Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

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(III) **Tonsillar herniation (F9-82) is displacement of the cerebellar tonsils through the foramen magnum.**

☠ This herniation is **life-threatening & usually ☠ fatal**, because it causes brain stem compression & compromises vital respiratory & cardiac centers in the medulla.

Lec. 5

CEREBROVASCULAR DISEASES ("Stroke")

▲ Cerebrovascular disease is the 3rd (after IHD & cancer) common cause of death in US; & it is also, the most prevalent neurologic disorder in terms of both morbidity & mortality.

★ *Cerebrovascular disease* means **{any abnormality of the brain caused by blood vessel (BV) pathologic process}.**

Brain injury. Atheroma في BVs في lesion ← ischemic heart disease

☹ The 3 basic processes are occlusion of BV by (1) **Thrombus** or (2) **Embolus; or** (3) **BV rupture**, causing **Hemorrhage**

★ The first 2 share many characteristics, because their effect on the brain is the same ➔ the loss of oxygen & metabolic substrates, resulting in **ischemic injury** ➔ **brain infarction** of specific regions of the brain **(regional effect),** depending on the BV involved.

permenant death of the neurological area.

★A similar pattern of **ischemic injury** may occur **diffusely** when there is complete loss of perfusion (**Global ischemia**).

★**Rupture of BV results in hemorrhage,** leads to direct tissue damage + as well as secondary ischemic injury.

►**"Stroke" (i.e., Hit or Blow)** is the clinical designation that applies to all these conditions, particularly when symptoms begin **acutely**.

Hypoxia, Ischemia, & Infarction

☺ The brain requires a constant delivery of glucose& oxygen from the blood. Although the **brain** accounts for only **1% to 2%** of **body weight**, it receives **15% of the resting cardiac output** & accounts for **20% of the total body oxygen consumption**.

☺ Cerebral blood flow remains constant over a wide range of blood pressure & intracranial pressure because of autoregulation of vascular resistance (What are these?)

☹ The **brain is a highly aerobic tissue, & can be deprived** of oxygen by one of several mechanisms:

{A} ***Functional hypoxia*** in a setting of a low partial pressure of oxygen (PO_2); impaired oxygen-carrying capacity; inhibition of oxygen use by tissue; or

as anemia.

{B} Interruption or ↓ of the normal blood flow **with the resulting *Ischemia*, (*transient* or *permanent*),** due to either:

(1) Reduction in perfusion pressure, as in hypotension, or
(2) Secondary to vascular obstruction, or (3) Both.

Global Cerebral Ischemia

معلومة

▶When the **systolic BP decease to less than 50mm Hg** due to **(1) cardiac arrest, (2) shock, or (3) severe hypotension,** it causes generalized reduction of cerebral perfusion, **resulting** in widespread cerebral ischemic/hypoxic injury. → بتشمل كل الدماغ

▲The clinical outcome varies with the severity of the insult.
☺ When **mild**, there may be only a **transient post ischemic confusional** state, with eventual complete recovery. الشخص كس في حالة شبه إغماء وتشويش وبعدين بيختفي.
☹ **Irreversible** damage of CNS tissue does occur in some individuals who suffer mild or transient global ischemic insults.

☹ **Neurons** are much more sensitive to hypoxia than are **glial** cells. There is also variability in the susceptibility of different populations of neurons in different regions of the CNS; ☹ **Pyramidal cells of the Sommer sector** (CA1) of the hippocampus, **Purkinje cells of the cerebellum**, & **pyramidal neurons in the neocortex** are the *most susceptible* to ischemia of short duration.

▼ In **severe** global cerebral ischemia, **widespread** neuronal death, irrespective of regional vulnerability, occurs. Individuals who survive in this state often remain severely impaired neurologically, & deeply comatose **(persistent vegetative state)**.

☠ Other patients are in **"brain death,"** state with cortical injury **(isoelectric or flat electroencephalogram, EEG)** & brain stem damage, including absent reflexes & respiratory drive.

☠ When patients with this severe form of injury are maintained on mechanical ventilation, the **brain** gradually undergoes an **autolytic** process, resulting in the so-called **"respirator brain."**

▶**GROSSLY,** in **global ischemia**, the brain is **swollen**, with **wide gyri** & **narrowed sulci, C/S** shows **poor demarcation between gray & white matter.**

◘ H, the changes of infarction is grouped into 3 categories:

(1) **Early changes,** occurring 12 to 24 hours after the insult, include acute **neuronal cell change** (red neurons; F23-1A) characterized → initially by microvacuolization, → followed by cytoplasmic eosinophilia, & → later nuclear pyknosis & karyorrhexis **(necrosis).** Similar changes occur somewhat later in **astrocytes & oligodendroglia**. After this, the **reaction** to tissue damage begins with infiltration by neutrophils (F23-6A).

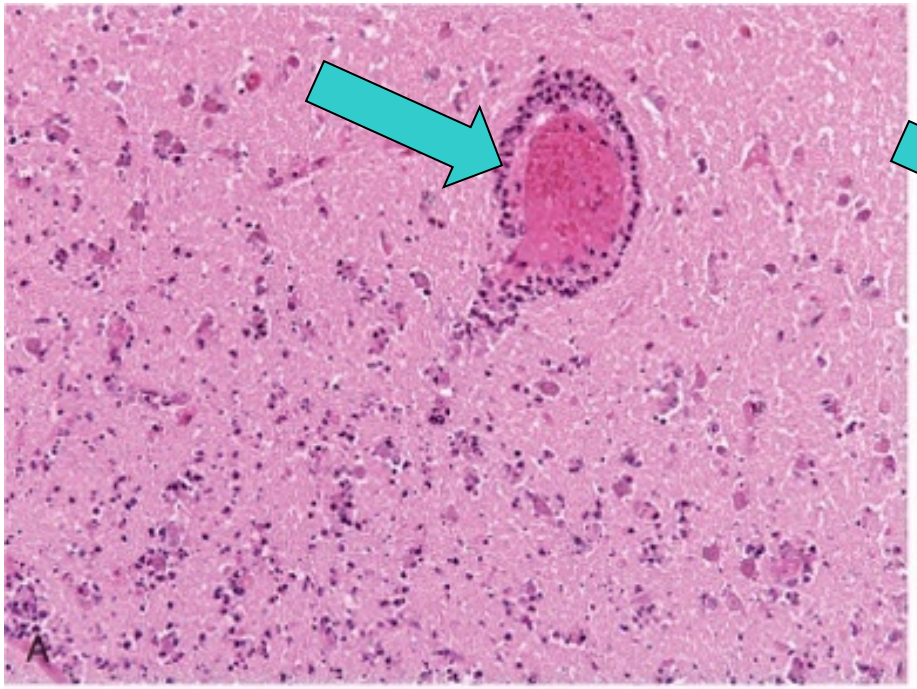
(2) **Subacute changes,** occurring at 24 hours to 2 weeks, include necrosis of tissue, influx of macrophages, vascular proliferation, & reactive gliosis (F23-6B).

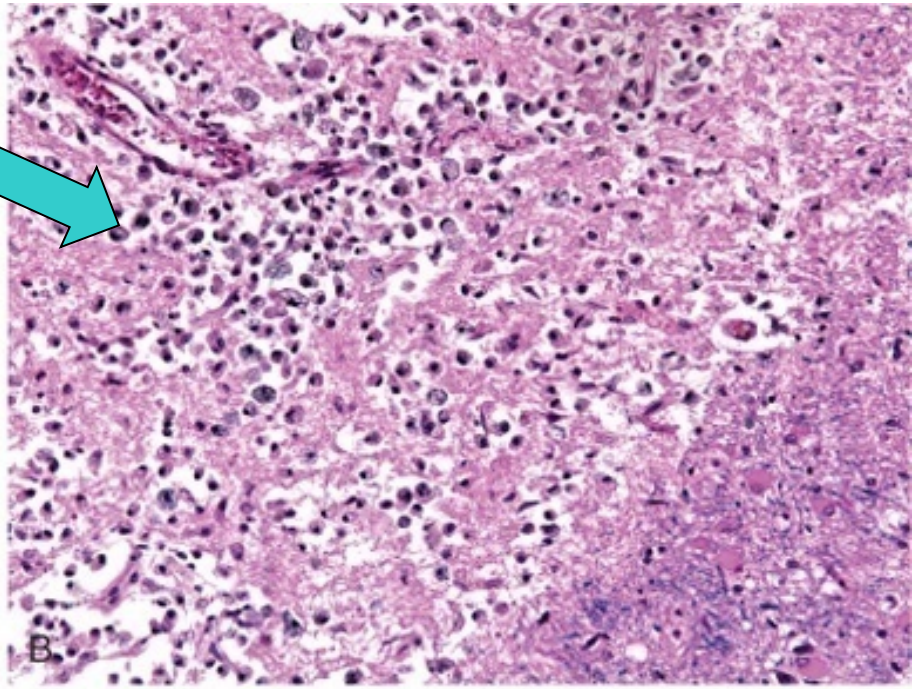
(3) **Repair,** seen after 2 weeks, is characterized by **removal** of all necrotic tissue, **gliosis & loss of organized CNS structure,** (F23-6C & ◘ 4.4). In the cerebral cortex the neuronal loss & gliosis produce an uneven destruction of the neocortex, with preservation of some layers & involvement of others - a pattern termed **pseudo laminar necrosis.**

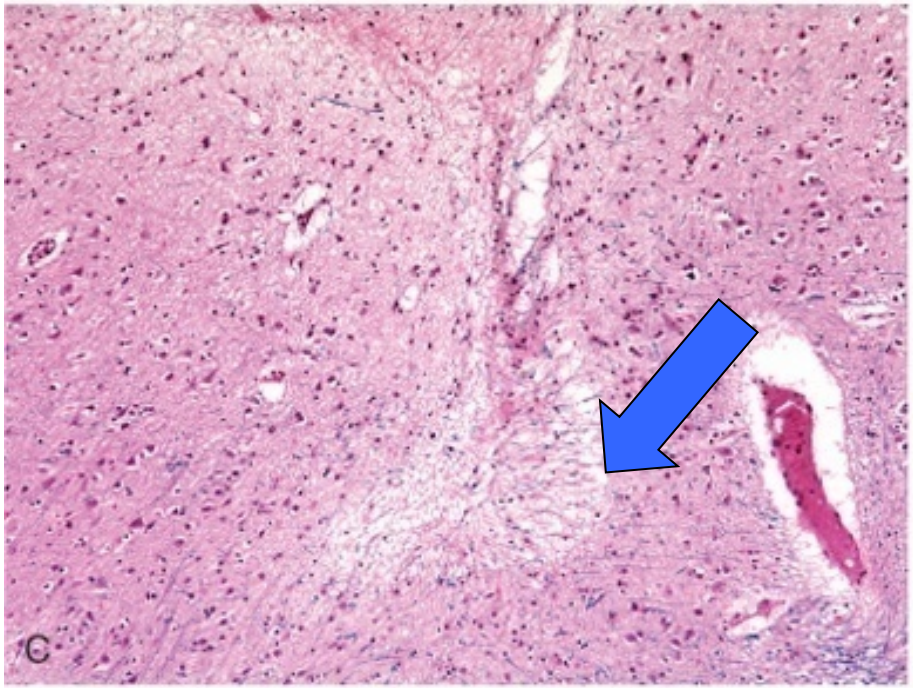
ذوبان النواة nucleus.

white, grey matter all are lost.

fibrous tissue ولكن هو مجرد neuron كاذب تُمثل pattern







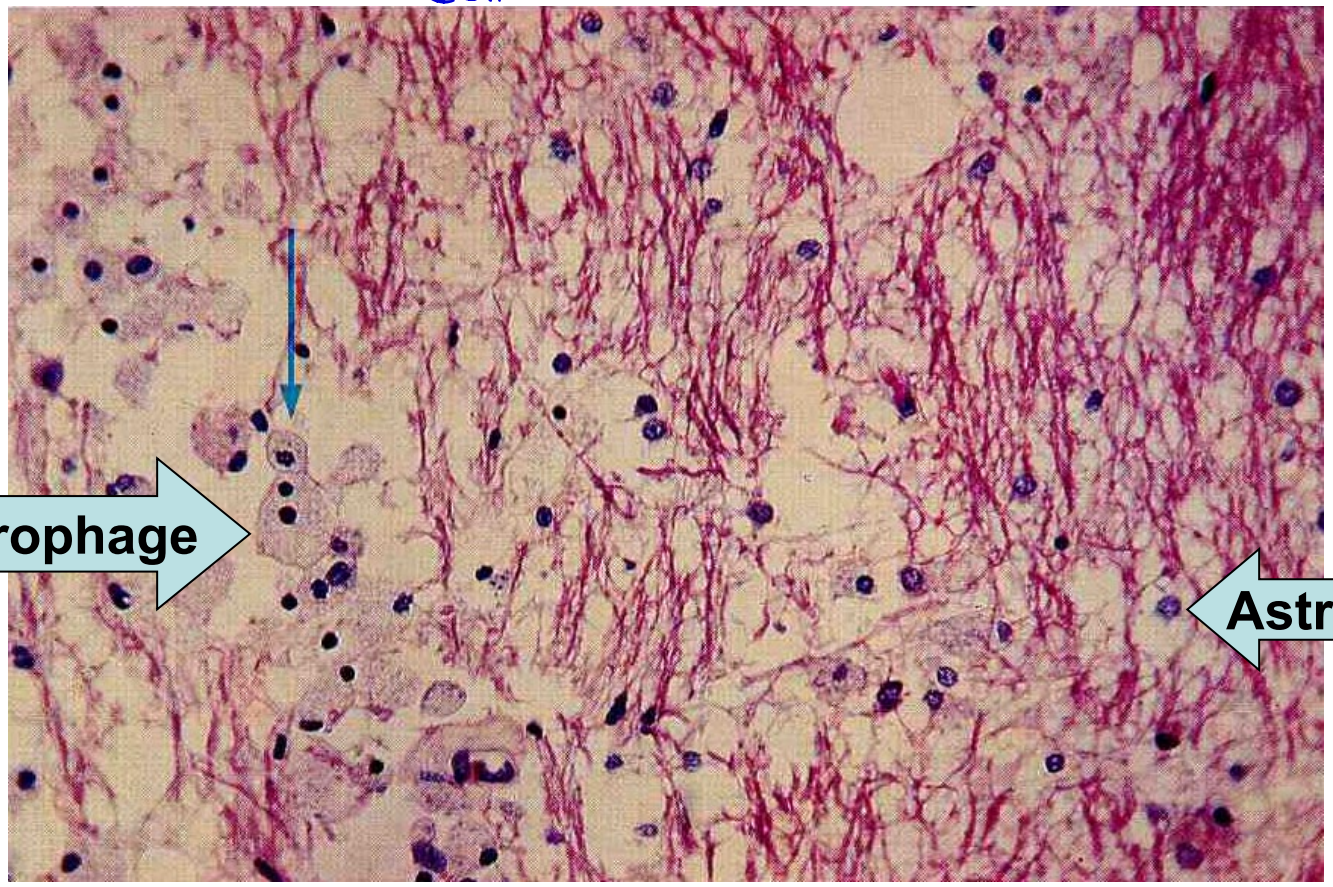
F 23-6: Cerebral infarction **(CI)** .

A, Recent CI **infiltrated** by neutrophils, begins at the edges of the lesion from intact BV.

B, After 10 days, the CI is infiltrated by macrophages & surrounded by reactive gliosis. → dead neurons ميت تحوّض اك

C, Old small intracortical CI seen as areas of tissue loss with a small amount of residual gliosis. no any neuron. ما بنقدر نعرف عمرها

◘4.4; **Brain infarction** of 6 weeks duration X335. White matter (I) Most **myelinated fibers** undergone ischemic necrosis & **disappeared.** (II) large round **Macrophages** with foamy cytoplasm **(**from phagocytosed lipoproteins of the necrotic tissue), lying in the spaces between the surviving fibers. (III) **Astrocytes** with small round basophilic nuclei & ill-defined cytoplasmic boundaries. foamy cell ابتلعت كل ال lipoprtns لذلك بتبين ال macrophages



★**Border zone ("watershed") infarcts {**usually seen **after hypotensive episodes}** are 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**. → are the least perfused.

★In the cerebral hemispheres, the border zone between the anterior & the middle cerebral artery distributions is at **greatest risk**. Damage to this region produces a band of necrosis over the cerebral convexity, a few cm lateral to the interhemispheric fissure.

Focal Cerebral Ischemia

Cerebral arterial **occlusion** leads to → **focal ischemia** **& -if sustained- to** ➔ **infarction** of CNS tissue in the distribution of the occluded BV.

★ The site, size, & shape of the resulting infarct are determined by many factors, the most important of which is 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 the **thalamus**, **basal ganglia, & deep white matter**. مافي collaterals في هذه المناطق

☹ Arterial occlusion leading to cerebral infarction is due to: معهم

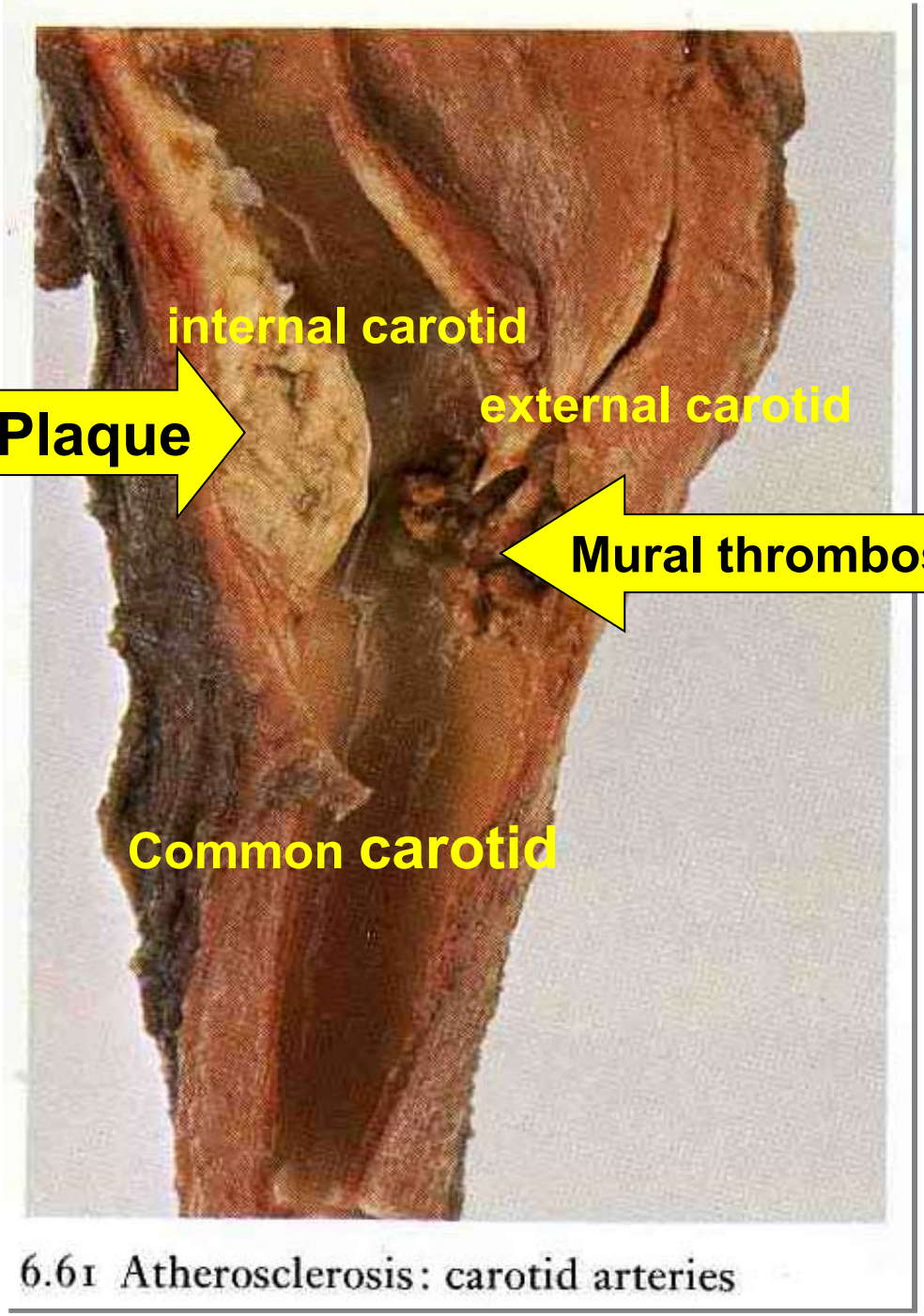
(1) Most commonly, ***Embolization*** from a distant source, Or
(2) Less commonly, ***In situ thrombosis.***

➔ (1) Overall, **embolic** infarctions are **more common**.
★**Cardiac mural thrombi** are a frequent source, including:
• atrial fibrillation • valvular disease, & • MI; most common.
★ *Thromboemboli* arising most often from atheromatous plaques within the carotid **arteries** (F6-61). atrial septic defect منها طلعت ال embolus ووصلت لل brain.
★ **Other** sources are • **paradoxical** emboli, particularly in children with cardiac anomalies; • emboli associated with **cardiac surgery**; & • other rare **tumor, fat, or air** emboli.

☹ The **territory** of distribution of the **middle cerebral artery** (the direct extension of the internal carotid artery) is **most** frequently affected by embolic infarction; **emboli tend to lodge** where vessels **branch** or in areas of preexisting luminal **stenosis.**

معرضة

ال emboli بتوقف في نقطة ال branching او في اي نقطة فيها narrowing.



6.61 Atherosclerosis: carotid arteries

F6.61: Yellow-white ☹ **calcified atheromatous plaque** at the origin of the Rt internal carotid artery (top left), causing marked luminal stenosis. Opposite the plaque, at the origin of the Rt. external carotid artery, there is an irregular small brown mass of ☹ **mural thrombosis**.

➔ (2) Most of ***in situ*** primary ***thrombotic occlusions*** causing cerebral infarctions are due to ***atherosclerosis;*** **the most common sites** of which are the:

(1) **carotid bifurcation** (F6.61), the

(2) **origin of the middle cerebral artery**, &

(3) at either end of the **basilar artery**.

→ **Thrombosis,** superimposed on atherosclerotic stenoses, can be accompanied by anterograde (forwards) extension, fragmentation, & → **distal embolization!**

►Based on their macroscopic & corresponding radiologic appearance, infarcts (F23-7) can be divided into 2 groups:

(A) ***Nonhemorrhagic infarcts*** can be treated, ☺ if identified **shortly** after presentation with thrombolytic = thrombolysis = dissolution of thrombus therapies, by **streptokinase** or tissue plasminogen activator, **(t-PA)**,

Thrombolytic therapies approach for the ***Nonhemorrhagic infarcts*** is **contraindicated** when lesions are of the second group, the…

- (B) ***Hemorrhagic infarcts*** (F23-7A & B), in which, multiple confluent petechial hemorrhages occurs secondary to **Reperfusion** of ischemic tissue, either through
  (1) **collaterals** or,
  (2) after **dissolution** of intravascular occlusions.

Reperfusion injury → أذى بسبب إعادة الدم.

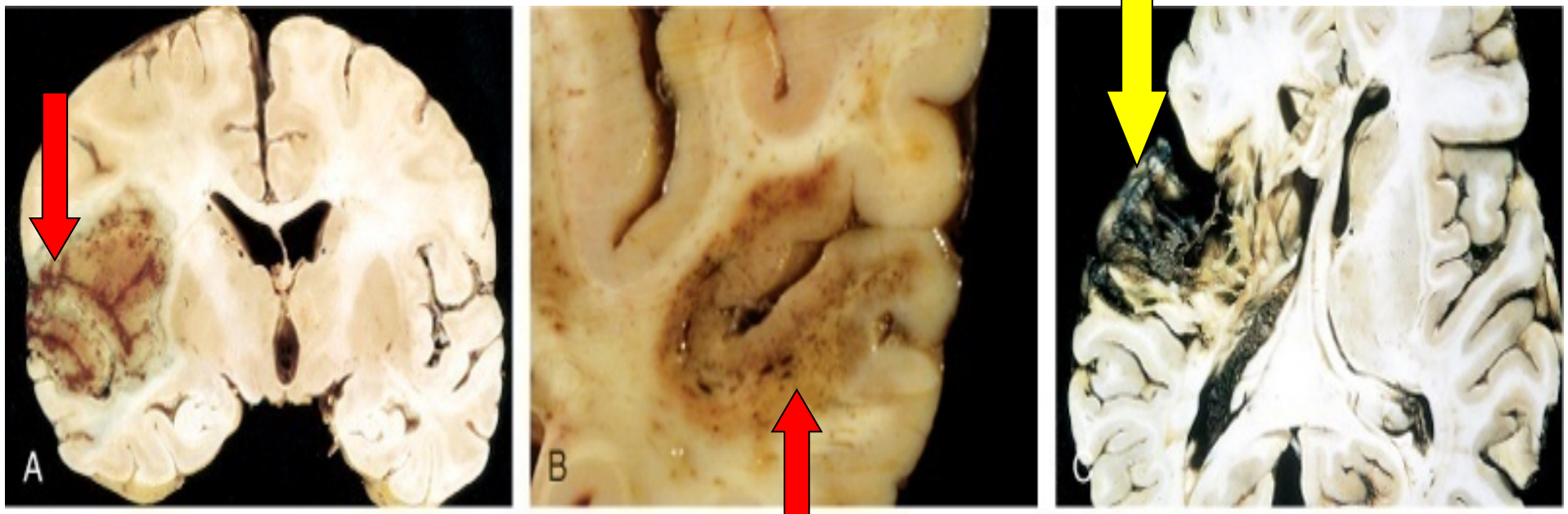
😐 is **mediated** by oxygen free radicals (**FR**) generated by the ↑ number of infiltrating WBC facilitated by reperfusion;

☹ it can incite *greater* local damage than might have otherwise occurred without **rapid** restoration of blood flow! لذلك لازم الـ restoration يكون gradual.

Reperfusion-induced microvascular injury, causes **hemorrhage.**

F23-7: **Cerebral infarction**. Brain sections showing:
A, Large red hemorrhagic infarct in the distribution of the left middle cerebral artery.
B, Temporal lobe red infarct, with punctate hemorrhages, due to **ischemia-reperfusion injury**,
C, Old cystic infarct, shows destruction of cortex & surrounding gliosis.

multiple tiny hemorrhages.



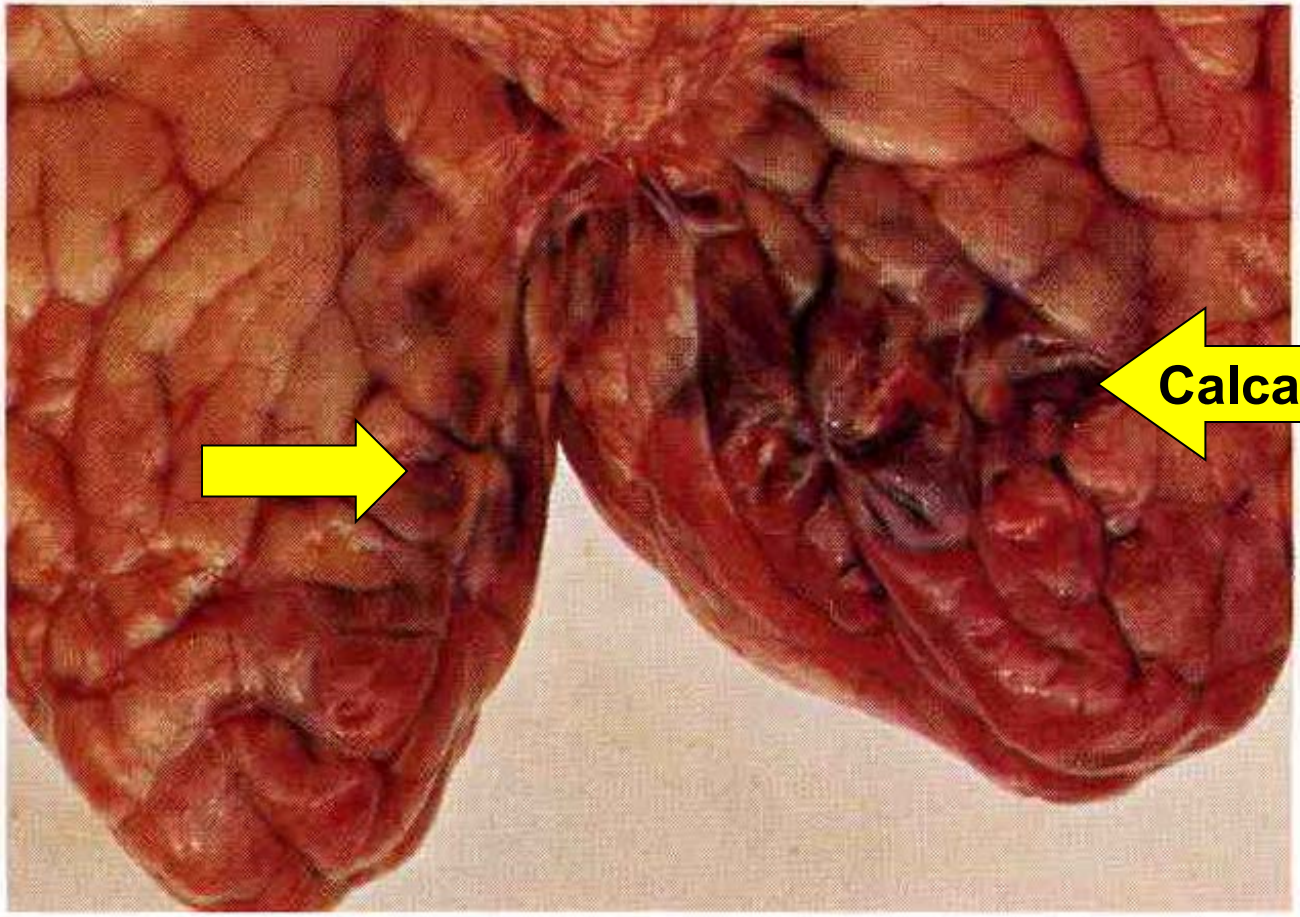
▶ Grossly, the **nonhemorrhagic infarct** changes in time.

- In the first **6 hours** of irreversible injury, **little** can be seen.
- By **48 hours**, the infarct becomes **pale**, **soft** & **swollen**, & the corticomedullary junction becomes **indistinct.**
- From **2 to 10 days** the infarct becomes **gelatinous & friable**, & the previously ill-defined boundary between normal & abnormal tissue becomes **more distinct** as edema resolves in the adjacent tissue that has survived (F9-47).
- From **10 days to 3 weeks**, the necrotic tissue **liquefies** (**Liquefaction necrosis**), eventually leaving **a fluid-filled cavity** (F1-11) **lined by dark gray tissue**, which gradually expands as dead tissue is removed (F23-7C & 9-46).

◙ H, the tissue reaction follows a characteristic sequence:

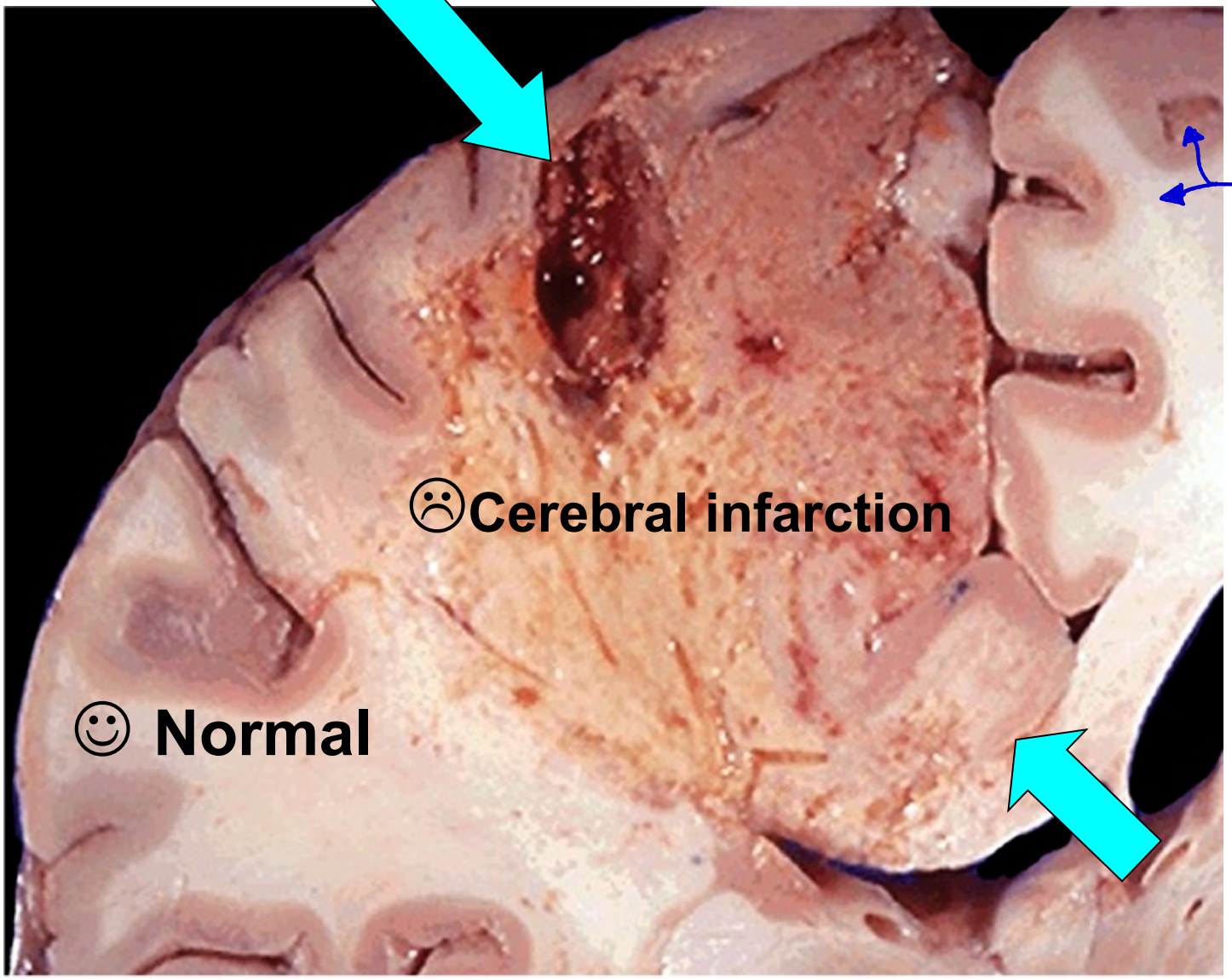
★ **After the first 12 hours** ischemic **neuronal necrosis** (**red neurons,** F23-6A) & **edema** (both cytotoxic & vasogenic) predominate. There is loss of the usual tinctorial characteristics of white & gray matter structures. EC & glial cells (mainly astrocytes) swell, & myelinated fibers begin to disintegrate.

F 9.47: Infarction: Brain. ☠The patient had transtentorial herniation obstructing the posterior cerebral arteries, resulting in **recent hemorrhagic infarction** of the infero-medial aspects of both occipital lobes, especially affecting the calcarine area.



9.47 Infarction: brain

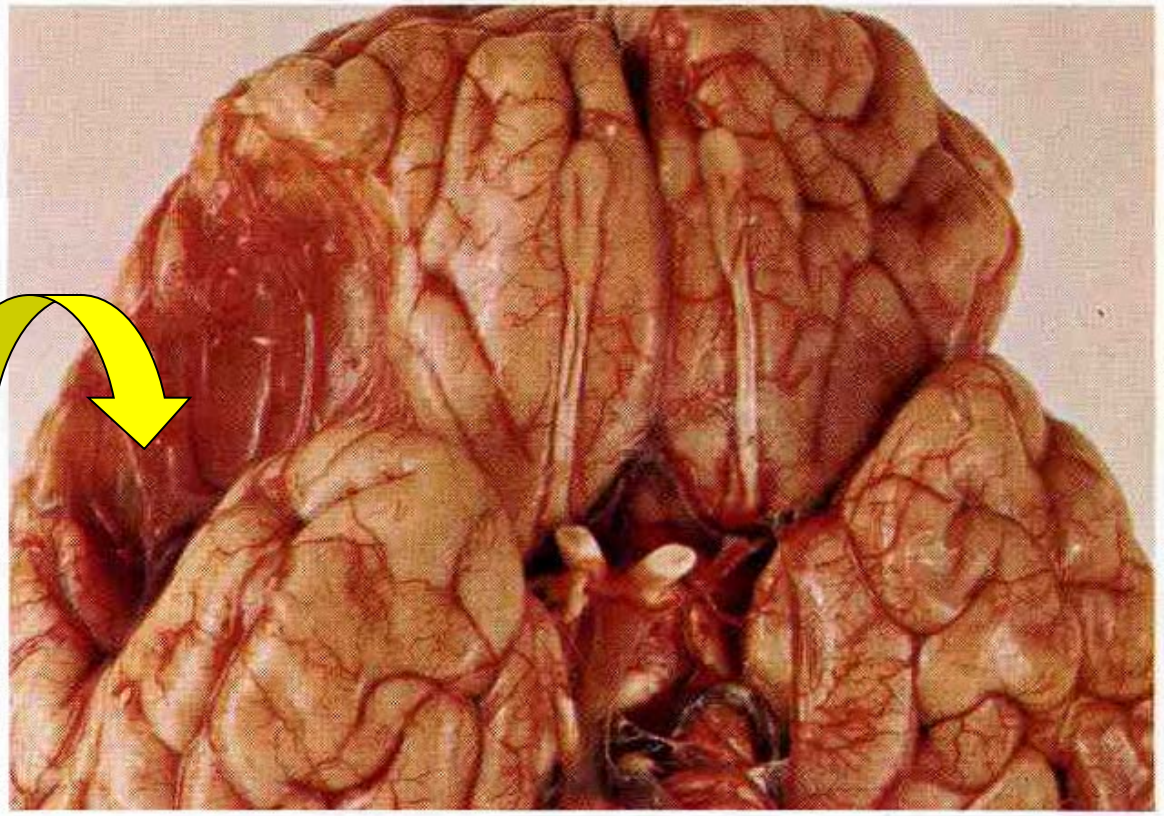
F1-11: **Brain:** Cerebral infarct, 10 to 21 days after stroke, liquefactive necrosis of the brain tissue, eventually leaving **a fluid-filled cavity.**



Normal Cerebral grey & white matter.

F 9.46: Infarction: Brain. The patient had chronic RHD with left **atrial thrombus** ⇨ **embolization** of which in the ⇨ Rt. middle cerebral artery causes large **infarction** of the ⇨ inferior aspect of the right fronto-temporal region. The **old infarct** appears as a large '**cavity**', covered by a thin, brown membrane, which is either filled with clear fluid or, appears collapsed (as here).

Old infarct



9.46 Infarction: brain

★**Up to 48 hours,** there is **neutrophilic** emigration followed by **mononuclear** phagocytic cells in the following **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 & liquefaction proceeds, **astrocytes** at the edges of the lesion progressively enlarge, divide, & develop a prominent network of protoplasmic extensions. "Gliosis" NO هل في دور لـ fibroblasts هنا؟ → فقط في الـ Abcess or penetrating brain injury.

★ **After several months** the striking astrocytic nuclear & cytoplasmic enlargement recedes.

• In the **wall** of the cavity, astrocyte processes form a dense **gliosis** (network of **glial fibers admixed with new capillaries)** & a few perivascular connective tissue fibers.

In the cerebral cortex, the cavity is delimited (separated) from the meninges & subarachnoid space by a **gliotic layer of tissue**, derived from the molecular layer of cortex.

The pia & arachnoid are not affected & do not contribute to the healing process.

(B)◘ The H & evolution of **hemorrhagic** infarction **parallel ischemic** infarction, with the **addition of blood extravasation & resorption**.

لذلك الـ macrophages تحتوي على hemosidren أكثر

☹ In persons receiving anticoagulant treatment, hemorrhagic infarcts may be associated with extensive intracerebral hematomas.

Intracranial Hemorrhage (H)

معلومة

➔**H** within the skull can occur in many locations, & each one is associated with a set of underlying causes:

★ **Intraparenchymal H** = **H** within the brain itself : أكثر من 90٪ من الحالات

(1) Most commonly occur secondary to **hypertension**, or

(2) other forms of vascular wall injury, or specific lesion like an arteriovenous **(AVM)** or cavernous malformation, or / an intraparenchymal tumor.

معلومة

★**Subarachnoid H most commonly** result from (1) rupture of **Berry aneurysms**, (2) less commonly from rupture of other vascular malformations.

★**Dural (epidural or subdural) H** are usually **traumatic**.

Primary Brain Parenchymal Hemorrhage (H)

▶ **Spontaneous (nontraumatic)** intraparenchymal **H** occur most commonly in mid to late adult life, with a peak incidence at about 60 years of age. Most are caused by **rupture** of ***Charcot-Bouchard microaneurysms*** in an hypertensive.

★ **Hypertension** is the most common underlying cause & brain **H** accounts for **15%** of deaths among chronic hypertensives.

★ Typically, hypertensive intraparenchymal H occurs in **basal ganglia, thalamus, pons, & cerebellum** (F23-8,9-42 & 43),

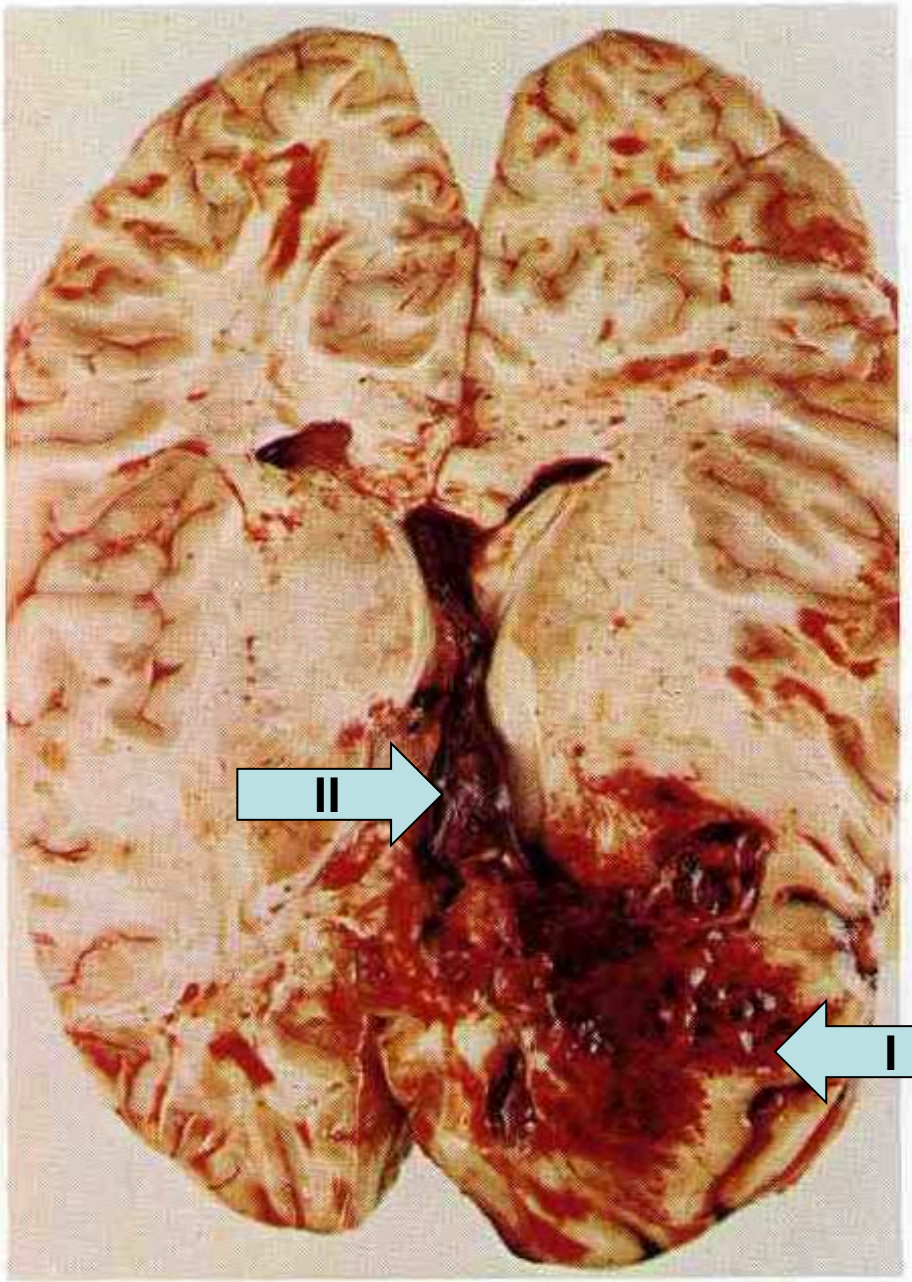
☠ Intracerebral **H can be clinically devastating** & ☠ **fatal** when it affects large portions of the brain; & it may extends into the ventricular system; or 😐 **Intracerebral H can affect small regions & be clinically silent.**

Over weeks or months there is a *gradual resolution* of the hematoma, sometimes with considerable clinical improvement.

😐 Again, the **site & size** of the **H** will determine the clinical manifestations.

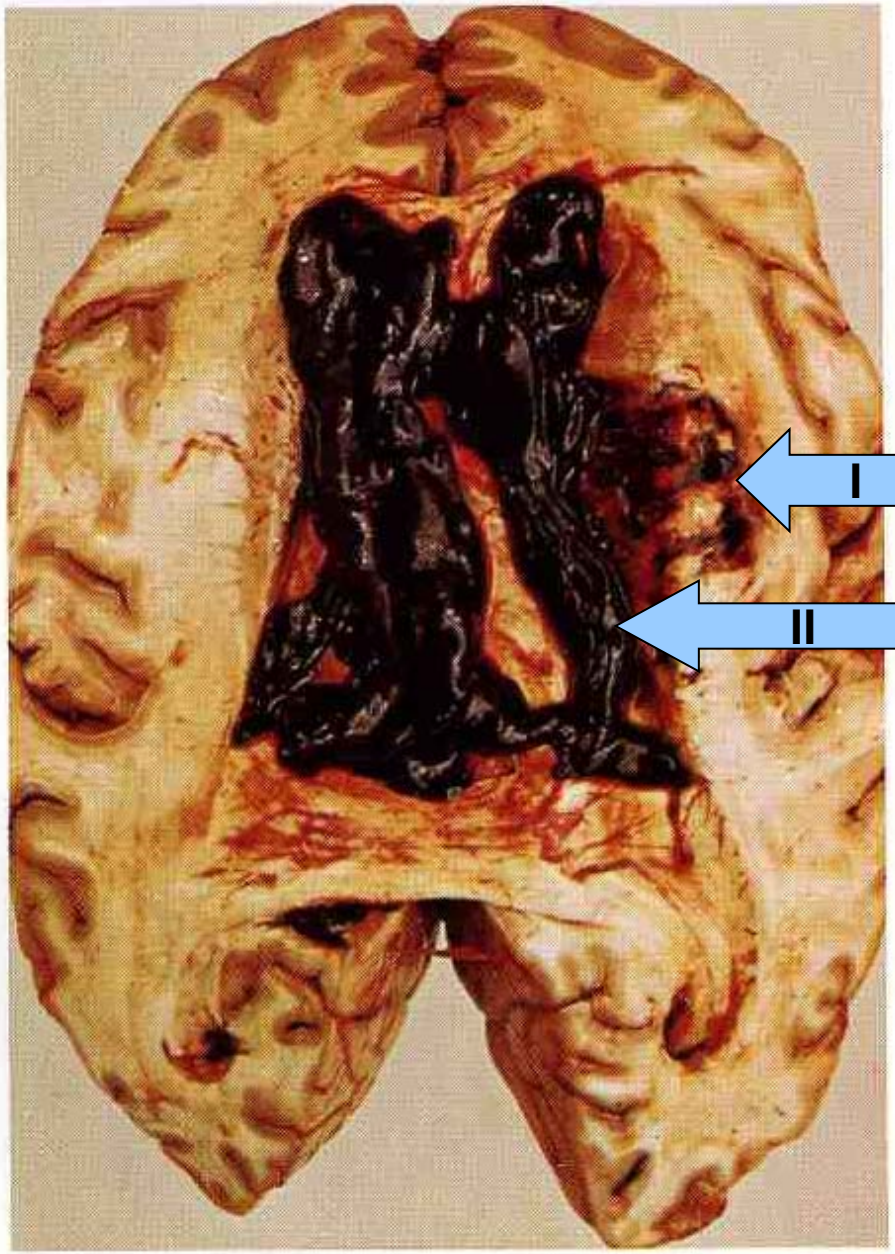
* small → may be clinically silent
* Moderate → may undergo resorption followed by gliosis
* Devastating → fatal (secondary ventricular hemorrhage)

F23-8: **Cerebral hemorrhage.** Massive hypertensive hemorrhage rupturing into a lateral ventricle.



9.41 Intracerebral haemorrhage: brain

F 9-41: **Recent intracerebral hemorrhage: brain.**
(I) Recent, large hemorrhage in the right occipital pole, extending to **(II)** the lateral ventricle.



9.42 Intracerebral haemorrhage: brain

F 9-42: **Intracerebral hemorrhage: brain.**

(I) There is ragged → ممزق. hypertensive intracerebral hemorrhage in the region of **right lentiform nucleus** (top right) which ruptured into & fills **(II)** both lateral ventricles.

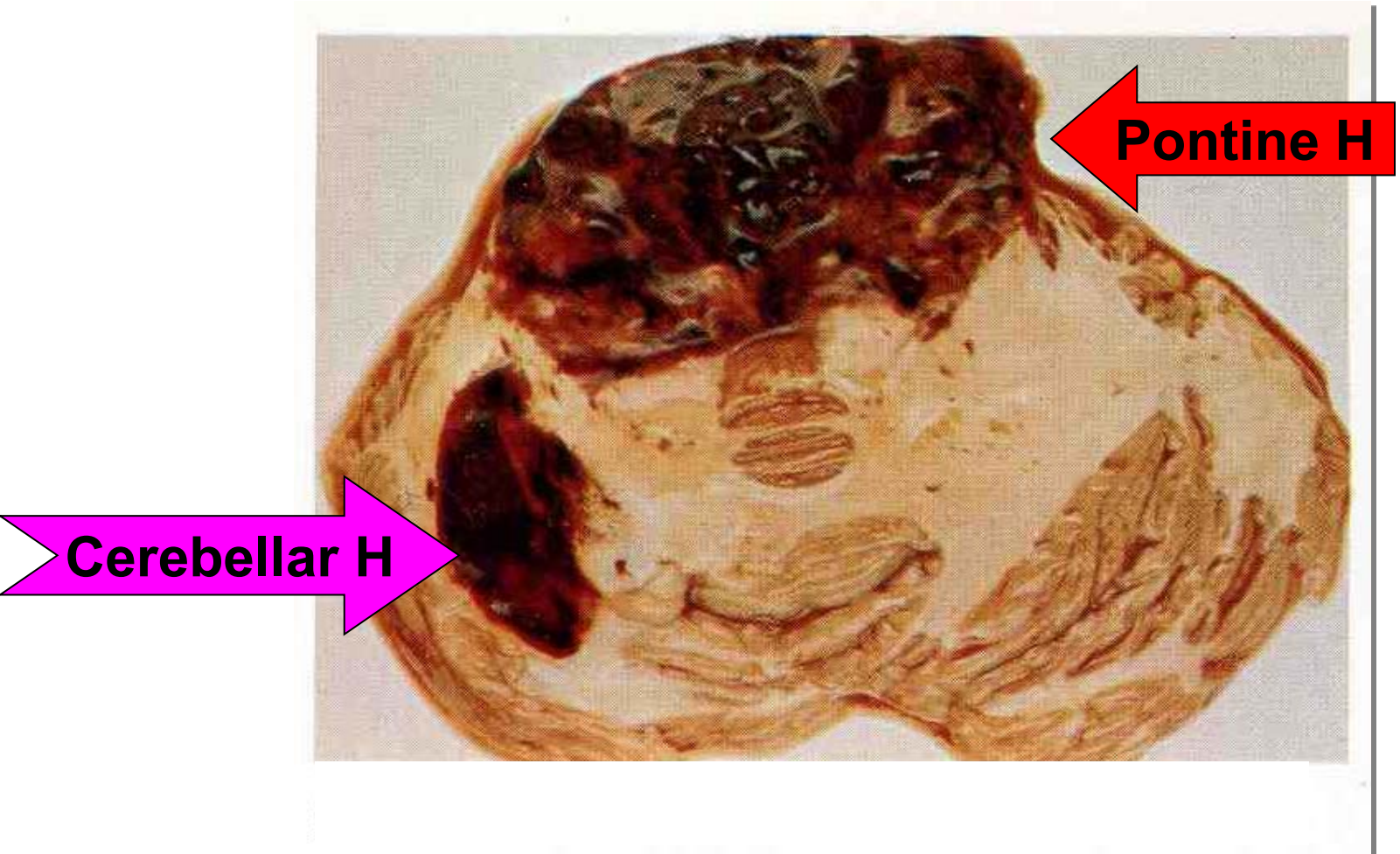
NB. This **intraventricular hemorrhage** may pass through the foramina of the fourth ventricle **into…Where?**

to subarachnoid space.

This is a cause of death.

F 9- 43: **Massive** (more than 1.5 cm in ∅) **recent hemorrhage** destroying the **pons** (above ⬅), & with 2nd hemorrhage in the central white matter of the **cerebellar hemisphere**(➡).

☠ The occurrence of **any one** of the above 2 hemorrhages alone, is almost always, rapidly ☠ fatal.



Morphology of *Brain Parenchymal Hemorrhage (H)*

► **Acute H,** Grossly (F 9-41, 42 ,& 43) show extravasation of blood with compression of the adjacent parenchyma, &
◘ H, (◘ 4.5) consists of a (I) **central core of clotted blood** surrounded by a (II) **rim of necrotic & edematous neuronal & glial brain tissue.**

يعني ما قتل المريض وفيه موجود

►**Old H,** Grossly, (F9-44) show:
(I) central cavity of brain destruction, filled by partly-organized, brown **hematoma** retracted from the surrounding brain;
(II) surrounded by thick capsule of reactionary astrocytic proliferation; Both…
(III) the thick capsule & the adjacent brain rim are stained **golden-brown** by breakdown products of hemoglobin → (hemosidren pigment)

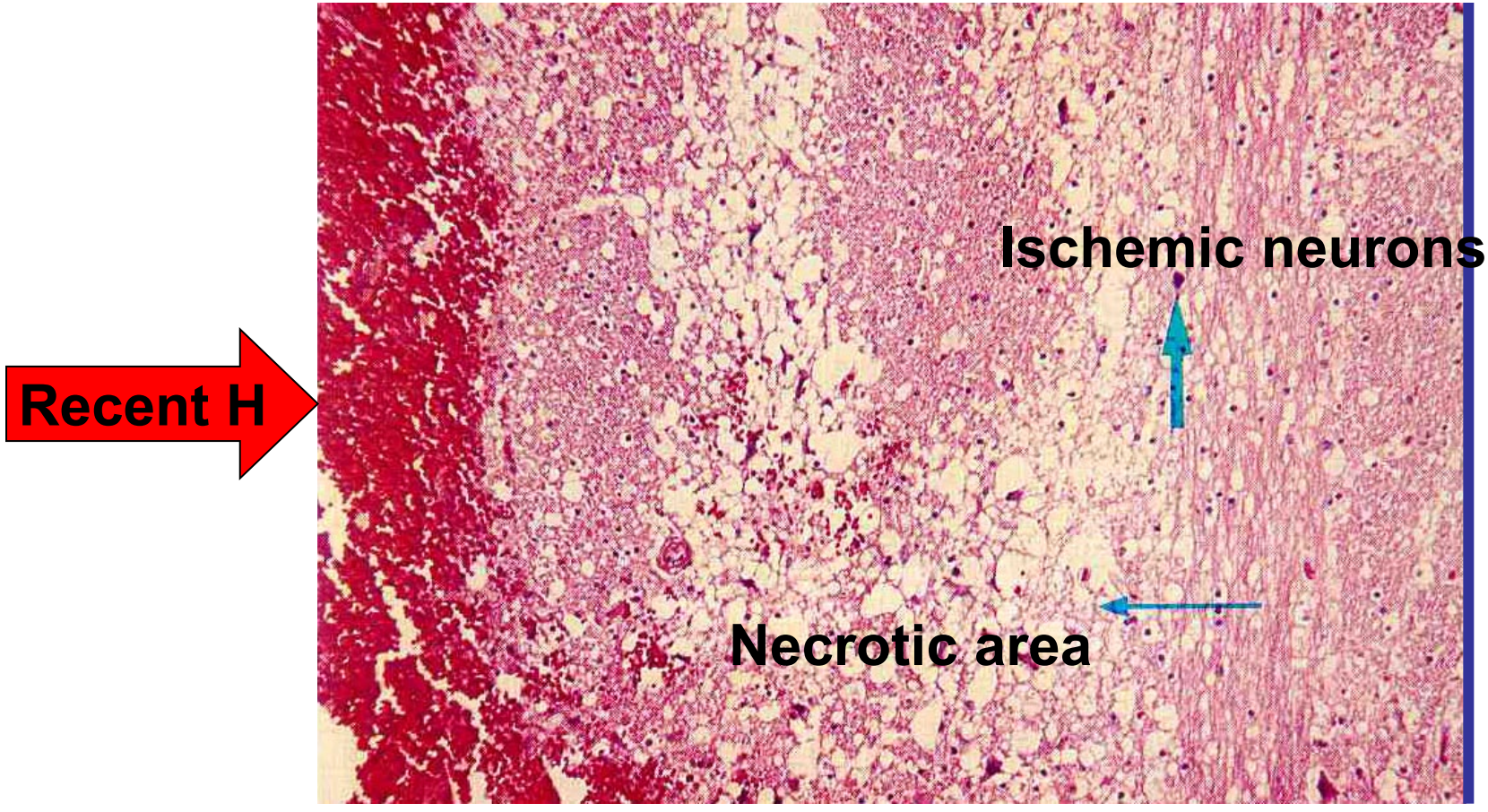
◘ H, at the periphery of the lesion, there is (1) **astrocytes** proliferation with (2) pigment & lipid-laden **macrophages.**
The cellular events then follow the same time course observed after cerebral infarction.

↳ formation of a cyst.

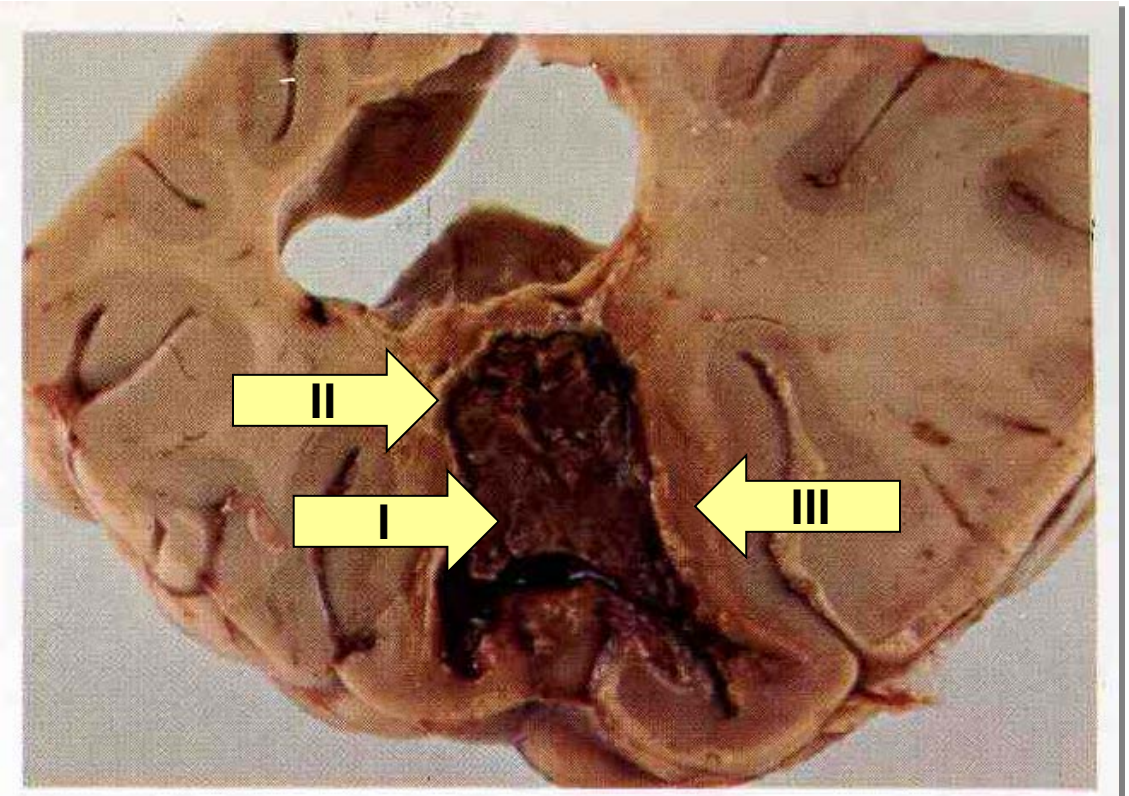
نتيجة تراكومات كبيرة من الحديد.

لأنه الـ RBCs ما زالت موجودة.

■ 4.5: **Recent Cerebral hemorrhage: Brain X145.** Edge of the hemorrhage. On the left, there is red zone of **recent blood clot**. Adjacent to it , there is an extensive **necrotic area** (thin arrow), pale, edematous & vacuolated (vacuoles contain water) & many neurons & glial cells have disappeared. Few ischemic neurons **survive** as basophilic round bodies (thick arrow)



F 9-44: **Old intracerebral hemorrhage: brain.** Coronal section of the occipital lobe, showing partly-organized old hemorrhage: **(I)** Central brown **hematoma** retracted from the surrounding brain, **(II)** thick **capsule** of reactionary astrocytic proliferation, **(III) both,** the capsule & the adjacent brain are stained **golden-brown** by breakdown products of hemoglobin.



9.44 Intracerebral haemorrhage: brain

Cerebral Amyloid Angiopathy (CAA)

► Cerebral amyloid angiopathy (CAA) is a disease in which amyloidogenic peptides-typically the same ones found in -Alzheimer disease- deposit in the walls of medium- & small-caliber meningeal & cortical BV. The deposition weakens the BV wall & ↑ the risk of H.

★ Since CAA is limited to leptomeningeal & cortical BV with sparing of the vasculature of white matter & deep gray structures, (the H associated with CAA have a **distribution that is different** from that of hypertensive intraparenchymal hemorrhages) not Lobular

★ CAA-associated H are often referred to as *lobar H* because of the involvement of the **cerebral cortex**.

■ Amyloid in the vessel walls **can be identified by Congo Red stains**. The affected vessels are rigid, with a pipe-like appearance.

Subarachnoid Hemorrhage & Saccular Aneurysms

➔ The **most frequent cause** of subarachnoid H **is rupture of a *saccular (Berry) aneurysm.***

★ **Other** causes include (1) **vascular malformation**, (2) **trauma** (in which case it is usually associated with other signs of the injury), (3) 2nd to **rupture** of an intracerebral H into the ventricular system, (4) **hematologic** disturbances, &(5) **tumors**.

★ Rupture can occur at any time, but in about **1/3 of cases** it is associated with **acute ↑ in intracranial pressure**, such as with **straining at stool or sexual orgasm**. there's elevation of ICP.

* It is arterial bleeding

★ Arterial blood is forced into the subarachnoid space, & with sudden, severe **excruciating headache** (the **worst headache** ever been felt) with **rapid lose of consciousness**. → due to rushing of blood

☠ **50% of individuals die with the first rupture;**
☺ those who survive (due to **vasospasm**) typically improve & recover consciousness in minutes.

★ But in the early period after a subarachnoid H, there is a risk of **additional ischemic injury from vasospasm.**

في ال 50% الآخرين
* بنحط clips في مكان الفتحة تبعت ال aneurysm والشخص بعيش حياته طبيعي.

★ ***Clinically,*** *patients can be* ***lucid*** *for several* ***hours*** *between the moment of trauma & the development of neurologic signs.* The arterial epidural H may expand rapidly & ... is a ☠ neurosurgical emergency requiring prompt drainage, (usually through Burr hole).

Subdural Hemorrhage

★ The rapid movement of the brain that occurs in trauma can **tear the bridging veins,** majority of which **extend from the ➔ cerebral hemispheres through the ➔ subarachnoid & subdural space ➔ to empty into superior sagittal dural sinuses.** These veins are particularly **prone to tearing**, & their rupture leads to H into the subdural space, most lesions begin in the parasagittal region

☹ In **elderly patients,** with brain atrophy, the bridging veins are stretched out & the brain has additional space for movement, accounting for the higher rate of subdural H in **elderly** patients, even after relatively **minor head trauma**.

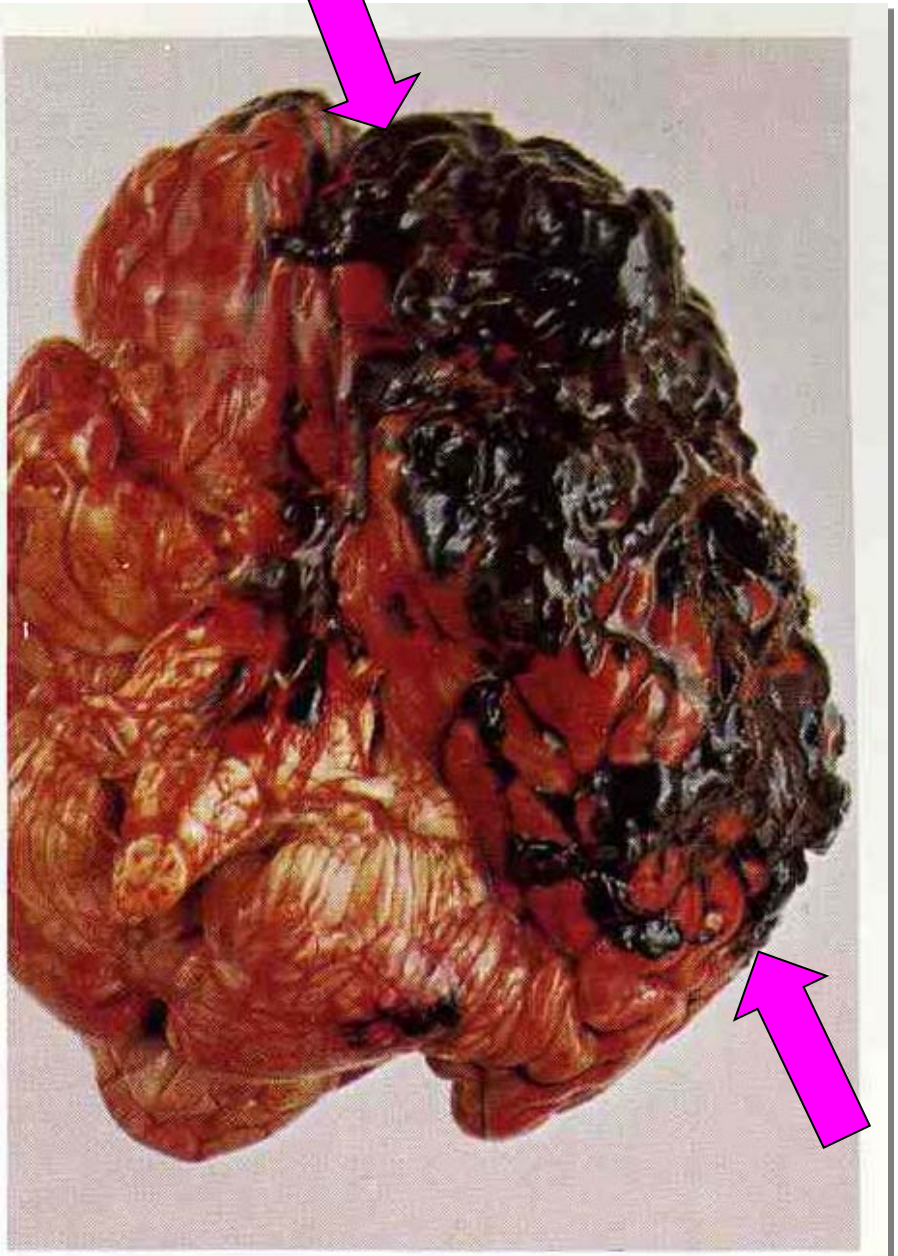
☹ **Infants** are also susceptible to subdural H, because **their bridging veins are thin-walled.**

▶Subdural H **most** often become **manifest within the first 48 hours after injury.** They are most common over the lateral aspects of the cerebral hemispheres & are bilateral in about 10% of cases. (I) **Focal neurologic signs** are attributable to the pressure exerted on the adjacent brain, but (II) often the clinical manifestations are **nonlocalizing** & include headache or confusion. ☹ In time there may be slowly progressive neurologic deterioration, **rarely** with acute decompensation.

slower than — life threatening — due to ↑ICP.

▶**Grossly**, the acute subdural H appears as a **collection of freshly clotted blood apposed along the contour of the brain** surface, without extension into the depths of sulci (F23-13C & 9- 21). The underlying **brain is flattened.**

➔ Subdural H is **venous bleeding**, & is self-limited; breakdown & organization of the H take place over time:
(1) by lysis of the RBC (in about 1 week),
(2) growth of fibroblasts from the dural surface into the H (in 2 weeks), & (3) early development of hyalinized connective tissue (in1-3 months), which is ***attached to the inner surface of the dura*** & is not adherent to the underlying arachnoid.



9.21 Subdural haemorrhage (subdural haematoma): brain

F 9-21: **Subdural hemorrhage (hematoma): brain.**

☠ A massive subdural hemorrhage over the left **fronto, temporo, parietal** regions extends over the inferior surface of the hemisphere.

★ **Most** subdural hemorrhages follow **blunt** injury to the skull ; & in the elderly they may occur without a history of direct injury to the head. But in this case, the cause was an ☠ **extensive fracture of the skull.**

►Subdural hematomas commonly rebleed (**chronic subdural hematomas**), presumably from the thin-walled vessels of the granulation tissue.

more common than acute.

▲The treatment of subdural hematomas is to remove the organized blood & associated organizing tissue.

MRI/CT ال scan

اعدوا في ايجاد هذه ال Hematomas . (باقي السلايد مش داخل)

INFECTIONS OF THE CNS

★The brain & its coverings can be affected by many infectious agents, some have a **relative or absolute predilection for the nervous system** (e.g., **rabies)**, **others can affect many other organs** as well as the brain (e.g., *Staphylococcus aureus*).

★ Damage of the infectious agents to nervous tissue may be the consequence of:

(1) Direct injury by the **infectious agent** to neurons or glia, or
(2) Indirectly, through the **microbial toxins**, or through the
(3) Destructive effects of the inflammatory response, or the
(4) Influence of immune-mediated mechanisms.