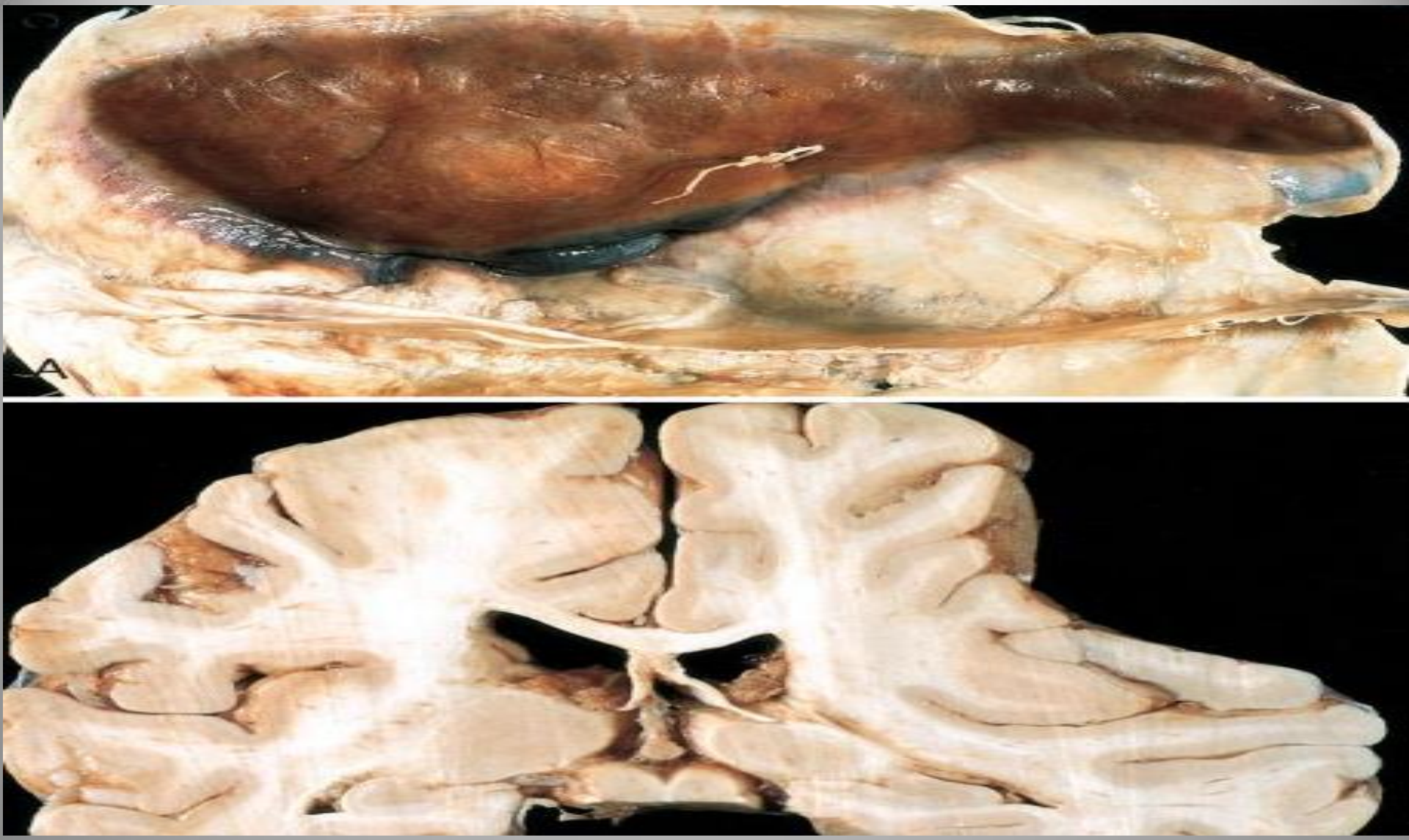


FIGURE 28-12 A, Large organizing subdural hematoma attached to the dura. B, Coronal section of the brain showing compression of the hemisphere underlying the subdural hematoma shown in A

Infections

- **With infection, damage to nervous tissue may be the consequence of direct injury of neurons or glia by the infectious agent or may occur indirectly through the elaboration of microbial toxins, destructive effects of the inflammatory response, or the result of immune-mediated mechanisms. There are four principal routes by which infectious microbes enter the nervous system. *Hematogenous spread* is the most common means of entry; infectious agents ordinarily enter through the arterial circulation, but retrograde venous spread can occur through anastomoses with veins of the face**

- **. *Direct implantation* of microorganisms is almost invariably traumatic or is associated with congenital malformations (such as meningomyelocele). *Local extension* can come from any of several adjacent structures (air sinuses, an infected tooth, cranial or spinal osteomyelitis). Transport along the *peripheral nervous system* occurs with certain viruses, such as rabies and herpes zoster.**

ACUTE MENINGITIS

- ***Meningitis*** **refers to an inflammatory process of the leptomeninges and CSF within the subarachnoid space, while *meningoencephalitis* combines this with inflammation of the brain parenchyma. Meningitis is usually caused by an infection, but may also occur in response to a nonbacterial irritant introduced into the subarachnoid space *(chemical meningitis)*. Infectious meningitis is broadly classified into *acute pyogenic* (usually bacterial meningitis), *aseptic* (usually acute viral meningitis), and *chronic* (usually tuberculous, spirochetal, or cryptococcal) on the basis of the characteristics of inflammatory exudate on CSF examination and the clinical evolution of the illness.**

Acute Pyogenic (Bacterial) Meningitis

- **The microorganisms that cause acute pyogenic meningitis vary with the age of the affected individual. In neonates, they include *Escherichia coli* and the group B streptococci; at the other extreme of life, *Streptococcus pneumoniae* and *Listeria monocytogenes* are more common. Among adolescents and in young adults, *Neisseria meningitidis* is the most common pathogen. The introduction of immunization against *Haemophilus influenzae* has markedly reduced the incidence of meningitis associated with this organism in the developed world; the population that was previously at highest risk (infants) now has a much lower overall risk of meningitis, with *S. pneumoniae* being the most prevalent organism.**

- **Affected individuals typically show systemic signs of infection superimposed on clinical evidence of meningeal irritation and neurologic impairment, including headache, photophobia, irritability, clouding of consciousness, and neck stiffness. A spinal tap yields cloudy or frankly purulent CSF, under increased pressure, with as many as 90,000 neutrophils per cubic millimeter, an increased protein concentration, and a markedly reduced glucose content. Bacteria may be seen on a smear or can be cultured, sometimes a few hours before the neutrophils appear.**

- **Morphology. The normally clear CSF is cloudy and sometimes frankly purulent. In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain . The meningeal vessels are engorged . The location of the exudate varies; in *H. influenzae* meningitis, for example, it is usually basal, whereas in pneumococcal meningitis it is often densest over the cerebral convexities near the sagittal sinus. From the areas of greatest accumulation, tracts of pus can be followed along blood vessels on the surface of the brain. When the meningitis is fulminant, the inflammation may extend to the ventriclproducing ventriculitis**

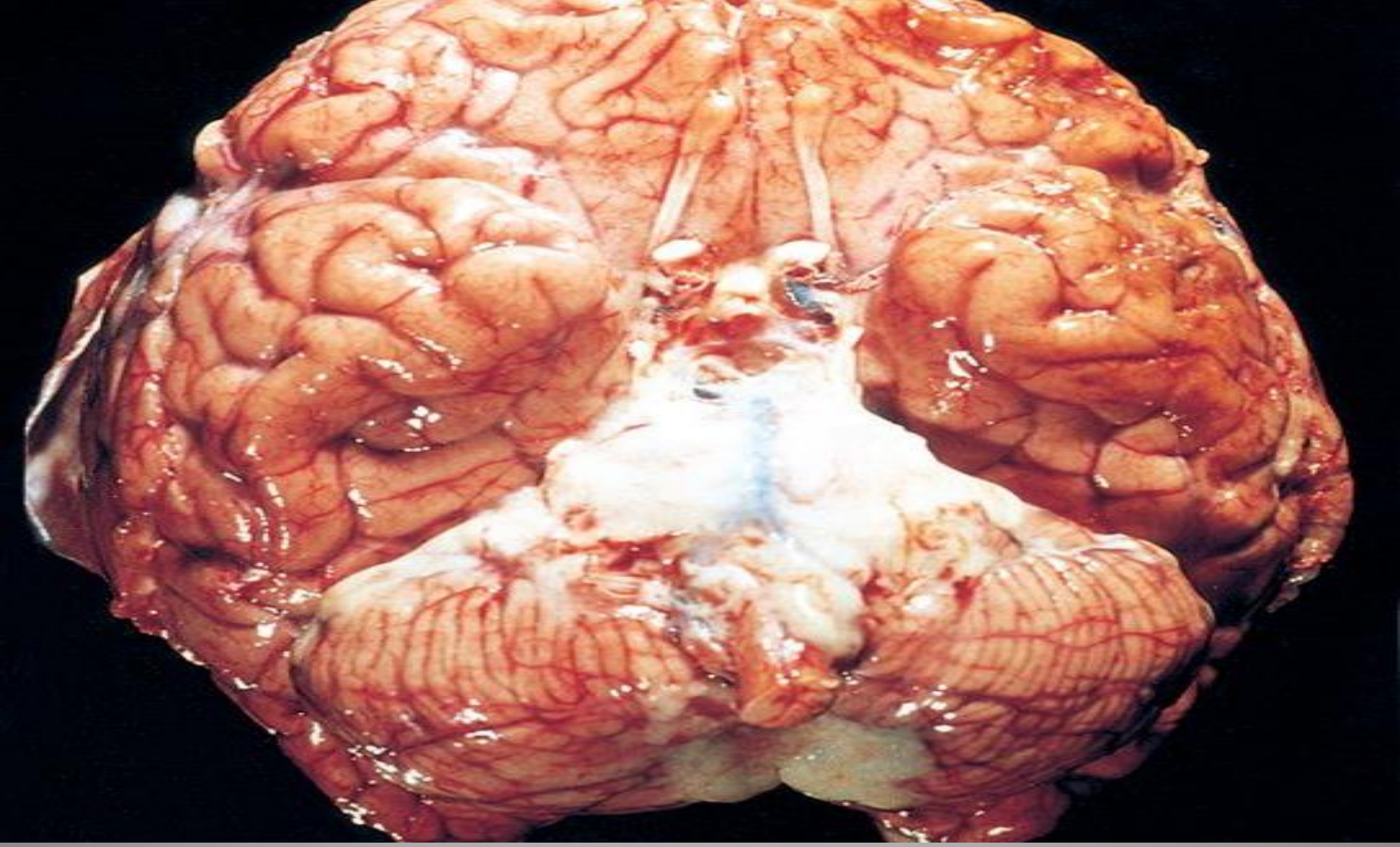


FIGURE 28-21 Pyogenic meningitis. A thick layer of suppurative exudate covers the brainstem and cerebellum and thickens the leptomeninges.

Acute Aseptic (Viral) Meningitis

- **Aseptic meningitis is a clinical term referring to the absence of recognizable organisms in a patient with meningeal irritation, fever, and alterations of consciousness of relatively acute onset. The clinical course is less fulminant than that of pyogenic meningitis, and the CSF findings also differ; in aseptic meningitis there is a lymphocytic pleocytosis, the protein elevation is only moderate, and the glucose content is nearly always normal. The viral aseptic meningitides are usually self-limiting and are treated symptomatically. The spectrum of pathogens varies seasonally and geographically. An aseptic meningitis–like picture may also develop subsequent to rupture of an epidermoid cyst into the subarachnoid space or the introduction of a chemical irritant ("chemical" meningitis). In these cases the CSF is sterile, there is pleocytosis with neutrophils and an increased protein concentration, but the sugar content is usually normal.**

ACUTE FOCAL SUPPURATIVE INFECTIONS

Brain Abscess

- **Brain abscesses may arise by direct implantation of organisms, local extension from adjacent foci (mastoiditis, paranasal sinusitis), or hematogenous spread (usually from a primary site in the heart, lungs, or distal bones or after tooth extraction). Predisposing conditions include *acute bacterial endocarditis*, which tends to produce multiple abscesses; *congenital heart disease* with right-to-left shunting and loss of pulmonary filtration of organisms; *chronic pulmonary sepsis*, as can be seen with bronchiectasis; and *immunosuppression*. Streptococci and staphylococci are the most common offending organisms identified in non immunosuppressed populations.**

- **Morphology. Grossly, abscesses are discrete lesions with central liquefactive necrosis surrounded by fibrosis and swelling . On microscopic examination there is exuberant granulation tissue with neovascularization around the necrosis that is responsible for marked vasogenic edema. A collagenous capsule is produced by fibroblasts derived from the walls of blood vessels. Outside the fibrous capsule is a zone of reactive gliosis with numerous gemistocytic astrocytes.**

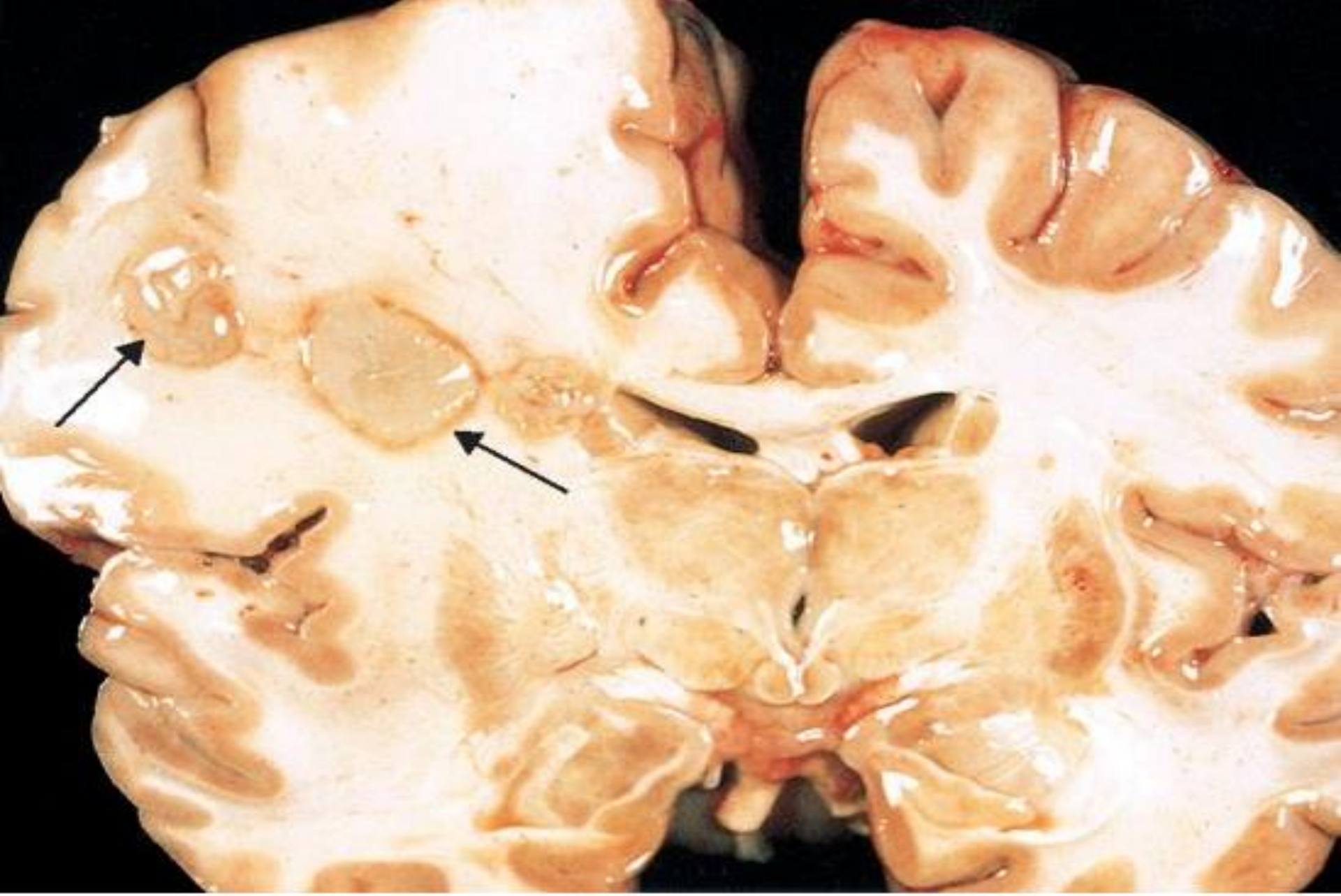


FIGURE 28-22 Frontal abscesses *(arrows)*.

- It gives signs of raised intracranial pressure. The CSF is under increased pressure, the white cell count is raised, and protein concentration is increased, but the glucose content is normal.

Extradural Abscess

Extradural abscess, commonly associated with osteomyelitis, often arises from an adjacent focus of infection, such as sinusitis or a surgical procedure. When the process occurs in the spinal epidural space, it may cause spinal cord compression and constitute a neurosurgical emergency.

- **CHRONIC BACTERIAL MENINGOENCEPHALITIS**

Chronic bacterial infection of the meninges and the brain may be caused by *M. tuberculosis*, *T. pallidum*, and *Borrelia* species. Each of these is briefly described next.

- Tuberculosis

Tuberculosis of the brain may be part of systemic disease or apparently isolated, the brain having been seeded from a silent, usually pulmonary, lesion. It may involve the meninges or the brain, often together.

- **Morphology. On macroscopic examination, the subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain, obliterating the cisterns and encasing cranial nerves. There may be discrete, white granules scattered over the leptomeninges. The most common pattern of involvement is a diffuse meningoencephalitis. On microscopic examination, there are mixtures of lymphocytes, plasma cells, and macrophages. Florid cases show well-formed granulomas, often with caseous necrosis and giant cells. Arteries running through the subarachnoid space may show obliterative endarteritis with inflammatory infiltrates in their walls and marked intimal thickening. Organisms can often be seen with acid-fast stains. The infectious process may spread to the choroid plexus and ependymal surface, traveling through the CSF.**

- **Another manifestation of the disease is the development of a single (or often multiple) well circumscribed intraparenchymal mass (tuberculoma), which may be associated with meningitis. A tuberculoma may be as large as several centimeters in diameter, causing significant mass effect. On microscopic examination, there is usually a central core of caseous necrosis surrounded by a typical tuberculous granulomatous reaction; calcification may occur in inactive lesions.**

Neurosyphilis

- **Neurosyphilis is a manifestation of the tertiary stage of syphilis and occurs in only about 10% of individuals with untreated infection. The major patterns of CNS involvement are meningovascular neurosyphilis, paretic neurosyphilis, and tabes dorsalis; affected individuals often show incomplete or mixed pictures, most commonly the combination of tabes dorsalis and paretic disease (taboparesis). Individuals infected with HIV are at increased risk for neurosyphilis, particularly as an acute syphilitic meningitis or meningovascular disease, because of impaired cell-mediated immunity.**

- **Morphology. Meningovascular neurosyphilis is a chronic meningitis involving the base of the brain and more variably the cerebral convexities and the spinal leptomeninges. In addition, there may be an associated obliterative endarteritis (Heubner arteritis) accompanied by a distinctive perivascular inflammatory reaction rich in plasma cells and lymphocytes. Cerebral gummas (plasma cell–rich mass lesions) may also occur in the meninges and extend into the parenchyma.**

- **Paretic neurosyphilis is caused by invasion of the brain by *Treponema pallidum* and is clinically manifested as insidious but progressive mental deficits associated with mood alterations (including delusions of grandeur) that terminate in severe dementia (general paresis of the insane). On microscopic examination, inflammatory lesions are associated with parenchymal damage in the cerebral cortex characterized by loss of neurons, proliferations of microglia (rod cells), gliosis, and iron deposits. The latter are demonstrable with the Prussian blue stain perivascularly and in the neuropil. The spirochetes can be demonstrated in tissue sections. There is often an associated hydrocephalus with damage to the ependymal lining and proliferation of subependymal glia, called granular ependymitis.**

- **Tabes dorsalis is the result of damage by the spirochetes to the sensory nerves in the dorsal roots, which produces impaired joint position sense and resultant ataxia (locomotor ataxia); loss of pain sensation, leading to skin and joint damage (Charcot joints); other sensory disturbances, particularly the characteristic “lightning pains”; and absence of deep tendon reflexes. On microscopic examination there is loss of both axons and myelin in the dorsal roots, with corresponding pallor and atrophy in the dorsal columns of the spinal cord. Organisms are not demonstrable in the cord lesions.**

VIRAL MENINGOENCEPHALITIS

- **Viral encephalitis is a parenchymal infection of the brain almost invariably associated with meningeal inflammation (meningoencephalitis) and sometimes with involvement of the spinal cord (encephalomyelitis).**
- **Some viruses tend to infect the nervous system. Such neural tropism takes several forms: some viruses infect specific cell types (such as oligodendrocytes), while others preferentially involve particular areas of the brain (such as medial temporal lobes or the limbic system). *Latency* is an important facet of several viral infections of the CNS (e.g., herpes zoster, progressive multifocal leukoencephalopathy). Systemic viral infections in the absence of direct evidence of viral penetration into the CNS may be followed by an *immune-mediated disease*, such as perivenous demyelination .Intrauterine viral infection may cause *congenital malformations*, as occurs with rubella.**

CMV

- **This infection of the nervous system occurs in fetuses and immunosuppressed individuals. The outcome of infection in utero is periventricular necrosis that produces severe brain destruction followed later by microcephaly and periventricular calcification. CMV is a common viral infection in individuals with AIDS, with CNS involvement being common in this setting.**
- **Morphology. In the immunosuppressed individual, the most common pattern of involvement is that of a subacute encephalitis, which may be associated with CMV inclusion-bearing cells. Although any type of cell within the CNS (neurons, glia, ependyma, endothelium) can be infected by CMV, there is a tendency for the virus to localize in the paraventricular subependymal regions of the brain. This results in a severe hemorrhagic necrotizing ventriculoencephalitis and a choroid plexitis. The virus can also attack the lower spinal cord and roots, producing a painful radiculoneuritis. Prominent cytomegalic cells with intranuclear and intracytoplasmic inclusions can be readily identified by conventional light microscopy and confirmed as CMV by immunohistochemistry.**

Demyelinating diseases:

Multiple sclerosis :

- Relapsing and remitting disease
- Young adults (20-40), more in female
- Genetic predisposition : HLA-DR2, 25% in twins
- Acquired environmental factors …immune insult

-CD4 & CD8 T lymphocytes in lesions

-AB against myelin components +complement are identified in lesions

-CSF… oligoclonal band , Ig G against myelin basic protein, increase protein , increase lymphocytes

- Characterstics patches in white matter (CT,MRI)

- Peripheral nervous system is spared
- Include :

-inheriterd diseases involving myelin synthesis and turnover e.g. leukodystrophies

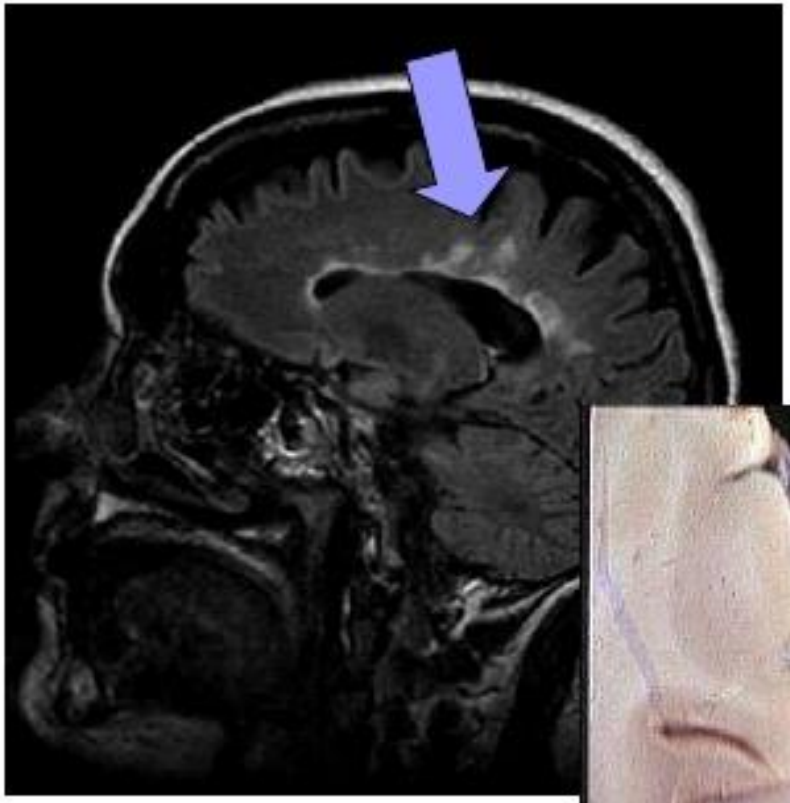
-acquired diseases :

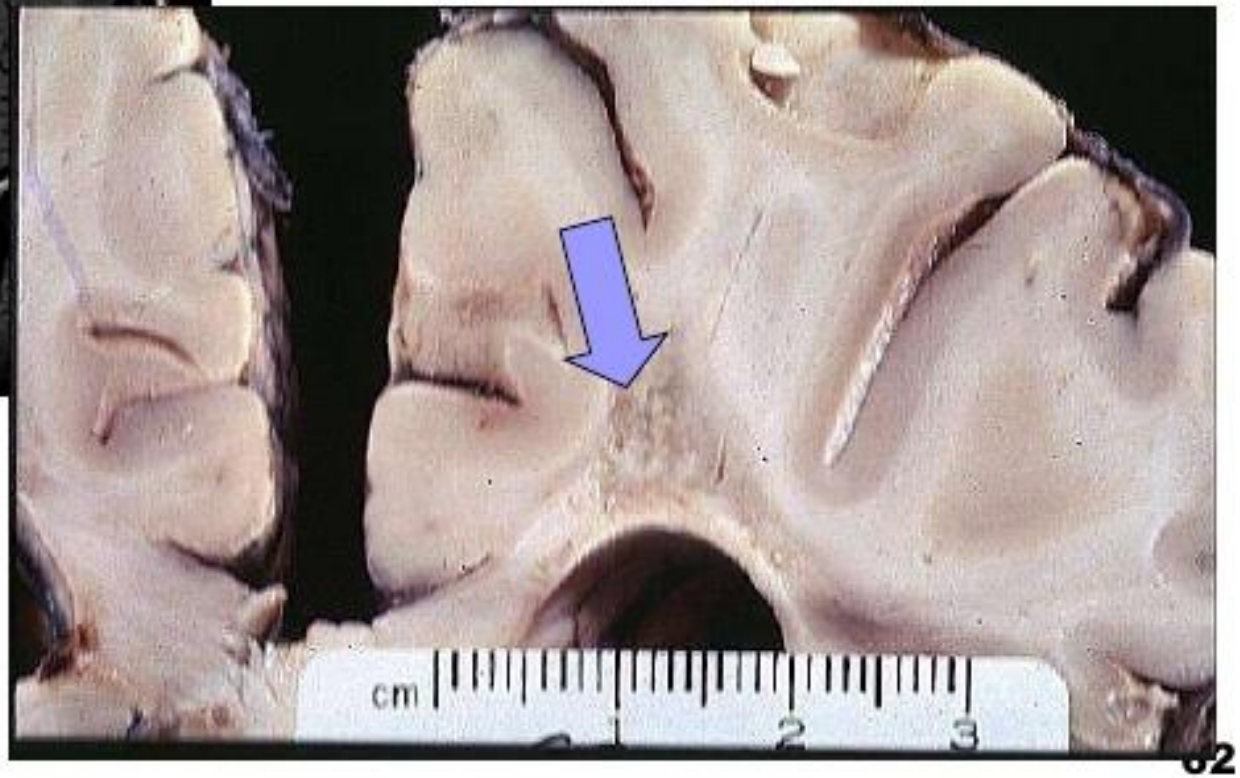
- Viral infection by JC virus
- Acute disseminated encephalomyelities
- Idiopathic or acquired multiple sclerosis
- Central pontine myelinolysis

MS pathology :

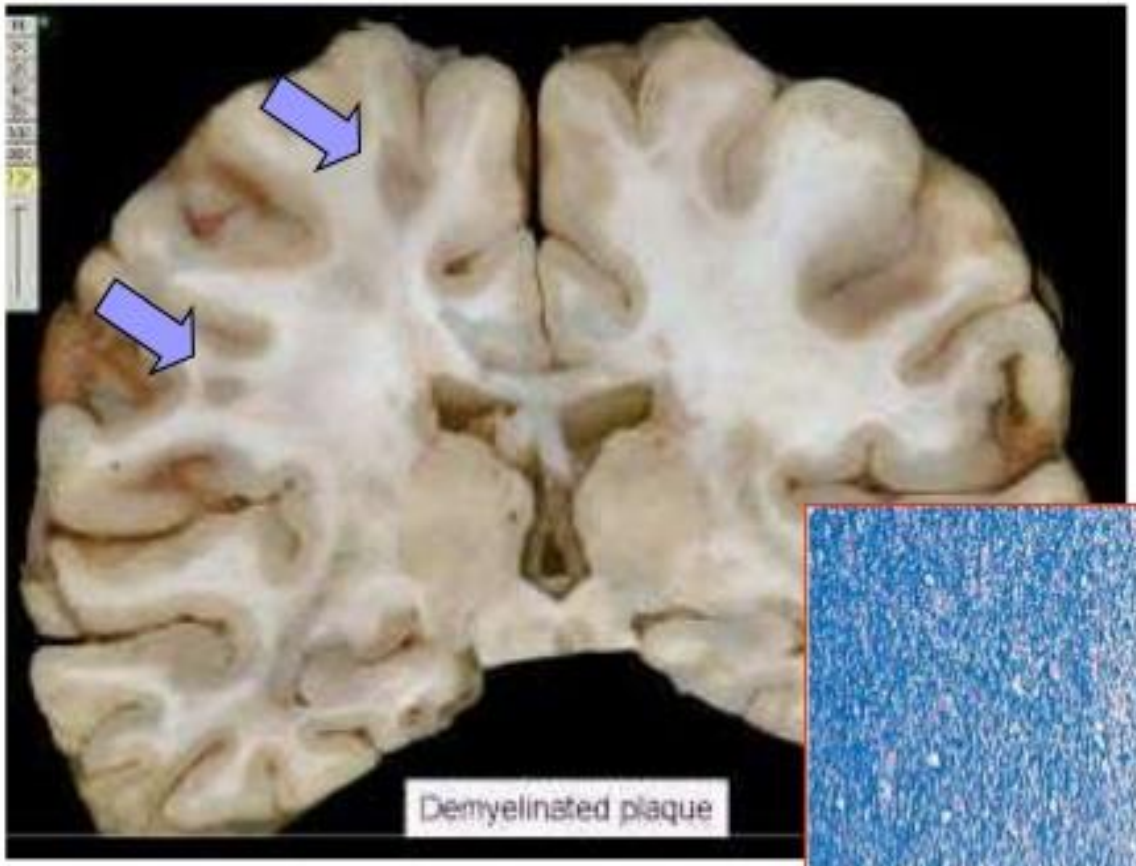
- Patchy demyelination in white matter of brain, periventricular areas, optic nerves & in spinal cord
- Acute stage : soft pink plaque : myelin breakdown , phagocytosis & perivascular lymphocytic infiltration , odema
- Chronic stage : hard grey plaques : total myelin loss, no inflammation, loss of oligodendrocytes, reactive gliosis
- Shadow plaques : remyelination

Multiple Sclerosis - plaques





Multiple Sclerosis: Demyelinated plaques



Microscopy showed loss of myelination with many lipid macrophages.

Degenerative disorders:

Alzheimer's disease:

- Commonest cause of dementia in the west
- Age more than 50
- Insidious progressive neurological disorders
- Sporadic or familial (10-15%)
- Basic pathogenesis of the disease is linked to diposition of amyeloid in the brain

Pathogenesis :

1. Genetic : abnormalities in ch. 21,19,14,12,1

*ch. 21… amyloid precursor protien (APP) increase risk in Down's syndrome

*preselin genes (14,1) …amyloid

*AD is associated with Apolipo-protien E4 allele in late onset sporadic or familial cases …amyloid fiber formation

2. Defects in processing of APP:

*secretase enzymes α, β, ϒ on APP… soluble & insoluble components

*APP….ϒ secretase …..β amyloid

*β amyloid depsited in senile plaques & wall of blood vessels

*this is induced by mutation in presenilin genes

3. Hyperphosphorylation of the protien Tau:

*Tau is a normal protein involved in assembly of axonal microtubules and their stability.

Pathology :

- Atrophy of frontal and temproparietal cortex
- Microscopical changes:

1. Amyloid angiopathy
2. Neurofibrillary tangles, mainly in pyramidal cells of hippocampus
3. Senile (neuritic) plaques, cerebral cortex
4. Granulovacular degeneration in pyramidal cells
5. Lewy bodies inside neurons

- Death in 5-15 years.

Parkinsonism :

- Disturbance in motor function with rigidity, slow movements, expressionless facies and tremor
- Adult in 6th decade
- Idiopathic : sporadic or familial, specific gene
- Secondary : trauma, vascular disorders , encephalitis, toxic agent , drugs

Pathology :

- loss of dopamine _secreting neurons in substantia nigra….depigmentation & gliosis
- Concentric laminated inclusions in central cortical neurons contain presynaptic protein (α-synuclein) ,
- lewy bodies.