Summary :

<table>
<tr><td rowspan="2">Stroke</td><td colspan="2">• Hemorrhagic in 32% of cases : etheir Intracerebral or Subarachnoid.
• Ischemic in 68% of cases : etheir Thrombotic or Embolic.</td></tr>
<tr><td colspan="2">Risk factors :
• Some increase the risk of one type of stroke (hemorrhagic or ischemic).
• Some increase the risk of both types. (e.g. : smoking, illegal drug use, high blood pressure)
• Occasionally, strokes occur in people who have no risk factors</td></tr>
<tr><td>Cell death mechanisms in cerebral ischemia</td><td colspan="2">Cell death :
• Necrosis is commonly observed early after severe ischemic insults.
• Apoptosis occurs with more mild insults and with longer survival periods.
The mechanism of cell death involves calcium-induced calpain-mediated proteolysis of brain tissue.
Substrates for calpain include: Cytoskeletal proteins, Membrane proteins and Regulatory and signaling proteins.</td></tr>
<tr><td rowspan="4">Biochemical Responses to Ischemic Brain Injury</td><td rowspan="4">Oxidative stress</td><td>A condition in which cells are subjected to excessive levels of Reactive oxidizing species (ROS or RNS) & they are unable to counterbalance their deleterious effects with antioxidants.
It has been implicated in the ageing process & in many diseases (e.g., stroke, atherosclerosis, cancer, neurodegenerative diseases)</td></tr>
<tr><td>❖ It happens because of of Reactive Oxygen Species (ROS) & Reactive Nitrative Species (RNS):
• They are mainly generated by microglia & astrocytes.
• hey modulate synaptic transmission & non-synaptic communication between neurons & glia.
• During periods of increased neuronal activity, ROS & RNS diffuse to the myelin sheath of oligodendrocytes activating Protein kinase C (PKC) → posttranslational modification of myelin basic protein (MBP) by phosphorylation.
• They regulate neuronal signaling in both central & peripheral nervous systems.</td></tr>
<tr><td>The brain is highly susceptible to ROS-induced damage because of:
High concentrations of peroxidisable lipids ,Low levels of protective antioxidants ,High oxygen consumption ,High levels of iron (acts as pro-oxidants under pathological conditions) , The occurrence of reactions involving dopamine & Glutamate oxidase in the brain.</td></tr>
<tr><td>❖ Molecular & Vascular effects of ROS in ischemic stroke :
• Molecular effects: DNA damage ,Lipid peroxidation of unsaturated fatty acids ,Protein denaturation , Inactivation of enzymes ,Cell signaling effects (e.g., release of Ca2+ from intracellular stores) ,Cytoskeletal damage ,Chemotaxis .
• Vascular effects: Altered vascular tone and cerebral blood flow ,Increased platelet aggregability ,Increased endothelial cell permeability</td></tr>
</table>

Biochemical Responses to Ischemic Brain Injury	**Oxidative stress**	❖ **The role of NO in the pathophysiology of cerebral ischemia :** • Ischemia → abnormal NO production. This may be both beneficial and detrimental, depending upon when and where NO is released. • NO produced by endothelial NOS **(eNOS) improving vascular dilation and perfusion (i.e. beneficial).** • In contrast, NO production by neuronal NOS **(nNOS) or by the inducible form of NOS (iNOS) has detrimental (harmful) effects**. • Increased iNOS activity generally occurs in a delayed fashion after brain ischemia and trauma and is associated with inflammatory processes
	Metabolic stress	❖ **Biochemical changes in The brain during ischemia** : Ischemia → interruption or severe reduction of blood flow, O2 & nutrients in cerebral arteries → energy depletion (depletion of ATP & creatine phosphate. **Result in :** • Inhibition of ATP-dependent ion pumps → Membranes depolarization → Perturbance of transmembrane ion gradients : **Ca2+ Influx , Na+ influx , K+ efflux** **OR :** • ↑ Lactic acid in neurons → acidosis → promotes the prooxidant effect → ↑ the rate of conversion of O2 → to H2O2 or to hydroxyperoxyl radical .
	neurochemical response	Following cerebral ischemia, extracellular levels of various neurotransmitters are increased . e.g.: • Glutamate. • Glycine. • GABA. • Dopamine