Pathogenesis and risk factors of cerebrovascular accidents

Pathology

Introduction

→ *Review the following terms:*

Hypoxia

Ischemia

Infarction

Introduction

- The brain may be deprived of oxygen by any of several mechanisms:
  - **functional hypoxia**, in:
    - a low partial pressure of oxygen
    - impaired oxygen-carrying capacity
    - inhibition of oxygen use by tissue

  →*list one example on each mechanism!*

  - **ischemia**, either *transient* or *permanent, in*:
    - a reduction in perfusion pressure, as in hypotension
    - vascular obstruction
    - both

Introduction

- 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

Stroke

- Definition:
  - It is the clinical term for a disease with acute onset of a neurologic deficit as the result of vascular lesions, either hemorrhage or loss of blood supply.

YouTube - Stroke Animation Video.flv

Thrombotic and embolic stroke

- Overall, embolic infarctions are more common
- Sources of emboli include:
  - Cardiac mural thrombi (frequent);
    - myocardial infarct
    - valvular disease
    - atrial fibrillation
  - Arteries; (often atheromatous plaques within the carotid arteries)
  - Paradoxical emboli, particularly in children with cardiac anomalies
  - Emboli associated with cardiac surgery
  - Emboli of other material (tumor, fat, or air)
- The territory of distribution of the middle cerebral arteries most frequently affected by embolic infarction
  → *WHY?*

Thrombotic and embolic stroke

- The majority of thrombotic occlusions causing cerebral infarctions are due to *atherosclerosis*
- The most common sites of primary thrombosis:
  - The carotid bifurcation
  - The origin of the middle cerebral artery
  - At either end of the basilar artery
- Atherosclerotic stenosis can develop on top a superimposed thrombosis, accompanied by anterograde extension, fragmentation, and distal embolization

Stroke
Clinical presentation

- Depends on which part of the brain is injured, and how severely it is injured
- Sometimes people with stroke have a headache, but stroke can also be completely painless
- It is very important to recognize the warning signs of stroke and to get immediate medical attention if they occur
- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation

Stroke
Clinical presentation

- Symptoms :
  - Sudden
  - The most common is weakness or paralysis of one side of the body with partial or complete loss of voluntary movement or sensation in a leg or arm
  - There can be speech problems and weak face muscles, causing drooling
  - Numbness or tingling is very common
  - A stroke involving the base of the brain can affect balance, vision, swallowing, breathing and even unconsciousness
  - In cases of severe brain damage there may be deep coma, paralysis of one side of the body, and loss of speech, followed by death or permanent neurological disturbances after recovery

Global Cerebral Ischemia

- Widespread ischemic/hypoxic injury occurs when there is a generalized reduction of cerebral perfusion, usually below systolic pressures of less than 50mmHg

- Causes include:
  - cardiac arrest
  - severe hypotension or shock

- The clinical outcome varies with the severity of the insult
  - If mild → may be only a transient postischemic confusional state, with eventual complete recovery

Global Cerebral Ischemia

- In severe global cerebral ischemia, widespread neuronal death, irrespective of regional vulnerability, occurs
- persistent vegetative state:
  - Individuals who survive in this state often remain severely impaired neurologically and deeply comatose
- respirator brain
  - Other patients meet the clinical criteria for "brain death," including evidence of diffuse cortical injury (isoelectric, or "flat," electroencephalogram) and brain stem damage, including absent reflexes and respiratory drive
  - When patients with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually undergoes an autolytic process

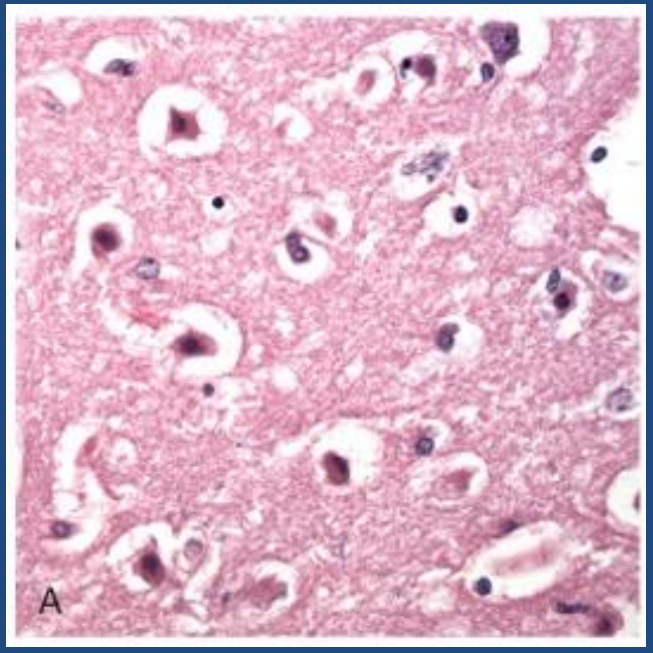
Global Cerebral Ischemia

- Sensitvity to ischemia:
  - Neurons are **much more** sensitive to hypoxia than are glial cells
  - The most susceptible to ischemia of short duration are:
    - pyramidal cells of the Sommer sector (CA1) of the hippocampus
    - Purkinje cells of the cerebellum
    - pyramidal neurons in the neocortex

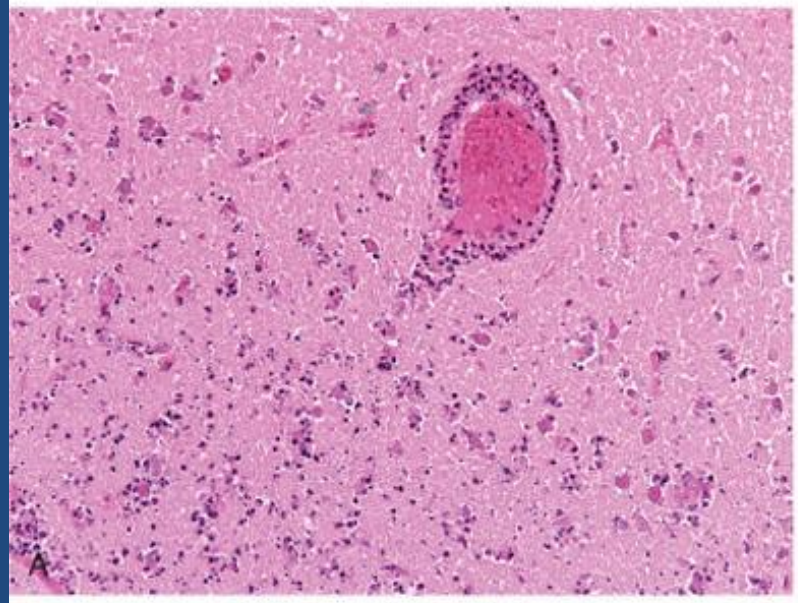
Global Cerebral Ischemia

- Gross pathology:
  - The brain is swollen, with wide gyri and narrowed sulci
  - The cut surface shows poor demarcation between gray and white matter

- Microscopically, infarction shows:
  - **Early changes:**
    - 12 to 24 hours after the insult
    - red neurons, characterized initially by microvacuolization →cytoplasmic eosinophilia, and later nuclear pyknosis and karyorrhexis.



- **Subacute changes:**
  - 24 hours to 2 weeks
  - The reaction to tissue damage begins with infiltration by neutrophils
  - Necrosis of tissue, influx of macrophages, vascular proliferation and reactive gliosis
- **Repair:**
  - after 2 weeks
  - removal of all necrotic tissue, loss of organized CNS structure and gliosis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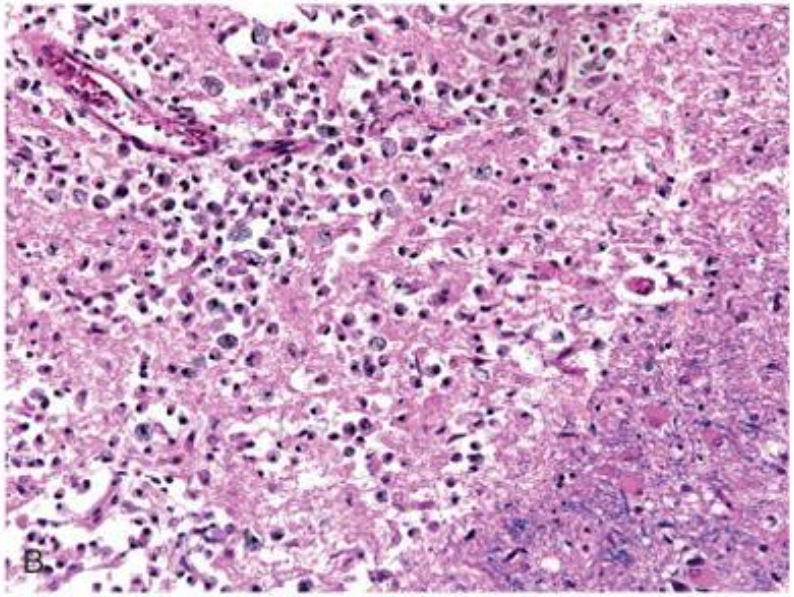
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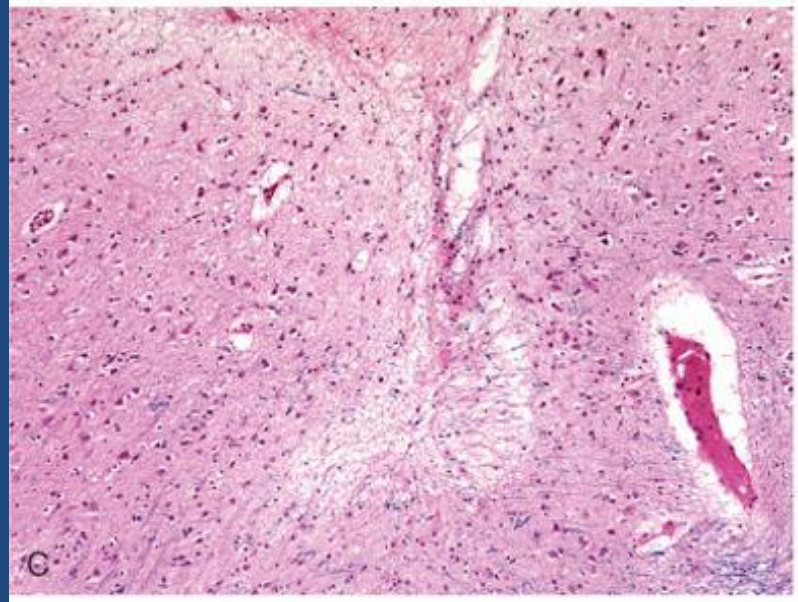
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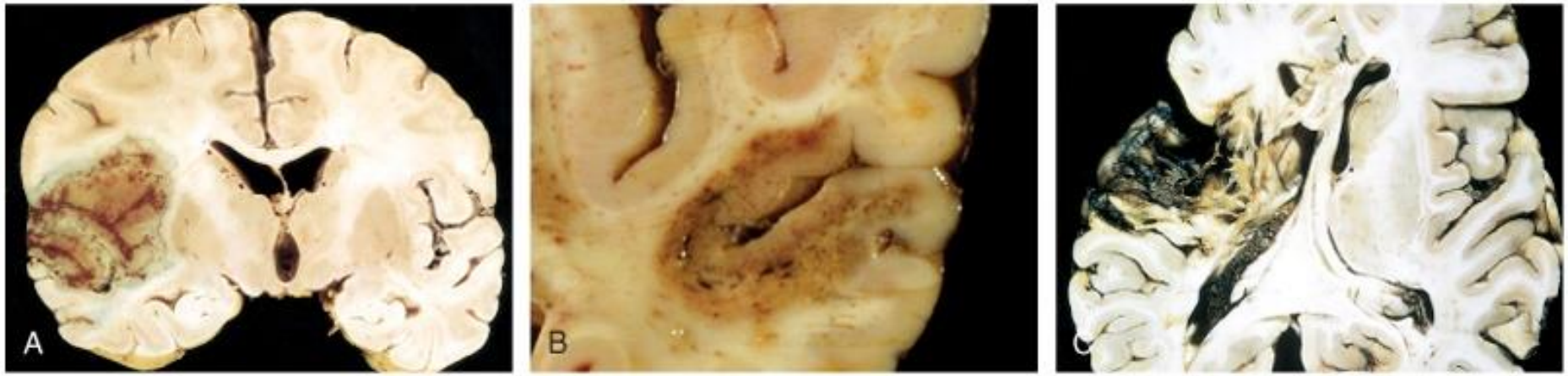
Focal Cerebral Ischemia

- Cerebral arterial occlusion → focal ischemia
- The size, location, and shape of the infarct and the extent of tissue damage that results are determined by modifying variables, most importantly the adequacy of collateral flow:
  - The major source of collateral flow is the circle of Willis
  - Partial collateralization is also provided over the surface of the brain through cortical-leptomeningeal anastomoses
  - In contrast, there is little if any collateral flow for the deep penetrating vessels supplying structures such as:
    - **Thalamus**
    - **Basal ganglia**
    - **Deep white matter**

Focal Cerebral Ischemia



Focal Cerebral Ischemia

- Gross pathology: :
  - **Nonhemorrhagic infarct:**
    - The first 6 hours of irreversible injury, little can be observed
    - By 48 hours the tissue becomes pale, soft, and swollen, and the corticomedullary junction becomes indistinct
    - From 2 to 10 days the brain becomes gelatinous and friable, and the previously ill-defined boundary between normal and abnormal tissue becomes more distinct as edema resolves in the adjacent tissue that has survived
    - From 10 days to 3 weeks, the tissue liquefies, eventually leaving a fluid-filled cavity lined by dark gray tissue, which gradually expands as dead tissue is removed

Focal Cerebral Ischemia

- Microscopically the tissue reaction follows a characteristic sequence:
  - **After the first 12 hours:**

    - Red neurons and both cytotoxic and vasogenic edema predominate

    - There is loss of the usual characteristics of white and gray matter structures

    - Endothelial and glial cells, mainly astrocytes, swell, and myelinated fibers begin to disintegrate
  - **Until 48 hours,** there is some neutrophilic emigration followed by mononuclear phagocytic cells in the ensuing **2 to 3 weeks.** Macrophages containing myelin breakdown products or blood may persist in the lesion for months to years
  - As the process of phagocytosis and liquefaction proceeds, astrocytes at the edges of the lesion progressively enlarge, divide, and develop a prominent network of protoplasmic extensions

Focal Cerebral Ischemia

- **After several months** the striking astrocytic nuclear and cytoplasmic enlargement recedes
- In the wall of the cavity, astrocyte processes form a dense feltwork of glial fibers admixed with new capillaries and a few perivascular connective tissue fibers
- In the cerebral cortex the cavity is delimited from the meninges and subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of cortex
- The pia and arachnoid are not affected and do not contribute to the healing process

Focal Cerebral Ischemia

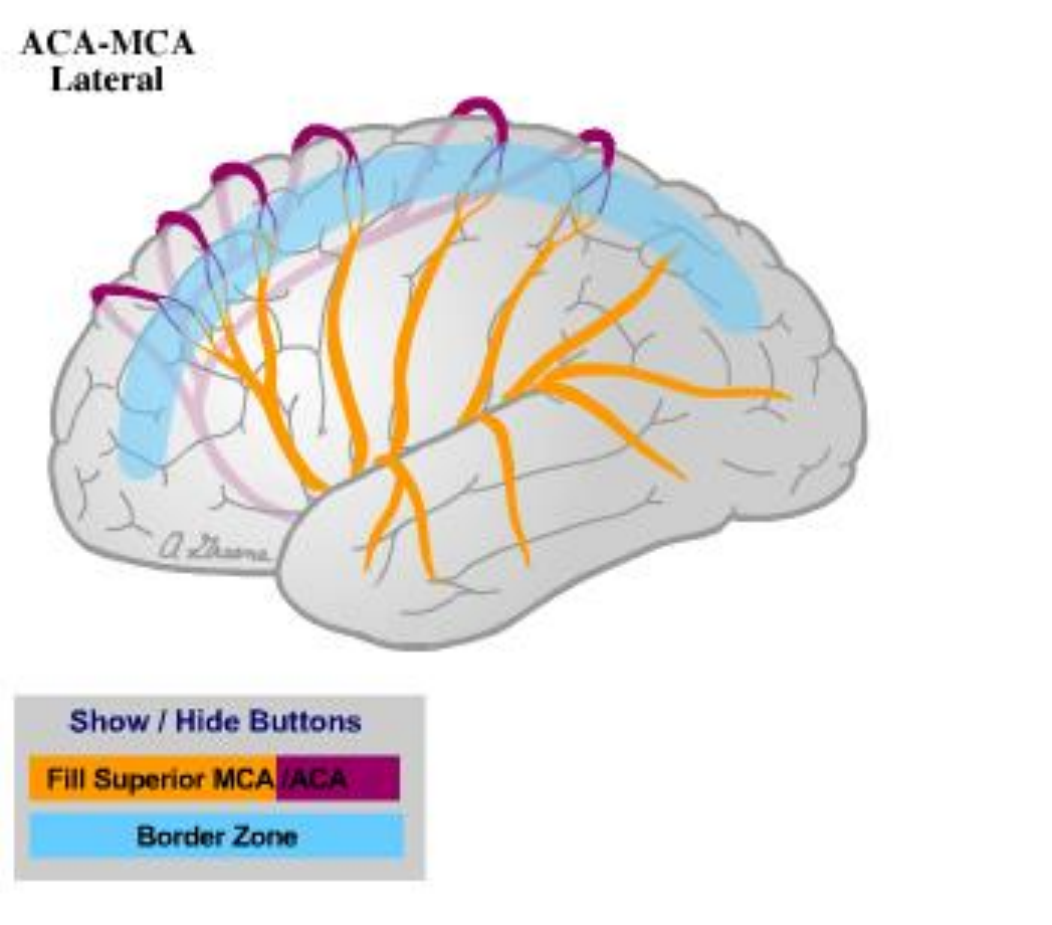
- The microscopic picture and evolution of **hemorrhagic infarction** parallel ischemic infarction, with the addition of blood extravasation and resorption
- In persons receiving anticoagulant treatment, hemorrhagic infarcts may be associated with extensive intracerebral hematomas

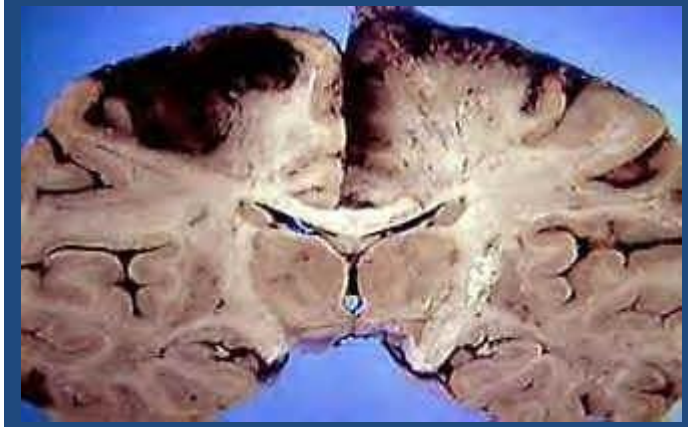
Border zone ("watershed") infarcts

- Wedge-shaped areas of infarction that occur in those regions of the brain and spinal cord that lie at the most distal fields of arterial perfusion
- In the cerebral hemispheres, the border zone between the anterior and the middle cerebral artery distributions is at greatest risk
- Damage to this region produces a band of necrosis over the cerebral convexity a few centimeters lateral to the interhemispheric fissure
- Border zone infarcts are usually seen after hypotensive episodes

Border zone ("watershed") infarcts

- Example

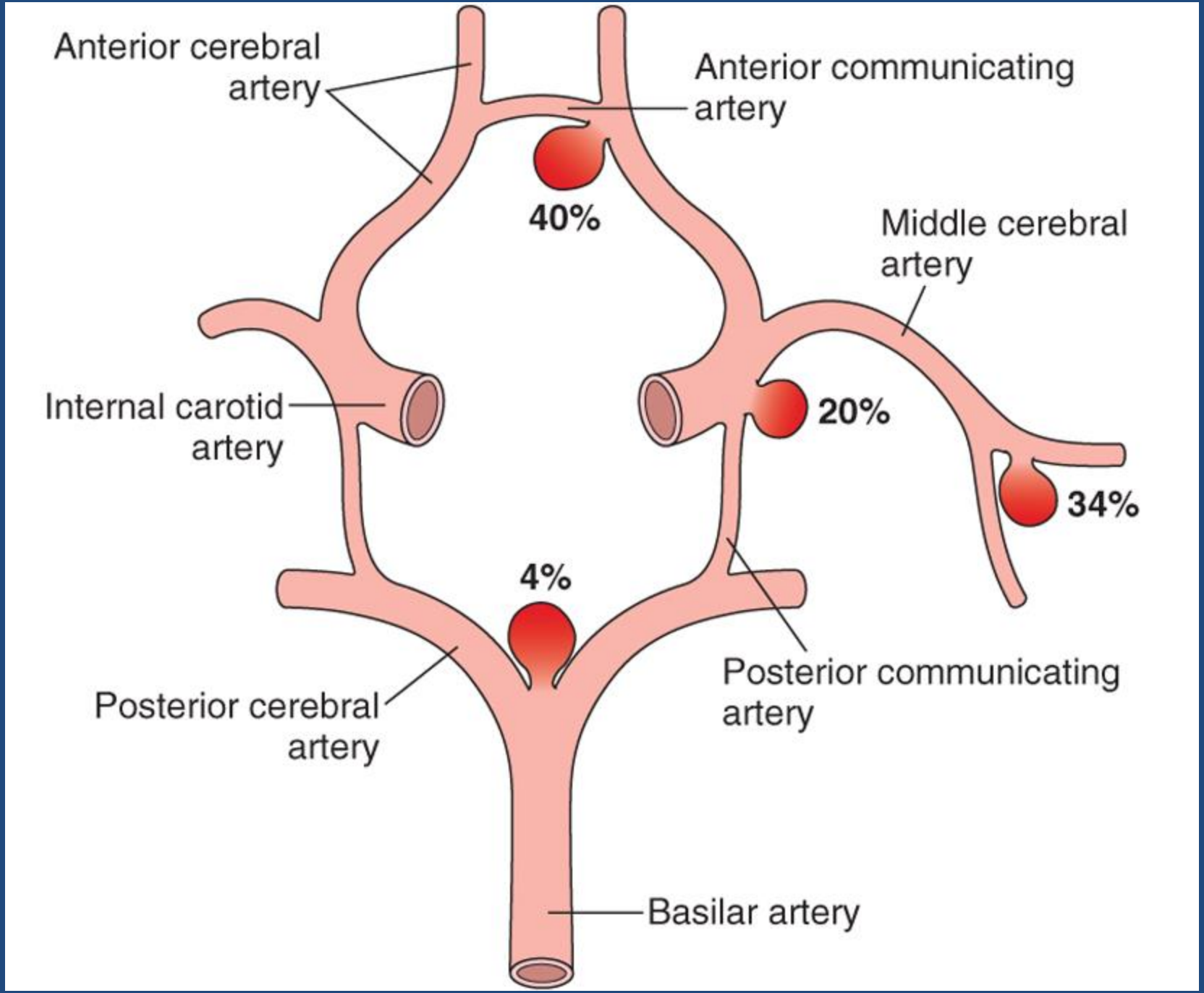




Intracerebral hemorrhage

- Hemorrhages within the brain (intracerebral) can occur secondary to:
  - Hypertension
  - Other forms of vascular wall injury (e.g. vasculitis)
  - Arteriovenous malformation
  - An intraparenchymal tumor

Hemorrhages associated with the dura (in either subdural or epidural spaces) make up a pattern associated with trauma (discussed in another lecture)


Anterior cerebral artery
Anterior communicating artery
40%
Middle cerebral artery
Internal carotid artery
20%
34%
4%
Posterior communicating artery
Posterior cerebral artery
Basilar artery

Subarachnoid Hemorrhage

- Causes of subarachnoid hemorrhage:
  - rupture of a saccular (berry) aneurysm (The most frequent cause of clinically significant)
  - vascular malformation
  - trauma (in which case it is usually associated with other signs of the injury)
  - rupture of an intracerebral hemorrhage into the ventricular system
  - hematologic disturbances
  - tumors
- Rupture can 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 individuals are stricken with sudden, excruciating headache (classically described as "the worst headache I've ever had") and rapidly lose consciousness

Subarachnoid Hemorrhage

- Between 25% and 50% of individuals die with the first rupture, although those who survive typically improve and recover consciousness in minutes
- Recurring bleeding is common in survivors; it is currently not possible to predict which individuals will have recurrences of bleeding
- The prognosis worsens with each episode of bleeding

Subarachnoid Hemorrhage

- About 90% of saccular aneurysms occur in the anterior circulation near major arterial branch points
- multiple aneurysms exist in 20% to 30% of cases. Although they are sometimes referred to as *congenital,* they are not present at birth but develop over time because of underlying defects in the vessel media

Subarachnoid Hemorrhage

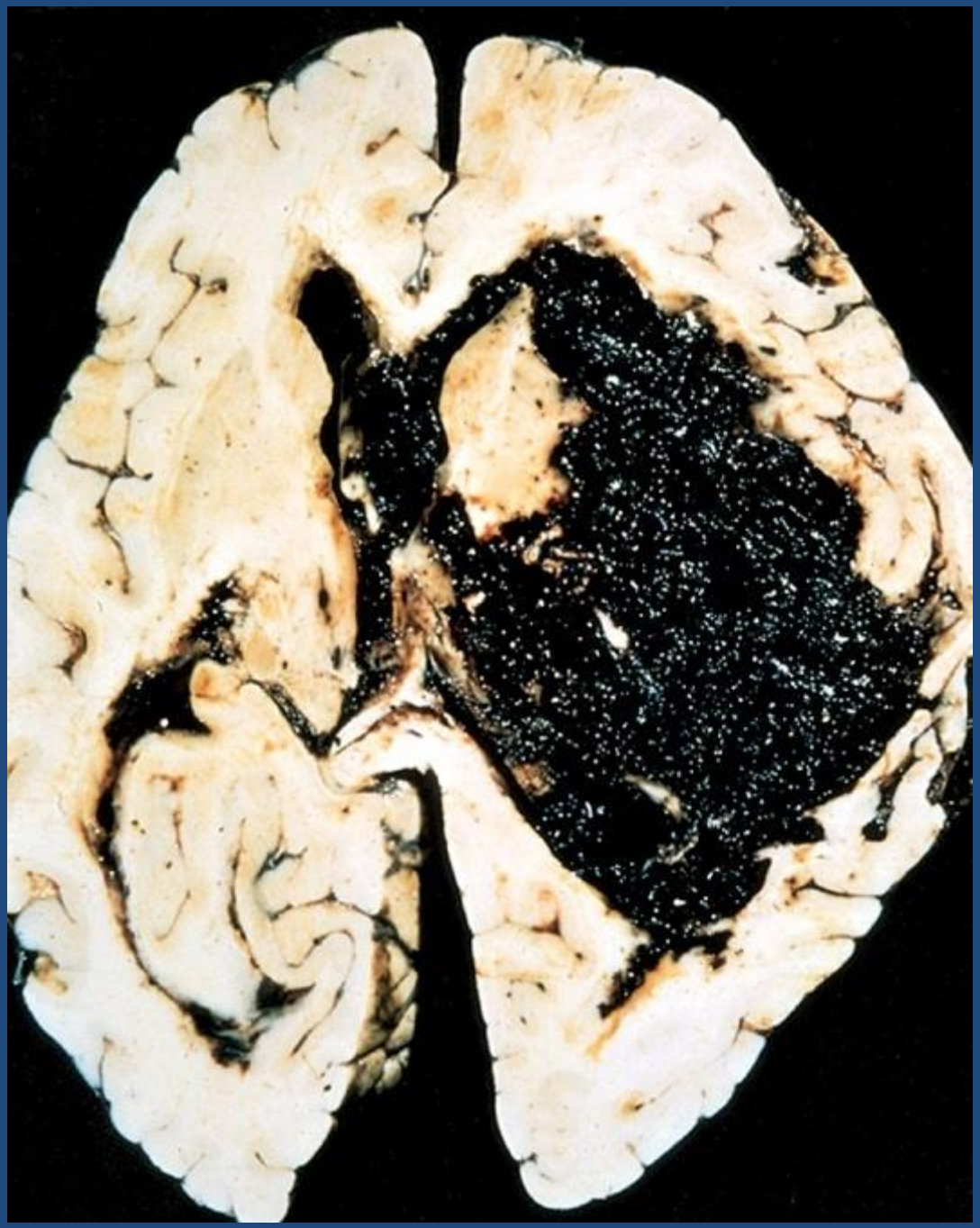
- The probability of aneurysm rupture increases with the size of the lesion, such that aneurysms greater than 10 mm have a roughly 50% risk of bleeding per year

Subarachnoid Hemorrhage

- In the early period after a subarachnoid hemorrhage, there is a risk of additional ischemic injury from vasospasm involving other vessels
- 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

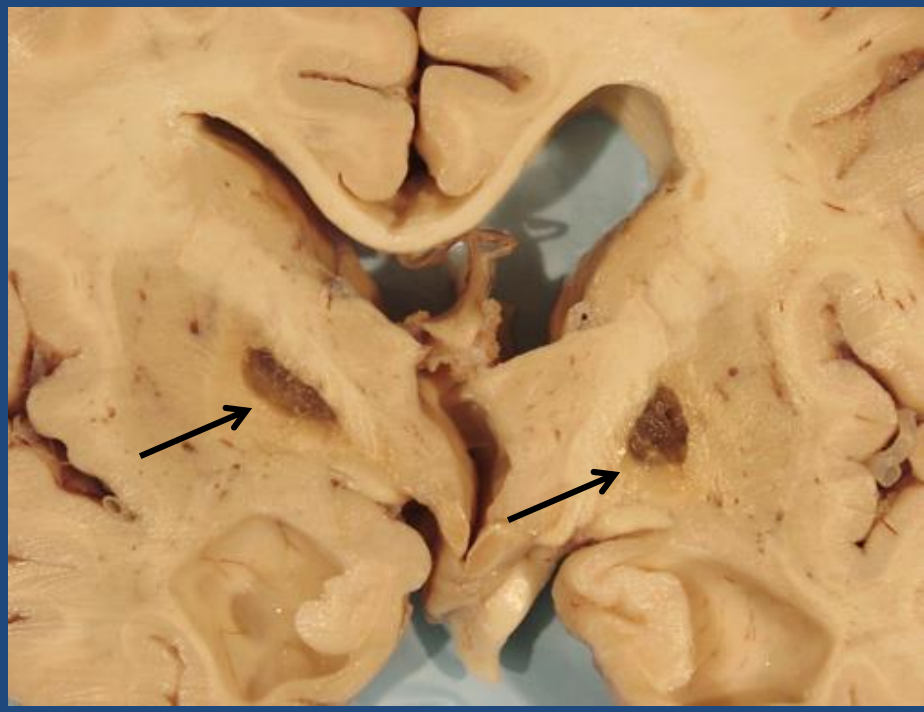
Hypertensive Cerebrovascular Disease

- The most important effects of hypertension on the brain include:
  - Massive hypertensive intracerebral hemorrhage (discussed earlier, most important)
  - Lacunar infarcts
  - Slit hemorrhages
  - Hypertensive encephalopathy
- Hypertension affects the deep penetrating arteries and arterioles that supply the basal ganglia and hemispheric white matter and the brain stem
- Hypertension causes several changes, including hyaline arteriolar sclerosis in arterioles → weaker than normal vessels and are more vulnerable to rupture
- In some instances, chronic hypertension is associated with the development of minute aneurysms in vessels that are less than 300 µm in diameter → *Charcot-Bouchard microaneurysms,* which can rupture



Hypertensive Cerebrovascular Disease

- Lacunar infarcts:
  - small cavitary infarcts
  - most commonly in deep gray matter (basal ganglia and thalamus), internal capsule, deep white matter, and pons
  - consist of cavities of tissue loss with scattered lipid-laden macrophages and surrounding gliosis
  - depending on their location in the CNS, lacunes can either be clinically silent or cause significant neurologic impairment



Hypertensive Cerebrovascular Disease

- Slit hemorrhage*:*
  - rupture of the small-caliber penetrating vessels and the development of small hemorrhages
  - in time, these hemorrhages resorb, leaving behind a slitlike cavity surrounded by brownish discoloration

Hypertensive Cerebrovascular Disease

- Acute hypertensive encephalopathy:
  - A clinicopathologic syndrome:
    - Diffuse cerebral dysfunction, including headaches, confusion, vomiting, and convulsions, sometimes leading to coma
    - Does not usually remit spontaneously
    - May be associated with 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

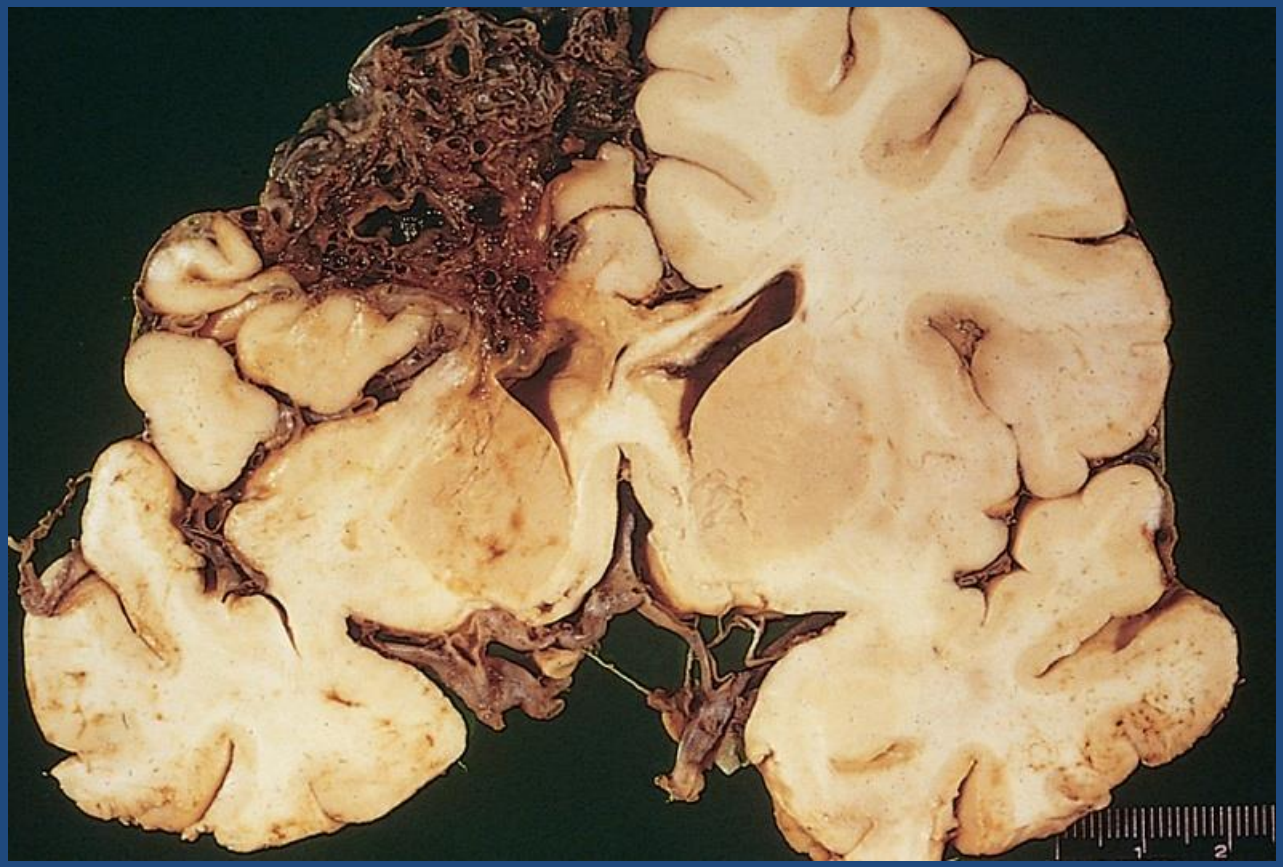
Vasculitis

- Infectious arteritis of small and large vessels:
  - Previously in association with syphilis and tuberculosis
  - Now more commonly occurs in the setting of immunosuppression and opportunistic infection (such as toxoplasmosis, aspergillosis, and CMV encephalitis)
- Systemic forms of vasculitis, such as polyarteritis nodosa, may involve cerebral vessels and cause single or multiple infarcts throughout the brain

Vasculitis

- Primary angiitis of the CNS:
  - An inflammatory disorder that involves multiple small to medium-sized parenchymal and subarachnoid vessels
  - Affected individuals manifest a diffuse encephalopathic clinical picture, often with cognitive dysfunction
  - Improvement occurs with steroid and immunosuppressive treatment

Arteriovenous malformation



→ So what can cause or contribute to a stroke?

- Hypertension
- Athersclerosis
- Thrombophilia, e.g. Sickle cell anemia
- Embolic diseases
- Systemic hypoperfusion/ Global hypoxia, e.g. shock
- Vascular malformations
- Vasculitis
- Tumors
- Venous thrombosis
- Amyloid angiopathy (leptomeningeal and cortical vessels)

Did you know !!

- Brain tissue ceases to function if deprived of oxygen for more than 60 to 90 seconds and after approximately three hours, will suffer irreversible injury possibly leading to death of the tissue

Homework

→*What are the risk factors of stroke?*

→*Define: Transient ischemic attack*