Pathogenesis and risk factors of cerebrovascular accidents (CVA) – Part 1

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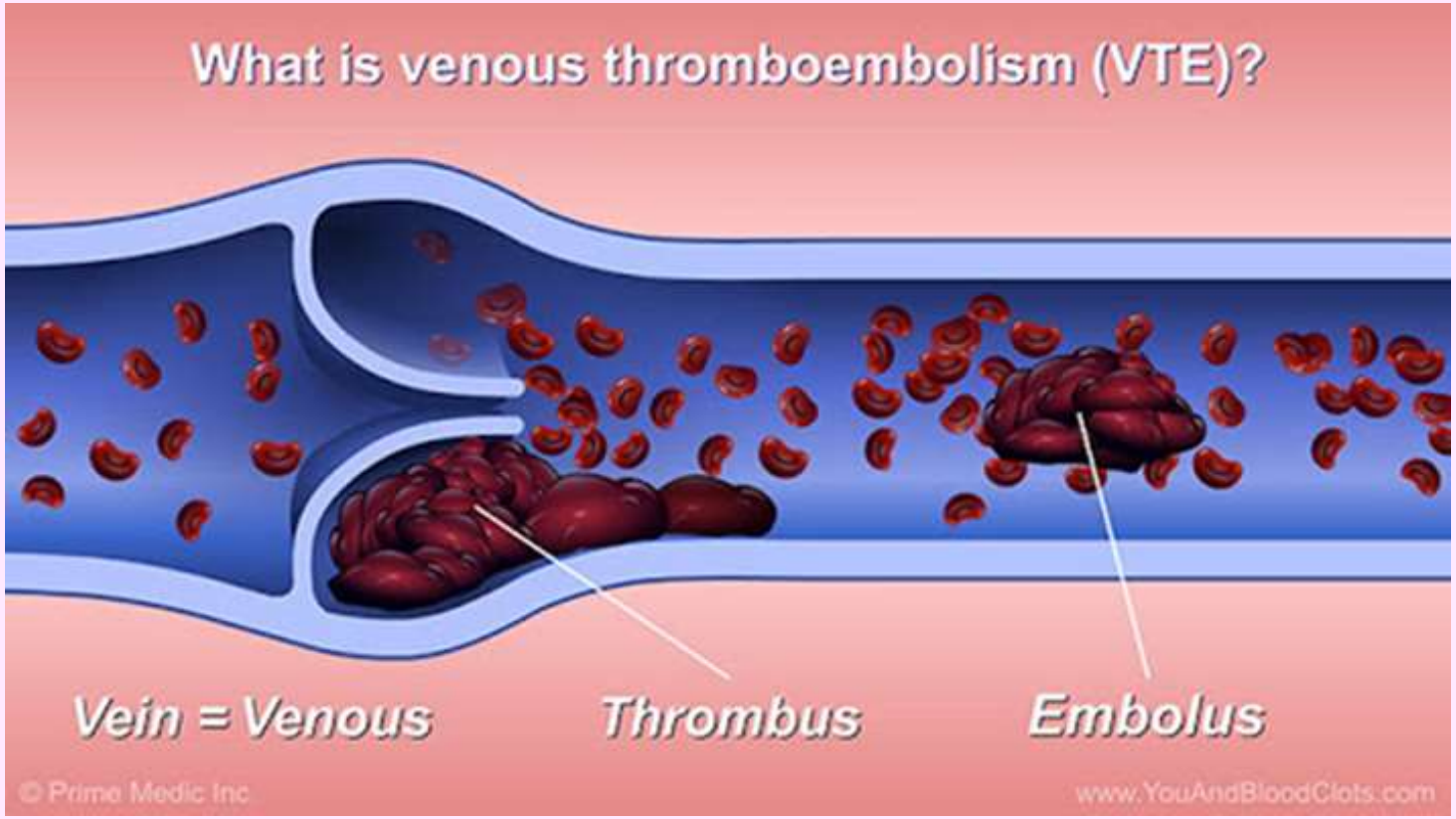
OBJECTIVES

1. Explain the concepts of brain “hypoxia”, “ischemia” and “infarction”.
2. Understand the pathogenesis of thrombotic and embolic strokes and be able to identify the clinical risk factors.
3. Identify the causes and consequences of subarachnoid and intracerebral hemorrhage.
4. Build a list of the different causes that can lead to a cerebrovascular accident.

Introduction

- Cerebrovascular diseases are brain disorders caused by pathologic processes involving blood vessels:


What is venous thromboembolism (VTE)?
Vein = Venous
Thrombus
Embolus
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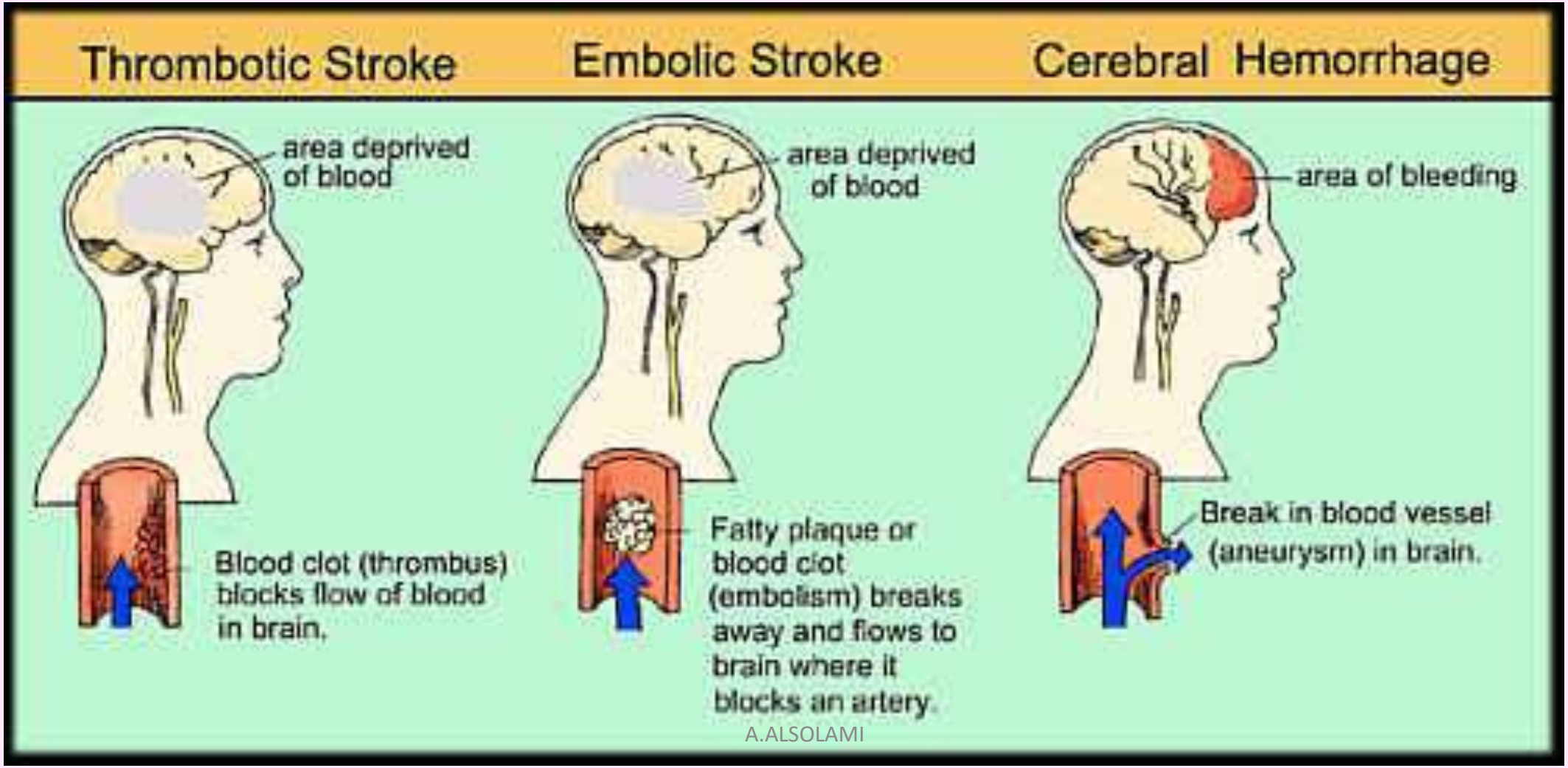
Introduction

- They are a major cause of death in the developed world and are the most prevalent cause of neurologic morbidity.

- **Thrombosis & embolism** have similar consequences for the brain: loss of oxygen & metabolic substrates, resulting in infarction or ischemic injury of regions supplied by the affected vessel.
- Infarction.. Complete loss of perfusion, hypoxemia (hypovolemic shock), or hypoglycemia.

- Hemorrhage accompanies **rupture** of vessels and leads to direct tissue damage as well as secondary ischemic injury (aneurysm or trauma).

Introduction



Hypoxia, Ischemia, Infarction

The brain may be deprived of oxygen by two general mechanisms:

1) Functional hypoxia	2) Ischemia
• Low partial pressure of **oxygen** (e.g. high altitude) • Impaired **oxygen**-carrying capacity (e.g. severe anemia, carbon monoxide poisoning) • Toxins that interfere with **oxygen** use (e.g. cyanide poisoning).	• Transient or permanent. • Due to tissue hypoperfusion, which can be caused by hypotension, vascular obstruction, or both.

Clinical Presentation of Stroke

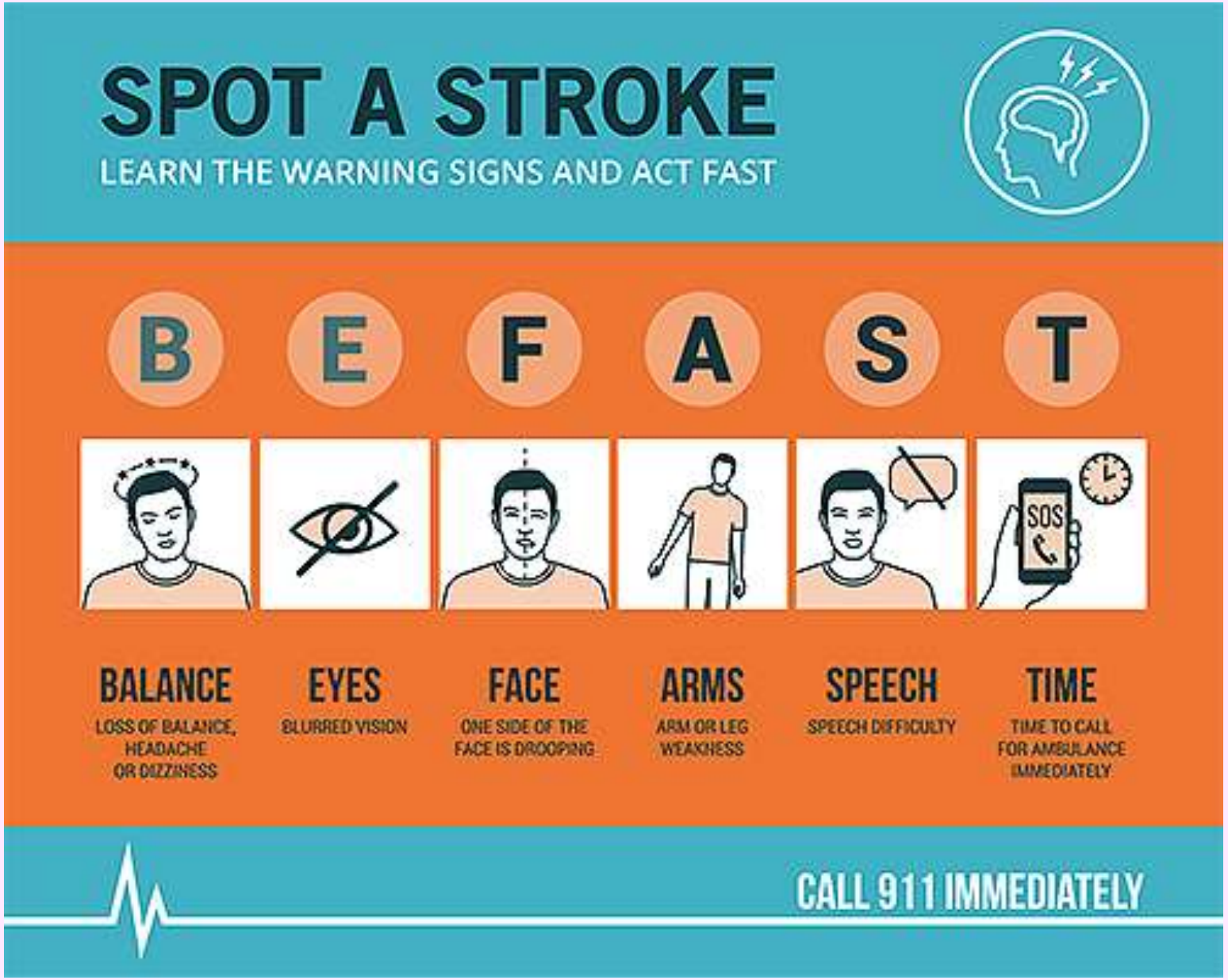
- Strokes can be asymptomatic or painless, however they may also present with symptoms depending on which part of the brain is injured, and how severely it is injured.

- It is very important to recognize the **warning signs** of a stroke and to get immediate medical attention if they occur.

Clinical Presentation of Stroke

- 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.
- Headache
- Speech problems and weak facial muscles, causing drooling
- Numbness or tingling
- A stroke involving the base of the brain can affect balance, vision, swallowing, breathing and even lead to 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.

Clinical Presentation of Stroke

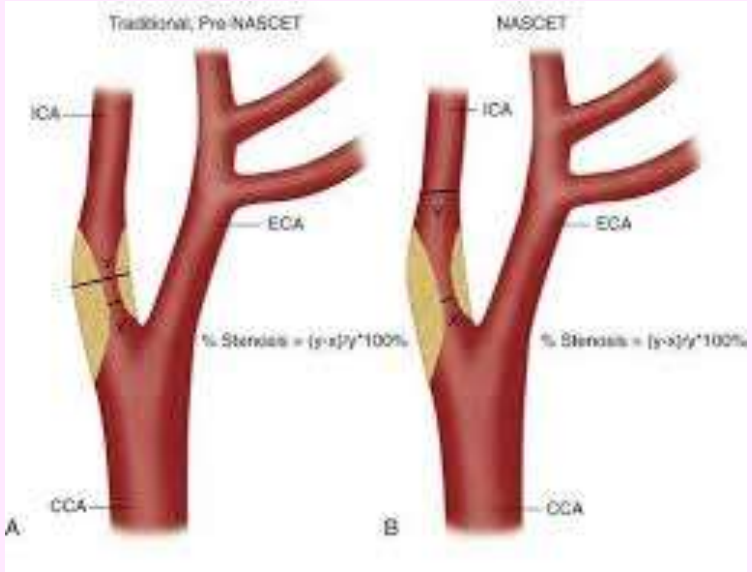

SPOT A STROKE
LEARN THE WARNING SIGNS AND ACT FAST
B E F A S T
SOS
BALANCE
LOSS OF BALANCE, HEADACHE OR DIZZINESS
EYES
BLURRED VISION
FACE
ONE SIDE OF THE FACE IS DROOPING
ARMS
ARM OR LEG WEAKNESS
SPEECH
SPEECH DIFFICULTY
TIME
TIME TO CALL FOR AMBULANCE IMMEDIATELY
CALL 911 IMMEDIATELY

Clinical Presentation of Stroke

- If the brain damage sustained is slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation.

Thrombotic & Embolic infarctions

- Overall, embolic infarctions are more common than thrombotic infarctions.
- The territory of distribution of the **middle cerebral arteries** (branches from the internal carotid arteries) are most frequently affected by **embolic infarctions.**
- Emboli tend to lodge where vessels branch or at stenotic areas caused by atherosclerosis.

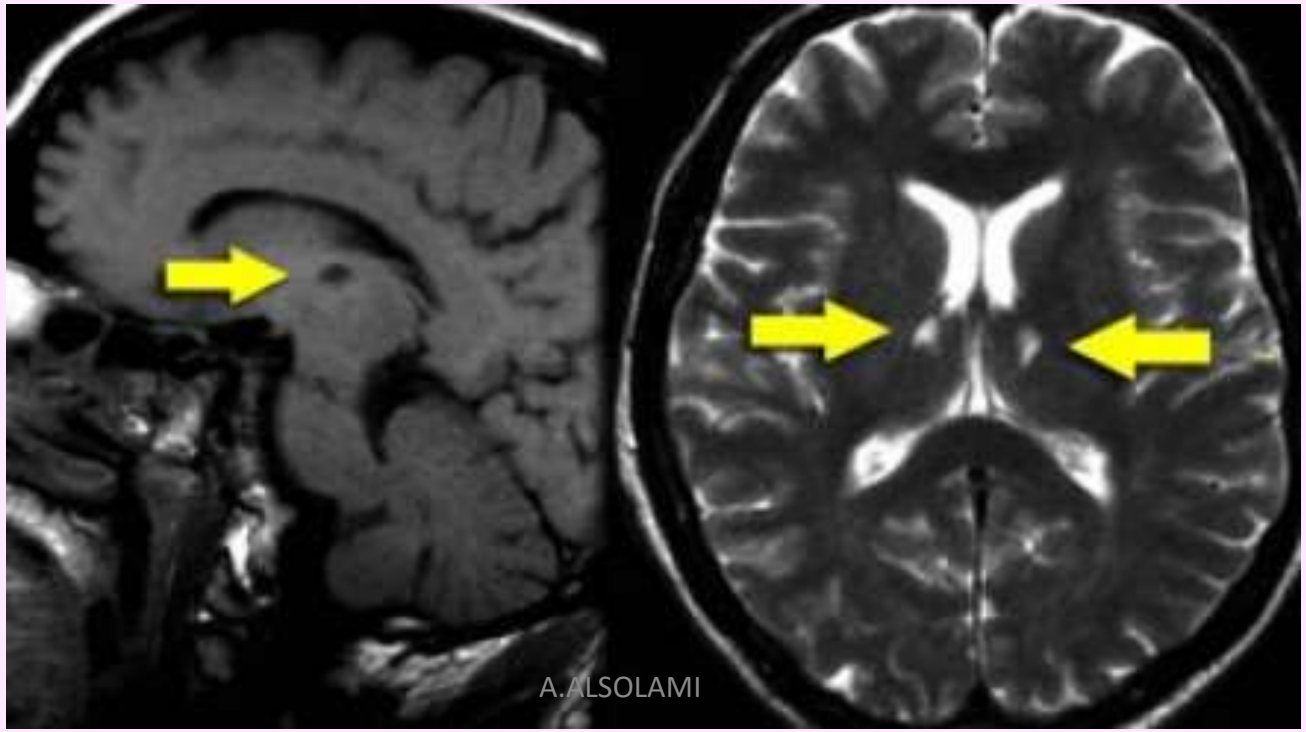


- Sources of emboli include:
  1- Cardiac mural thrombi (frequent):
  2- Arteries (often atheromatous plaques within the carotid arteries or the aortic arch).
  3- Paradoxical emboli.
  4- Emboli associated with cardiac surgeries.
  5- Emboli of other material (tumor, fat, or air).

- The majority of thrombotic occlusions causing cerebral infarctions are due to atherosclerosis.

- Thrombotic occlusions are usually superimposed on atherosclerotic plaques, accompanied by anterograde extension, fragmentation, and distal embolization.

- Thrombotic occlusions causing small infarcts of only a few millimeters, so-called “lacunar infarcts”, occurs when small penetrating arteries are occluded.



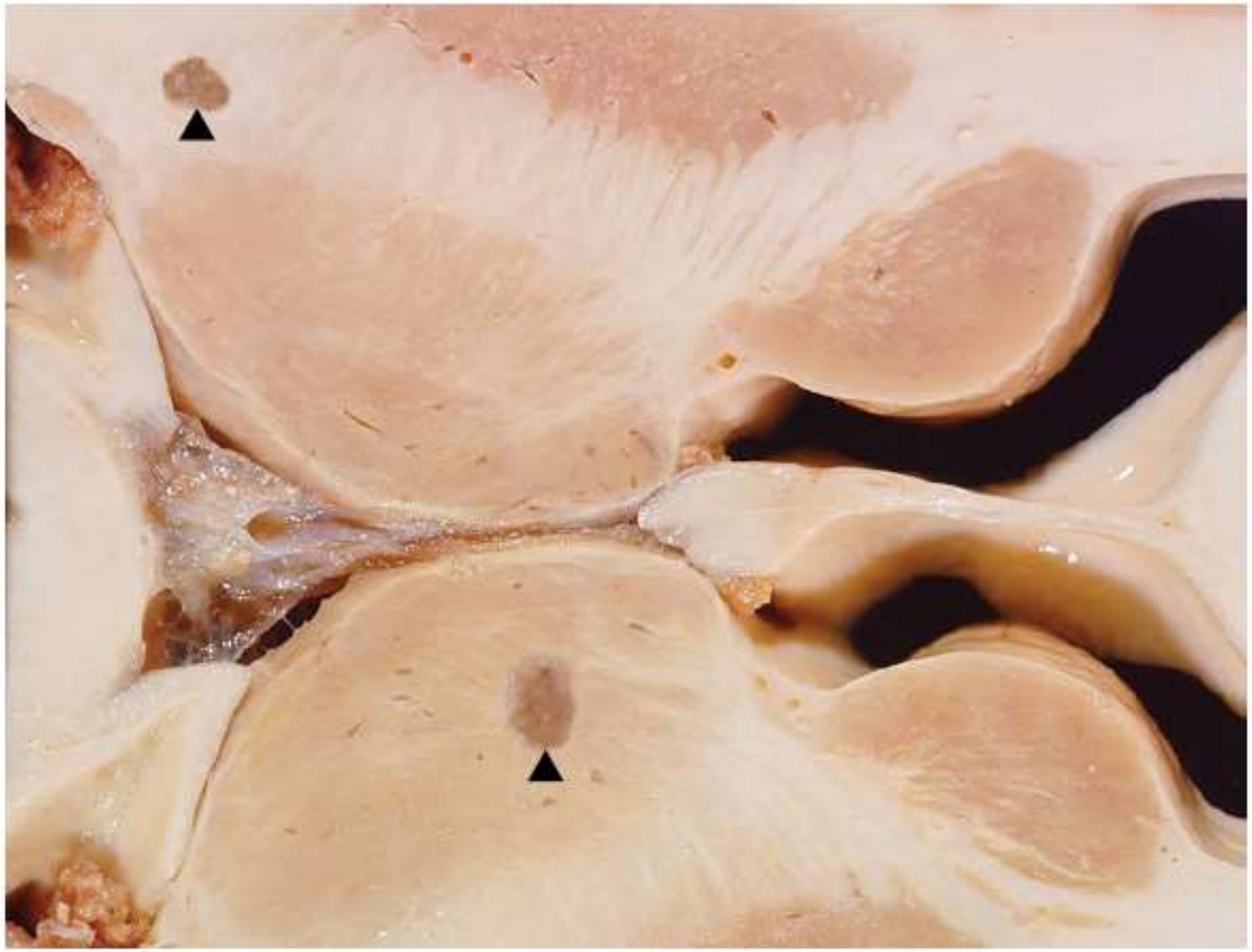


Figure 19-71 Lacunar infarction, gross
The arteriolar sclerosis that results from chronic hypertension leads to small lacunar infarcts (▲), or lacunes, two of which are shown here within the internal capsule at the top and the thalamus at the bottom. Such lesions are most common in lenticular nuclei, thalamus, internal capsule, deep white matter, caudate nucleus, and pons. Although these infarcts are typically smaller than 15 mm, and many result in no clinical findings, they can sometimes be strategically located where they damage important tracts, especially the descending corticospinal tracts, leading to hemiparesis, or the thalamus, leading to sensory problems.

- The most common sites of primary thrombosis (3)..

Global Cerebral Ischemia

- Widespread ischemic/hypoxic injury occurs when there is a generalized reduction of cerebral perfusion.
- Causes include:
  1. cardiac arrest
  2. severe hypotension or shock

- The clinical outcome varies with the severity of the insult.

Global Cerebral Ischemia

- When the insult is mild, there may be only a transient postischemic confusional state, with eventual complete recovery.

- In severe global cerebral ischemia, widespread neuronal death, and patients who survive often remain severely impaired neurologically & in a persistent vegetative state.

Global Cerebral Ischemia

- Other patients meet the clinical criteria for "brain death," including evidence of diffuse cortical injury (isoelectric, or "flat“ EEG) and brain stem damage, including absent reflexes and respiratory drive.

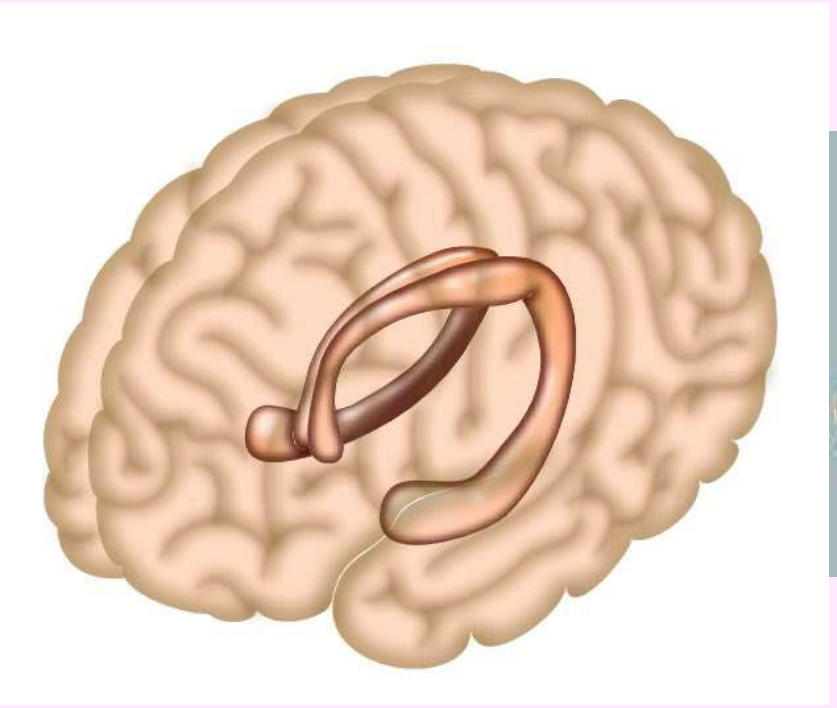
- When patients with this irreversible form of injury are maintained on mechanical ventilation, the brain gradually undergoes autolysis, results in the so-called “respirator brain”.

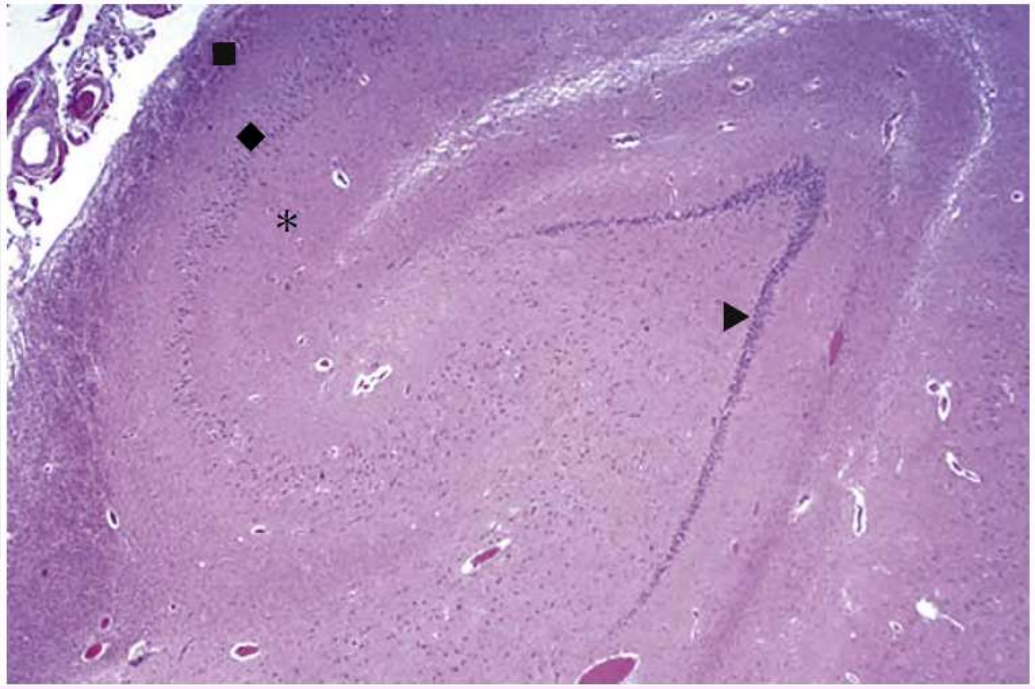
Histopathological Features (Global ischemia)

- Neurons are more susceptible to hypoxic injury than other glial cells.

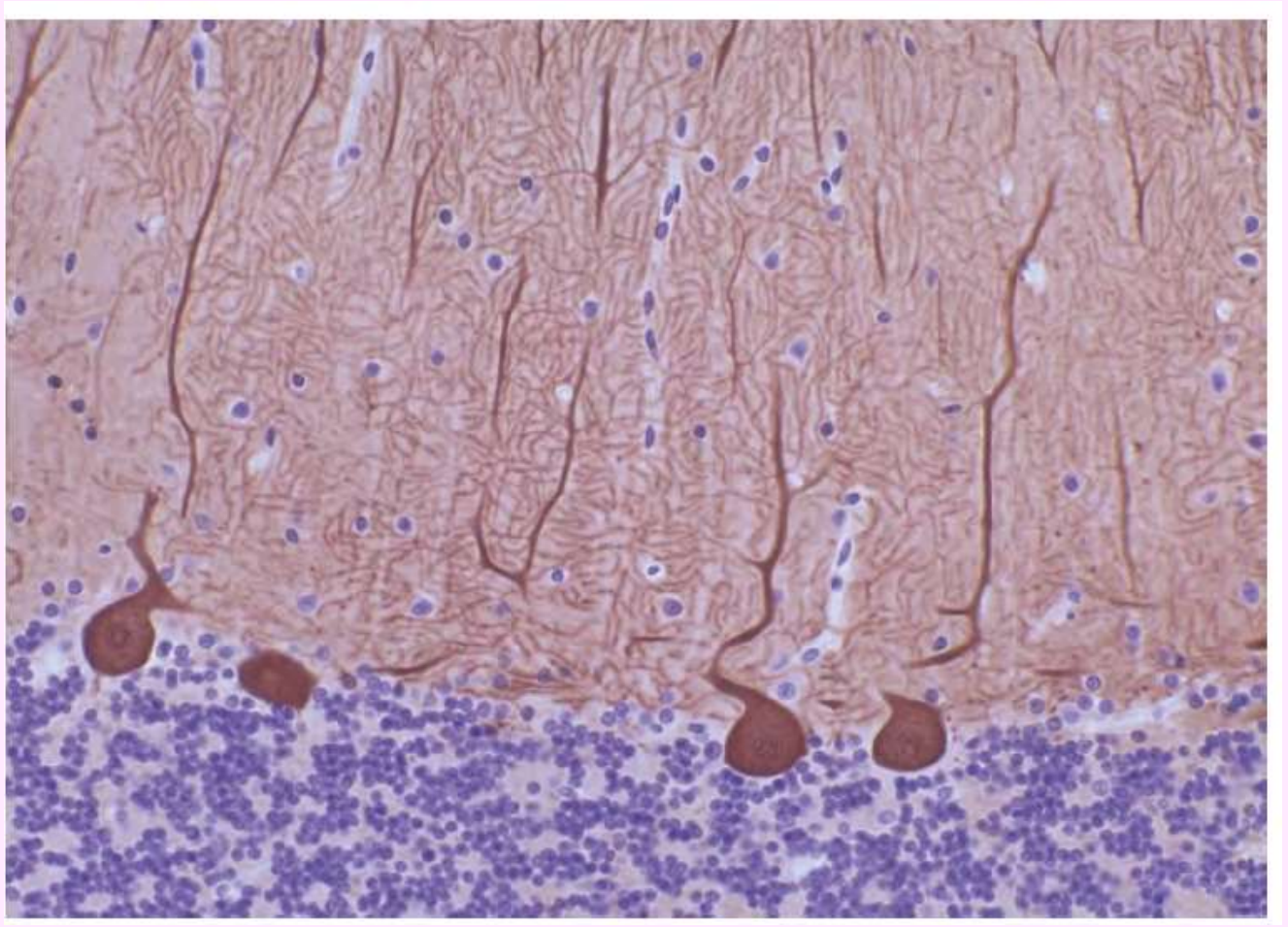
- The most susceptible neurons are:
  1. Pyramidal cells of the hippocampus and neocortex.
  2. Purkinje cells.

Hippocampus.. Pyramidal neurons





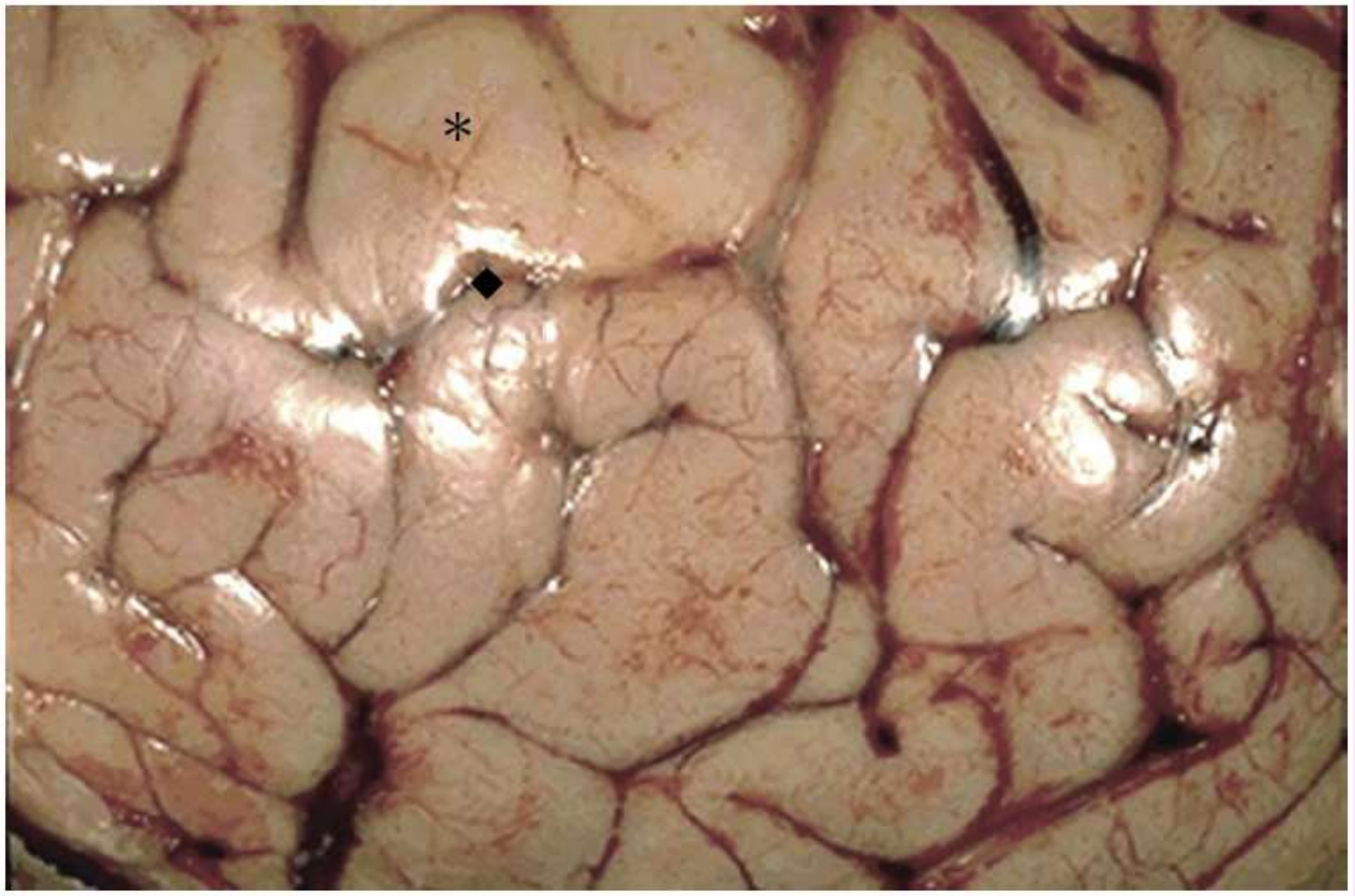
Purkinje cells



Histopathological Features (Global ischemia)

Macroscopically (Gross)	**Microscopically**
1. The brain is swollen, with wide gyri and narrowed sulci. 2. The cut surface shows poor demarcation between gray and white matter.	1- Early changes (**12-24 hours**) 2- Subacute changes (**24 hours-2 weeks)** 3- Repair **(more than 2 weeks)**

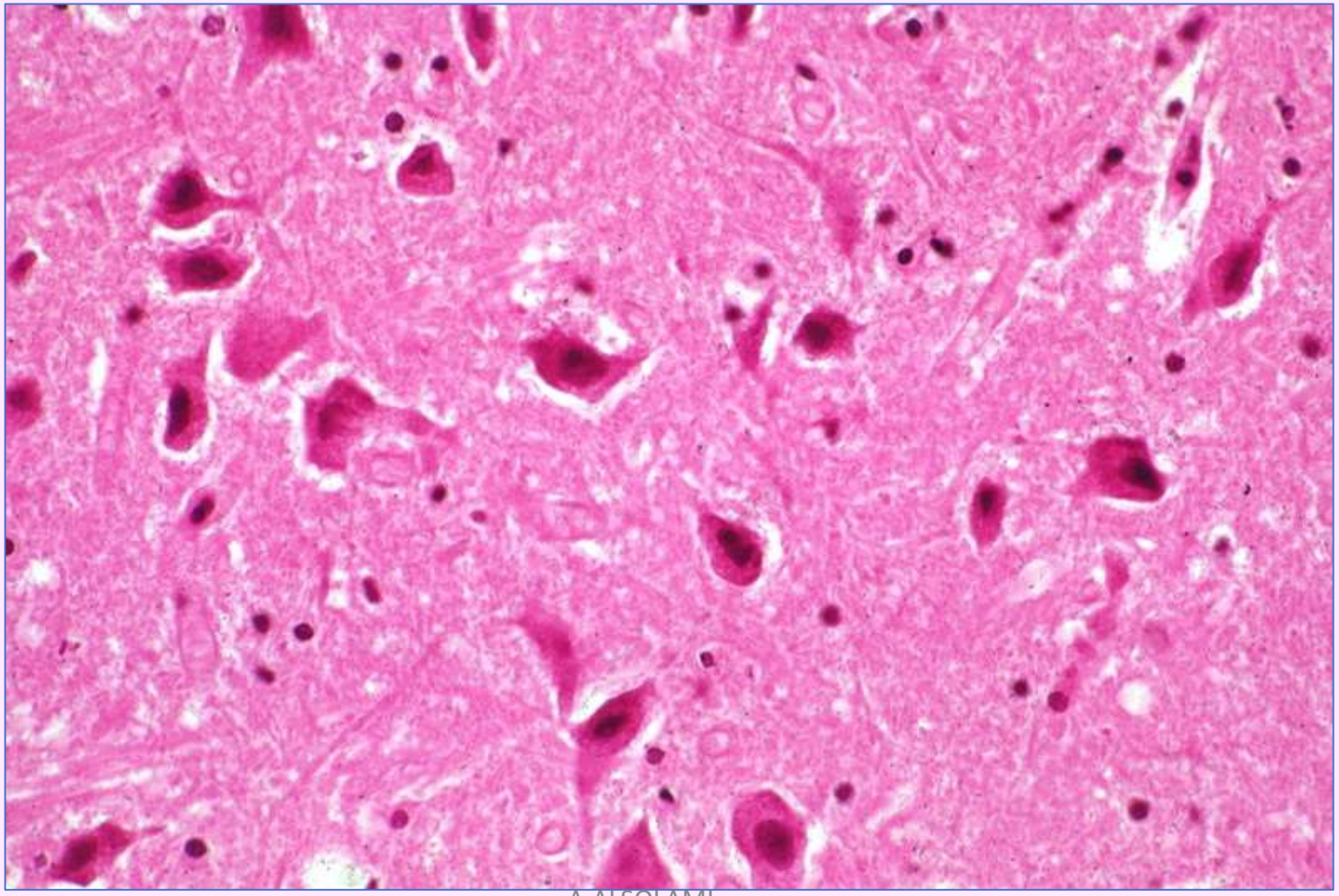
Edema



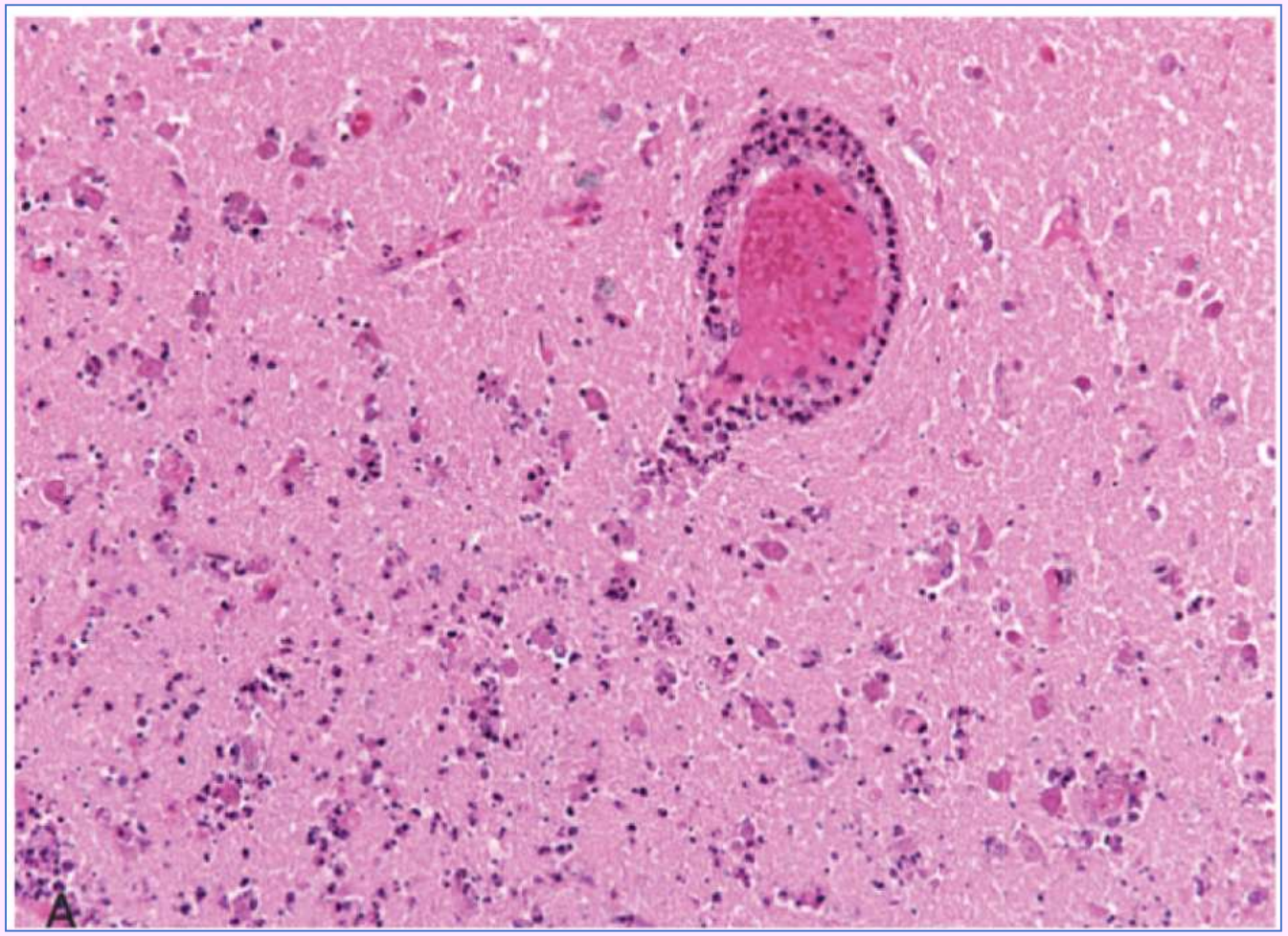
Microscopically

Early changes (12-24 H)	Subacute changes (24 H- 2 W)	Repair (after 2 W)
• Red neurons; characterized initially by microvacuolization, cytoplasmic eosinophilia, and later nuclear pyknosis and karyorrhexis. • Similar changes occur later in glial cells.	• The reaction to tissue damage begins with the infiltration by neutrophils. • Necrosis of tissue, influx of macrophages, vascular proliferation and reactive gliosis.	• Removal of all necrotic tissue • Loss of the organized CNS structure • Gliosis

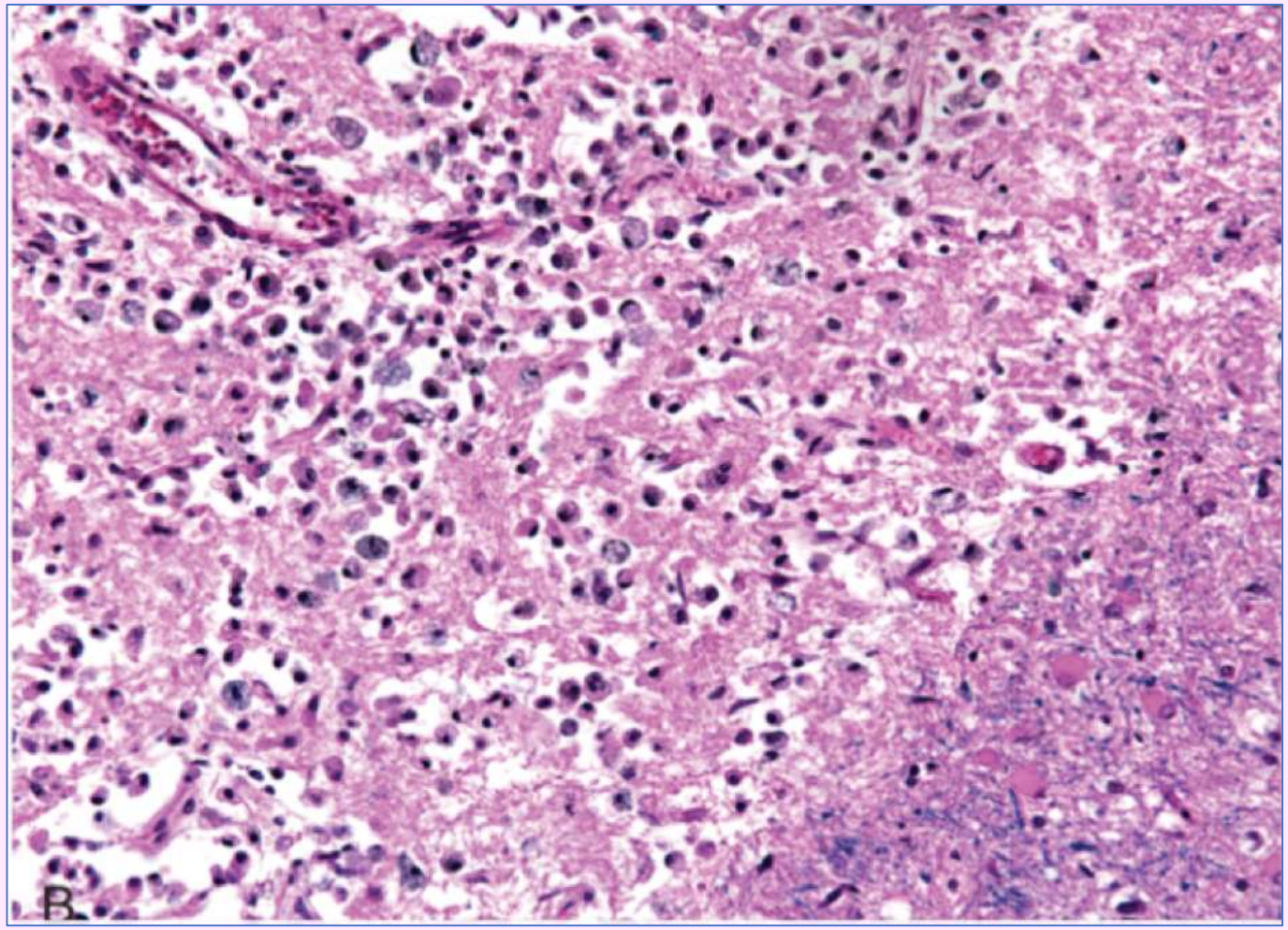
Red (angry) Neurons… Early



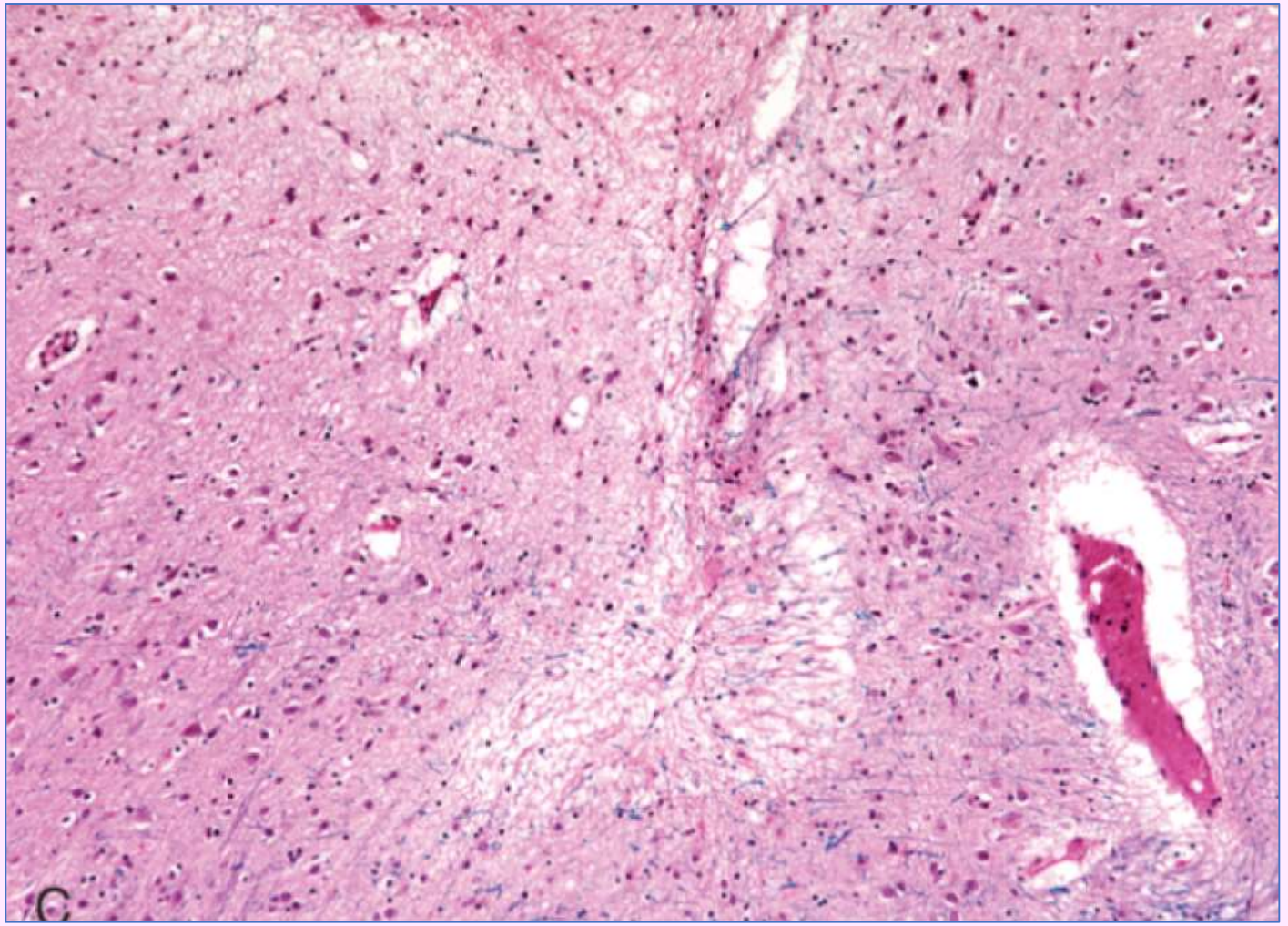
Infiltration of a cerebral infarction by neutrophils begins at the edges of the lesion where the vascular supply is intact…. **Subacute**



By day 10, an area of infarction shows the presence of macrophages and surrounding reactive gliosis… **Subacute**



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



Border Zone (Watershed) Infarcts

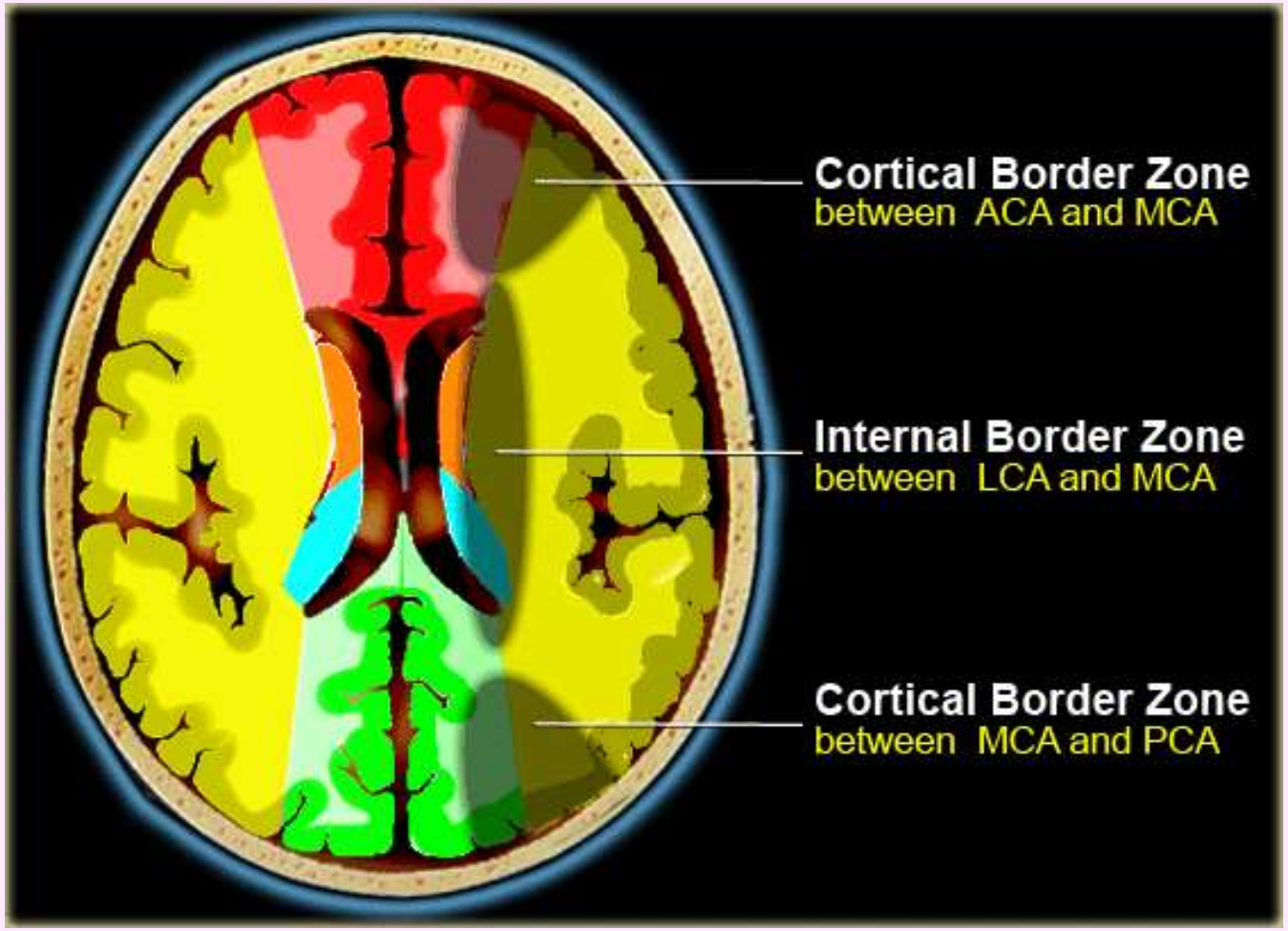
- Wedge-shaped areas of infarction that occur in those regions of the brain & spinal cord that lie at the most distal fields of arterial perfusion.

- In the cerebral hemispheres, the border zone between the anterior and the middle cerebral artery distributions is at greatest risk.

Border Zone (Watershed) Infarcts

- Damage to this region produces a wedge-shaped band of necrosis over the cerebral convexity.
- Border zone infarcts are usually seen after hypotensive episodes.

Border Zone (Watershed) Infarcts



Focal Cerebral Ischemia

- Cerebral arterial occlusion leads first to focal ischemia then an infarction in the distribution of the compromised vessels.

- The size, location and shape of the infarct and the extend of tissue damage may be modified by collateral blood flow.

Focal Cerebral Ischemia

- 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

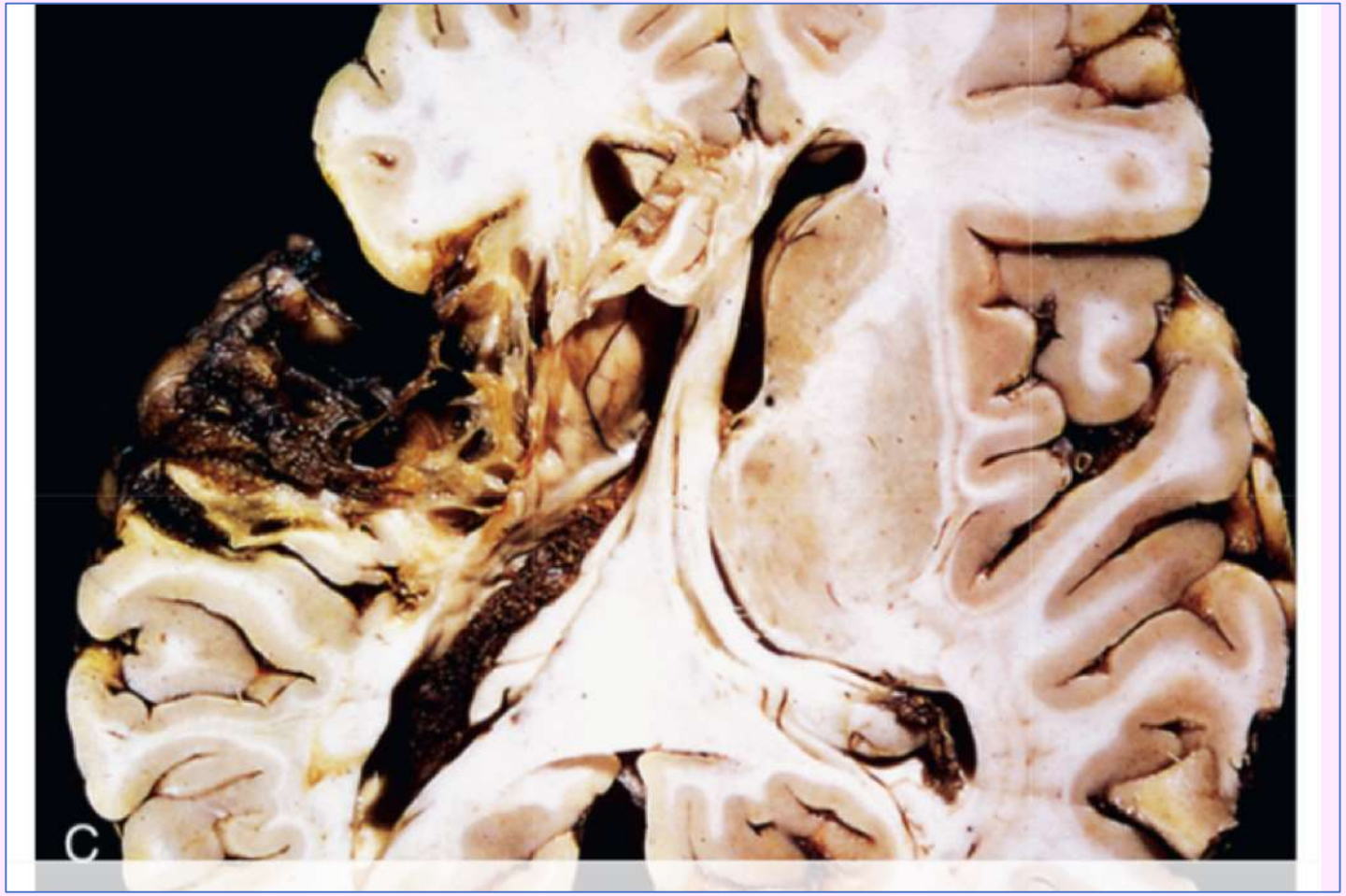
Focal Cerebral Ischemia

- Infarcts can be divided into two broad groups based on their macroscopic and corresponding radiologic appearance:
  - Non hemorrhagic infarcts; which result from acute vascular occlusions.
  - Hemorrhagic infarcts; which result from reperfusion of ischemic tissue, either through collaterals or after dissolution of emboli, and often produce multiple, sometimes confluent petechial hemorrhages.

Histopathological Features of Non-Hemorrhagic Infarcts macroscopically

First 6 hours	By 48 hours	2-10 days	Day 10- week 3
the tissue is unchanged in appearance.	the tissue becomes pales, soft and swollen.	the tissue becomes gelatinous, friable and the boundary between normal and abnormal tissue becomes more distinct as edema resolves in the adjacent viable tissue.	the tissue liquifies leaving a fluid-filled cavity which gradually expands as dead tissue is resorbed.

Old cystic infarct shows destruction of cortex and surrounding gliosis



Histopathological Features of Non-Hemorrhagic Infarcts Microscopically

- Microscopically:
  - After the first 12 hours:
    - Ischemic neuronal change (red neurons) and edema.
    - Endothelial & glial cells swell & myelinated fibers begin to disintegrate.
    - Loss of the usual characteristics of white and gray matter structures
  - During the first several days neutrophils infiltrate the area of injury.

Histopathological Features of Non-Hemorrhagic Infarcts

- Microscopically:
  - 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.

Histopathological Features of Non-Hemorrhagic Infarcts

- Microscopically:
    - 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 the cortex.
    - The pia and arachnoid are not affected and do not contribute to the healing process.

Histopathological Features of Hemorrhagic Infarcts

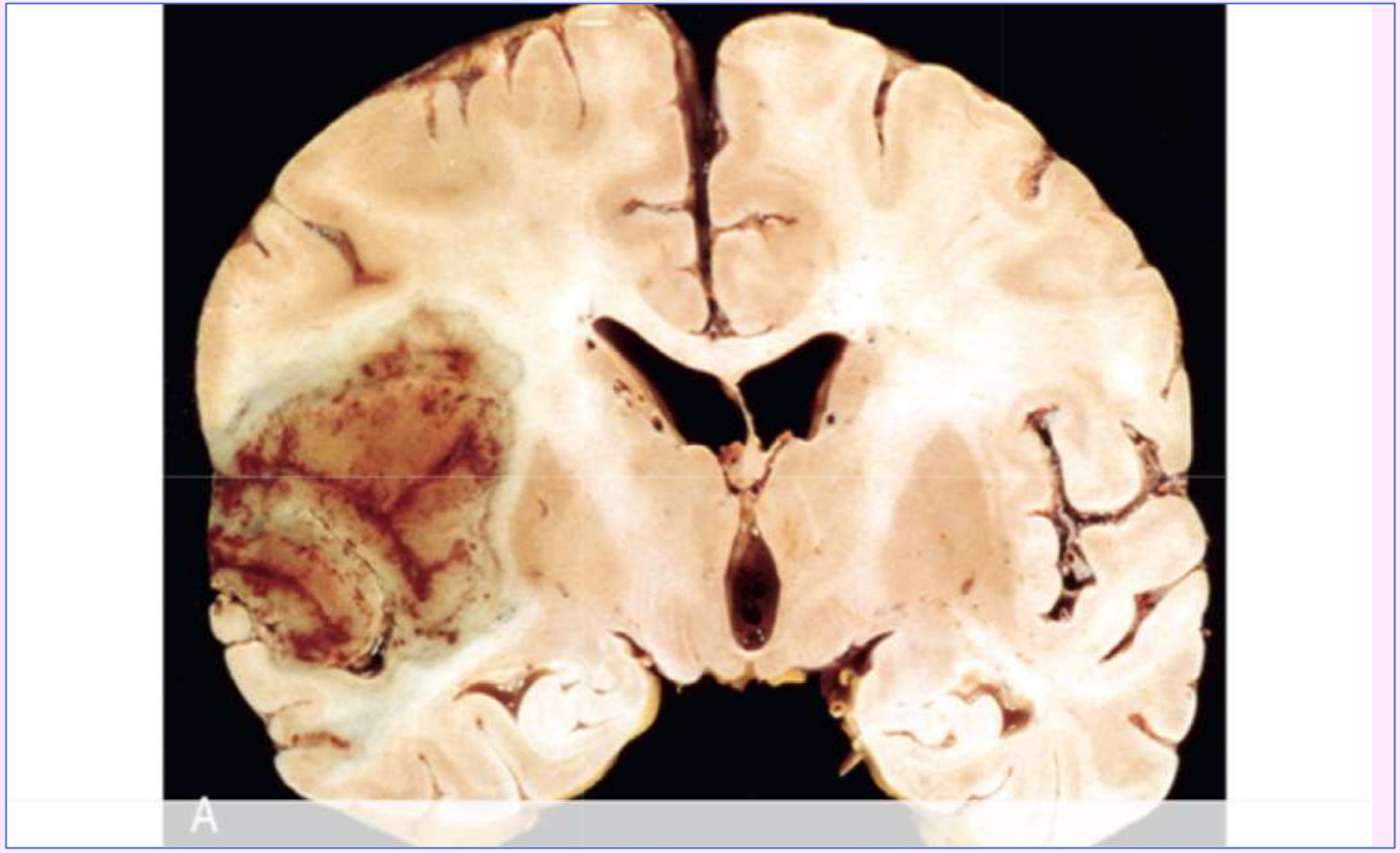
- Hemorrhagic infarcts usually manifest as multiple, sometimes confluent petechial hemorrhages.

- The microscopic picture and evolution of hemorrhagic infarction parallel those of ischemic infarction, with the addition of blood extravasation & resorption.

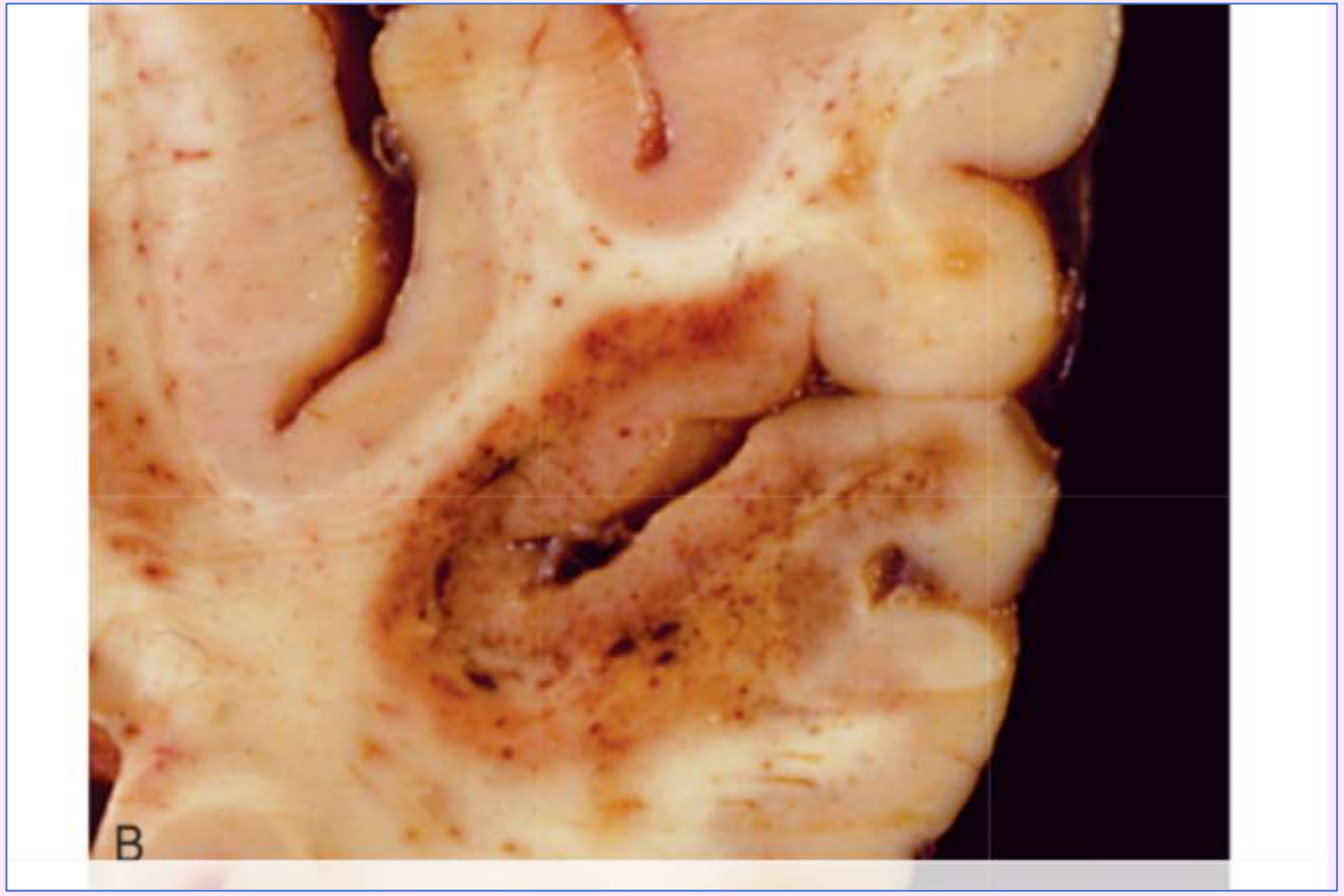
Histopathological Features of Hemorrhagic Infarcts

- In individuals with coagulopathies or receiving anti-coagulants, hemorrhagic infarcts may be associated with extensive intracerebral hematomas.

A section of the brain showing a large discolored focally hemorrhagic region in the left middle cerebral artery distribution (hemorrhagic or red infarction).



An infarct with punctate hemorrhages, consistent with ischemia-reperfusion injury, is present in the temporal lobe.



Reference

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