IV. Cerebrovascular diseases
- Cerebrovascular disease denotes brain disorders caused by pathologic processes involving the blood vessels.

- The three main pathogenic mechanisms are:
  1. Thrombotic occlusion of vessels
  2. Embolic occlusion of vessels

- Thrombosis and embolism cause ischemic injury or infarction of specific regions of the brain, depending on the vessel involved.
- Hemorrhage accompanies rupture of vessels, leading to direct tissue damage as well as secondary ischemic injury

**Stroke:**

- Is the clinical designation applied to
  a. Abrupt onset of focal or global neurological symptoms
  b. caused by ischemia or hemorrhage
  c. and these symptoms must continue for more than 24 hours
d. and there should be permanent damage to the brain.

**Transient ischemic attack (TIA):**

a- Applied that the neurological symptoms resolve within 24 hours

b. No irreversible tissue damage

c. The cause is small emboli from the carotids or vertebrobasilar circulation that resolve before causing irreversible injury

Example Amarex fugax
- From the standpoint of the pathophysiology and pathologic anatomy, it is convenient to consider cerebrovascular disease as two processes
  a. Hypoxia, ischemia and infarction
  b. Hemorrhage
A. Hypoxia, ischemia and infarction

- The brain may be deprived of oxygen by several mechanisms

  a. Functional hypoxia in a setting of a low partial pressure of oxygen or impaired oxygen-carrying capacity
  
  b. Global Ischemia; either transient or permanent due to tissue hypoperfusion, which can be caused by, hypotension or shock
  
  c. Vascular obstruction.
I. Global ischemia

- Widespread ischemic injury can occur in the setting of severe systemic hypotension, when systolic pressure fall below 50 mm Hg such as in cardiac arrest, and shock because of failure of autoregulation

- The clinical outcome varies with the severity and duration of the insult
A. Mild transient Global Ischemia

- There may be only a transient postischemic confusional state, with eventual complete recovery.

- Neurons are more susceptible to mild ischemic injury than glial cells

- Neurons are the most susceptible followed by oligodendrocytes, astrocytes then endothelial cells
The most susceptible neurons to mild transient global ischemia are:

1. The pyramidal cells of the CA1 region of the hippocampus
2. Middle cortical lamina of the neocortex, layers 3, 5, and 6 (called laminar necrosis)
3. Purkinje cells of the cerebellum.
Neuronal loss in transient global ischemia is due to excitotoxicity.

The susceptible neurons have many receptors to the excitatory neurotransmitter glutamate.

So in transient global ischemia, the astrocytes release glutamate that binds to its neuronal receptors NMDA (N-methyl D-aspartate) leading to increase intracellular calcium and activation of enzymes that leads to death of these neurons.
B. Severe global ischemia

- Widespread neuronal death occurs irrespective of regional vulnerability. (pan necrosis)
  
a. Persistent vegetative state (awake but not aware)
- In severe global cerebral ischemia, individuals who survive in this state often remain severely impaired neurologically.

b. Brain death
- Other patients meet the clinical criteria for "brain death," including:
1. Evidence of diffuse cortical injury (isoelectric, or "flat," electroencephalogram)
2. And brain stem damage, including absent reflexes and respiratory drive.

Border zone ("watershed") infarcts
- Are 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 (double watershed area).
Damage to this region produces a band of necrosis over the cerebral convexity a few centimeters lateral to the inter-hemispheric fissure.

Border zone infarcts are usually seen after hypotensive episodes.
2. Focal Cerebral Ischemia

- Cerebral arterial occlusion leads to focal ischemia and-if sustained-to infarction of CNS tissue in the distribution of the compromised vessel.

- 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.

- **NOTE**

- In contrast, there is little if any collateral flow for thalamus, basal ganglia, and deep white matter which are supplied by deep penetrating vessels.
- Occlusive vascular disease of severity sufficient to lead to cerebral infarction may be due to

1. *In situ thrombosis*

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

- The most common sites of primary thrombosis are
  a. The carotid bifurcation,
  b. The origin of the middle cerebral artery,
  c. And at either end of the basilar artery
- The venous side of the circulation may also undergo thrombosis and cause significant cerebral ischemia.

- The striking example is the thrombosis of the superior sagittal sinus which can occur with infections or hypercoagulability state.
2. *Embolization* from a distant source.
- Overall, embolic infarctions are more common than thrombosis.
- Sources of emboli:
  a. Cardiac mural thrombi are a frequent source
  b. Thromboemboli also arise in arteries, most often from atheromatous plaques within the carotid arteries.
  c. Paradoxical emboli, particularly in children with cardiac anomalies;
  d. Emboli of other materials (tumor, fat, or air).
- 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 pre-existing luminal stenosis

- Infarcts can be divided into two broad groups hemorrhagic and non-hemorrhagic based on their macroscopic and corresponding radiologic appearance
**Microscopically,**

1. **After the first 12 hours:**
   a. Red neurons and both cytotoxic and vasogenic edema predominate
   b. Swelling of endothelial and glial cells, mainly astrocytes
   d. Disintegration and myelinated fibers

2. **Up to 48 hours, there is some neutrophilic emigration**
3. **2-3 weeks**
   a. Mononuclear phagocytic cells predominate and macrophages containing myelin breakdown products or blood may persist in the lesion for months to years.
   b. As the process of phagocytosis and liquefaction proceeds, there will be gemistocytic gliosis

4. **After several months**:
   - Fibrillary astrocytosis
Notes:

a. 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.

b. The pia and arachnoid are not affected and do not contribute to the healing process.
Cerebral infarction
B. Intracranial Hemorrhage

- Hemorrhage within the skull can occur in a variety of locations, and each location is associated with a set of underlying causes.

1. Hemorrhages within the brain itself can occur:
   a. Secondary to hypertension (most common)
   b. Cerebral amyloid angiopathy
   c. Arterio-venous malformation,
   d. A cavernous malformation, or
   e. An intra-parenchymal tumor especially oligodendroglioma, glioblastoma or metastatic renal cell carcinoma and melanoma.
2. Subarachnoid hemorrhages:
- Are most commonly seen with aneurysms but also occur with other vascular malformations.

3. Hemorrhages associated with the dura (in either subdural or epidural spaces) usually due to trauma.
1. Primary Brain Parenchymal Hemorrhage

- Spontaneous (non-traumatic) intra-parenchymal hemorrhages 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 a small intraparenchymal vessel.

A. Hypertension:

- Is the leading underlying cause, and brain hemorrhage accounts for roughly 15% of deaths among persons with chronic hypertension.

- It has a peak incidence at about 60 years.
- Intracerebral hemorrhage can be clinically devastating when it affects large portions of the brain or extends into ventricular system or, it can affect small regions and be clinically silent.

- Massive Hypertensive intraparenchymal hemorrhages occur in:
  a. Basal ganglia, --most common location
  b. Thalamus
  c. Pons
  d. and Cerebellum
Mechanisms of massive hemorrhage in Hypertension:

1. Hyaline arteriolar sclerosis
   - Affects the deep penetrating arteries and arterioles that supply the basal ganglia and the brain stem
   - Affected arteriolar walls are weakened and are more vulnerable to rupture

2. Chronic hypertension results in formation of minute aneurysms (Charcot-Bouchard microaneurysms)
   - Form in vessels less than 300 μm in diameter.
Other CNS disorders caused by hypertension:

1. **Lacunes or lacunar infarcts**:
   - Small cavitory infarcts, just a few millimeters in size, and the main locations are:
     a. In basal ganglia and thalamus
     b. The internal capsule, and the pons.
   - Are caused by occlusion of a single penetrating vessel
2. Slit hemorrhages due to rupture of small penetrating vessels and with time, these hemorrhages resorb leaving slit-like cavities surrounded by black discoloration

3. **Acute hypertensive encephalopathy**:

- Most often is associated with sudden sustained rises in diastolic blood pressure to greater than 130 mm Hg and characterized:
a. By increased intracranial pressure and
b. Global cerebral dysfunction, manifesting as headaches, confusion, vomiting, convulsions, and sometimes coma.
- Rapid therapeutic intervention to reduce the intracranial pressure is essential.
2. Cerebral Amyloid Angiopathy (CAA):

- Is the second most common cause of spontaneous parenchymal hemorrhage
- Is a disease in which amyloidogenic peptides, deposit in the walls of meningeal and cortical vessels
- Amyloid deposition (Aβ amyloid) weakens vessel walls and increases the risk of hemorrhages
- The hemorrhage differs in distribution from those associated with hypertension