General PATHOLOGY for WKU B.PHO YII

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I hear, I forget
I see, I remember
I do, I understand

Chinese Proverb..

Course objectives

- After completing this course, students will
  - **Better understand pharmacotherapy of both communicable and non-communicable diseases which will prepare them to be competent providers of pharmaceutical service.**
  - **Be able to explain the concepts of pathology and the pathophysiology of cellular injury, wound healing, hemodynamic of cardiovascular diseases, immunopathology, neoplasia, endocrine disorders, common infectious diseases and CNS disorders.**
  - **Be able to explain the pathophysiologic mechanisms of common disorders.**

General pathology

- Cellular adaptation, cell injury & cell death
- Acute & chronic inflammation
- Tissue renewal & repair: regeneration, healing & fibrosis
- Hemodynamic disorders, thromboembolic disease, & shock
- Diseases of immunity
- Genetic diseases
- Neoplasia
- Infectious disease
- Metabolic diseases
- Diseases of the CNS

1. Pathophysiologic basics

- Pathology – study of disease
  - Patho – suffering
  - Logos – study
- It is devoted to the study of the structural & functional changes in cells, tissues, & organs underlying diseases.

Definition of pathology…

It is the "Scientific study of disease"

"scientific study of the molecular, cellular, tissue, or organ system response to injurious agents."

Pathology serves as a "**bridge**" or "**link**" between the preclinical sciences (**anatomy, physiology, ……etc**.) and the courses in clinical medicine.

Ctd…

- Pathology is divided in to :
- 1. General pathology – deals with basic reactions of cells & tissues to abnormal stimuli that underlie all disease.
- 2. Systemic pathology – specific responses of specialized organs & tissues to more or less well defined stimuli.

The core of pathology

- Pathology gives explanation of a disease by studying the four aspects of the disease
- 1. Etiology
- 2. Pathogenesis
- 3. Morphological changes
- 4. Functional derangement & clinical significance

Ctd…

1. Etiology

- Cause of the disease
- If the cause of the disease is known it is called primary etiology
- If the cause of the disease is unknown it is called idiopathic
- Knowledge or discovery of the primary cause remains the back bone on which a diagnosis can be made, a disease understood & a treatment developed

Ctd…

- Two factors:-
- ✓ Intrinsic or genetic
- ✓ Acquired (infectious, nutritional, chemical, physical…)

Etiology

- c



One etiologic agent- one disease, as Malaria



- **Several etiologic agents - one disease, as diabetes .**



- **One etiologic agent - several diseases, as smoking.**

Ctd…

2. Pathogenesis

- Mechanisms of disease development
- It refers to the sequence of events in the response of the cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease
- It means the mechanism through which the cause operates to produce the pathological & clinical manifestations
- The pathogenic mechanism could take place in the latent or the incubation period
- It will lead to morphological changes

Ctd…

3. Morphological changes

- Structural alterations induced in the cells & organs of the body
- Characteristic to the disease or diagnostic to the etiologic process
- Seen with naked eye or under the microscope

Ctd…

- Both the gross & the microscopic morphologic changes may only be seen in that disease, i.e. they may be specific to that disease (pathognomonic).
  - Therefore, such morphologic changes can be used by the pathologist to diagnose the disease
- In addition, the morphologic changes will lead to functional alteration & to the clinical signs & symptoms of the disease

Ctd…

4. Functional derangement & Clinical significance

- Functional consequence of the morphologic change
- The morphologic changes influence the normal function → determine the clinical feature
- Also the course & prognosis of the disease

Diagnostic modalities

- Most are based on morphologic changes
- Diagnostic techniques:

1. Histopathology
2. Cytopathology
3. Hematopathology
4. Immunohistochemistry
5. Microbiological examination
6. Biochemical examination
7. Cytogenetics
8. Molecular techniques
9. Autopsy

Histopathology

- Studies the tissue under the microscope
- Tissues are obtained by biopsy
- **Biopsy** – tissue sample from living person
- Biopsy – Incisional
  - Excisional
- Tissue examined grossly (macroscopically) & microscopically
- It is usually the **gold standard** for pathologic diagnosis

Ctd…

- Once the tissue is removed from the pt, it has to be immediately fixed by putting it into adequate amount of 10% formalin before sending it to the pathologist
- Once the tissue arrives at the pathology department, the pathologist will examine macroscopically

Ctd…

- Then the tissue is processed to make it ready for microscopic examination. The whole purpose of the tissue processing is to prepare a very thin tissue which can be clearly seen under the microscope
- The tissue is processed by putting it into different chemicals. It is then impregnated (embedded) in paraffin, sectioned (cut) into thin slices, & is finally stained.
- The stains can be Hematoxylin/Eosin stain or special stains such as PAS, immunohistochemistry, etc…

Ctd…

- The Hematoxylin/Eosin stain is usually abbreviated as H & E stain. It is routinely used.
- It gives the nucleus a **blue color**, the cytoplasm & the extracellular matrix a **pinkish color**

Ctd…

- Then the pathologist will look for abnormal structures in the tissue & based on this abnormal morphology s/he will make the diagnosis

Cytopathology

- Study the cells
- Used in:
  - Screening for early detection of cancer
  - Diagnosis of symptomatic cancer
  - Diagnosis of inflammatory condition, infectious
  - Surveillance of pts treated with cancer

Ctd…

- Its advantage:
- Cheap
- Takes less time
- Needs no anesthesia
- Cytopathological methods:

1. FNAC
2. Exfoliative cytology
3. Abrasive cytology

Ctd…

1. FNAC

- Easy in superficial organs
- May need guidance in deep seated mass

2. Exfoliative cytology

- From cells that are shed from spontaneously into body fluids or secretion

3. Abrasive cytology

- Cells are dislodged from skin or mucous membrane by various tools

Hematological examination

- This is a method by which abnormalities of the cells of the blood & their precursors in the bone marrow are investigated to diagnose the different kinds of anemia & leukemia.

Immunohistochemistry

- This is a method used to detect a specific antigen in the tissue in order to identify the type of the disease

Microbiological examination

- This is a method by which body fluids, excised tissue, etc… are examined by microscopical, cultural, serological techniques to identify microorganisms responsible for many diseases

Biochemical examination

- This is a method by which the metabolic disturbances of disease are investigated by assay of various normal & abnormal compounds in the blood, urine, etc...

Eg. High serum HCG level - choriocarcinoma

Clinical genetics (cytogenetics)

- This is a method in which inherited chromosomal abnormalities in the germ cells or acquired chromosomal abnormalities in somatic cells are investigated using the techniques of molecular biology

Molecular techniques

- Different molecular techniques such as fluorescent in situ hybridization, southern blot, etc… can be used to detect genetic diseases

Autopsy

- Autopsy is an examination of the dead body to identify the cause of death
- This can be for

  -- forensic or

  -- clinical purposes

Diseases

- Disease is defined as an abnormal variation in structure or function of any part of the body
- Causes of disease
  - Environmental
  - Genetic or
  - Both

Environmental factors

Are many & are classified into:-

1. Physical agents
2. Chemicals
3. Nutritional deficiencies & excesses
4. Infections & infestations
5. Immunological factors
6. Psychogenic factors

Genetic factors

- These are hereditary factors that are inherited genetically from parents

Course of disease

- The course of disease in the absence of any intervention is called the natural history of the disease.
- Stages

1. Exposure
2. Latency period
3. Biological onset
4. Incubation period
5. Clinical onset
6. Permanent damage
7. Death

Ctd…

The course of disease is shown with a simplified diagram as follows

Exposure →biological onset →clinical onset

↑ ↓

Latency period permanent damage

↓

death

Out come of diseases

- Resolution can occur leaving no sequelae
- The disease can settle down, but sequelae are left, or
- It may result in death

Clinical & biological death

- Clinical death is the reversible transmission between life & biological death.
- Clinical death is defined as the period of respiratory, circulatory & brain arrest during which initiation of resuscitation can lead to recovery

Signs indicating clinical death

- The pt is with out pulse or blood pressure & is completely unresponsive to the most painful stimulus.
- The pupils are widely dilated
- Some reflex reactions to external stimulation are preserved. For example, during intubations, respiration may be restored in response to stimulation of the receptors of the superior laryngeal nerve, the nucleus of which is located in the medulla oblongata near the respiratory center.
- Recovery can occur with **resuscitation**

Biological death

- Biological death (sure **signs of death**), which sets in after clinical death, is an irreversible state of cellular destruction.
- It manifests with irreversible cessation of circulatory & respiratory functions, or irreversible cessation of all functions of the entire brain, including brain stem

Postmortem changes

- Rigor mortis – contraction of muscle
- Livor mortis – bluish discoloration on dependent part of the body
- Algor mortis – cooling of the body
- Autolysis – degradation of the body

2. Cellular Response to injury

- **Cells: active participants in their environment, constantly adjusting structure & function to accommodate changing demands & extracellular stresses.**
- Normal cell is able to handle normal physiologic demands, maintaining steady state called ***homeostasis***.
- Severe physiologic stress & pathologic stimuli tend to disrupt the structural & functional aspects of the cell

→ Cellular adaptation occurs

Cellular adaptation

- More severe physiologic stimuli may bring about a number of physiologic & morphologic cellular adaptation.
- **It is an altered state, preserving the viability & function of the cell as it responds to such stimuli.**
- Cells adapt by undergoing changes in **size, number, & type.**

Ctd…

- The adaptive response includes:-
  - Hypertrophy
  - Hyperplasia
  - Atrophy
  - Metaplasia

Ctd…

- **<u>These adaptive changes can occur singly or in combination.</u>**
- **Normal – once the stimulus is removed, the adaptive response ceases unlike in abnormal.**

Hypertrophy

- Is an increase in the size of the cell resulting in the enlargement of **the organs**
- It results from an increase **functional demand** or due to a specific **hormonal stimulation**.
- By undergoing hypertrophy, the cell achieve equilibrium between its demand & functional capacity.
- The increase in size is due to synthesis of more **structural components**

Ctd…

- Hypertrophy commonly seen in **cardiac & skeletal muscle tissues.**
- Hypertrophy can be:-
- **Physiological**

  eg. Muscular hypertrophy due to exercise
- **Pathological**

  eg. myocardial hypertrophy due to hypertension.

Hyperplasia

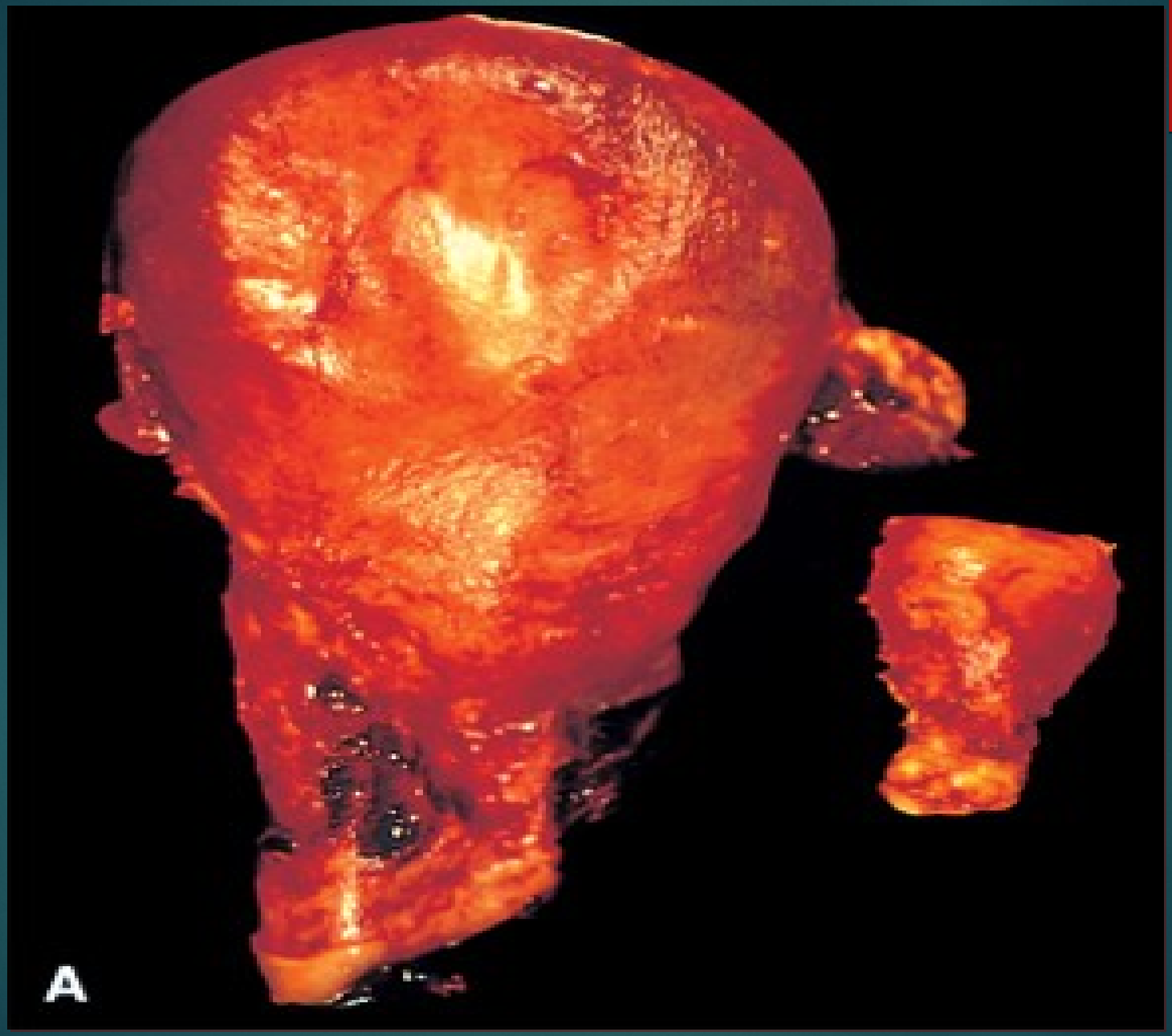
- Is an increase in the **number of cells of a tissue or an organ.**
- Occurs in those cells that are capable of **synthesizing DNA or undergo mitotic division**
- **Nerve cells, skeletal cells & cardiac cells** do not divide, hence an increase work load to skeletal & cardiac cells respond only by hypertrophy.

Ctd…

- Hyperplasia can be:-
- ***Physiologic hyperplasia***

1. Hormonal hyperplasia which increases the functional capacity of a tissue when needed.

- Exemplified by the proliferation of the glandular epithelium of the **female breast at puberty and during pregnancy.**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Ctd…

2. ***Compensatory hyperplasia***, that is, hyperplasia that occurs when a portion of the tissue is **removed or diseased**.

- For example, when **a liver is partially resected**, mitotic activity in the remaining cells begins as **early as 12 hours later**, eventually restoring the liver to its normal weight with in 3 months.

Ctd…

- ***Pathologic hyperplasia***
- Most are caused by **excessive hormonal stimulation or growth factors acting on target cells**.

  Eg. **Endometrial hyperplasia**
- Pathologic hyperplasia constitutes a fertile soil in which **cancerous proliferation** may eventually arise

Atrophy

- Is a **decrease in the size of the cell**, which might result in shrinkage of the organs.
- There is **loss of cellular substance**
- In an atrophic cell, the cell consists of fewer **mitochondria, myofilaments & endoplasmic reticulum**
- Due to decrease in the work load and demand

Ctd…

- Atrophy can be:-
- Physiological

  Eg. During embryogenesis.
- Pathological

Causes of atrophy

- ✓ Disuse
- ✓ Denervation
- ✓ Decreased blood supply
- ✓ Inadequate nutrition
- ✓ Loss of endocrine stimulation
- ✓ Aging
- ✓ Pressure

Ctd…

- ***Disuse atrophy***

- When there is decreased work load
- As in prolonged bed rest→ skeletal muscle
- Occurs in the muscle of the extremities

- ***Denervation atrophy***

- Is a form of Disuse atrophy
- Occurs in paralyzed extremities due to lack of innervation

Ctd…

- ✓ ***Lack of endocrine stimulation***
- Occurs when there is a lack of a hormone stimulating a tissue
- As in atrophy of the **reproductive structures after menopause**
- ✓ ***Inadequate nutrition***
- The body undergoes a general **wasting of tissue mass**

Ctd…

- ✓ ***Senile atrophy***
- Atrophy due to aging
- The aging process is associate with cell loss
- This is typically seen in tissue **containing permanent cells**
- ✓ ***Pressure atrophy***
- Occur as a result of tissue compression for some time like in **benign tumor**
- It is probably the result of **ischemic change caused by compressed blood vessel**.

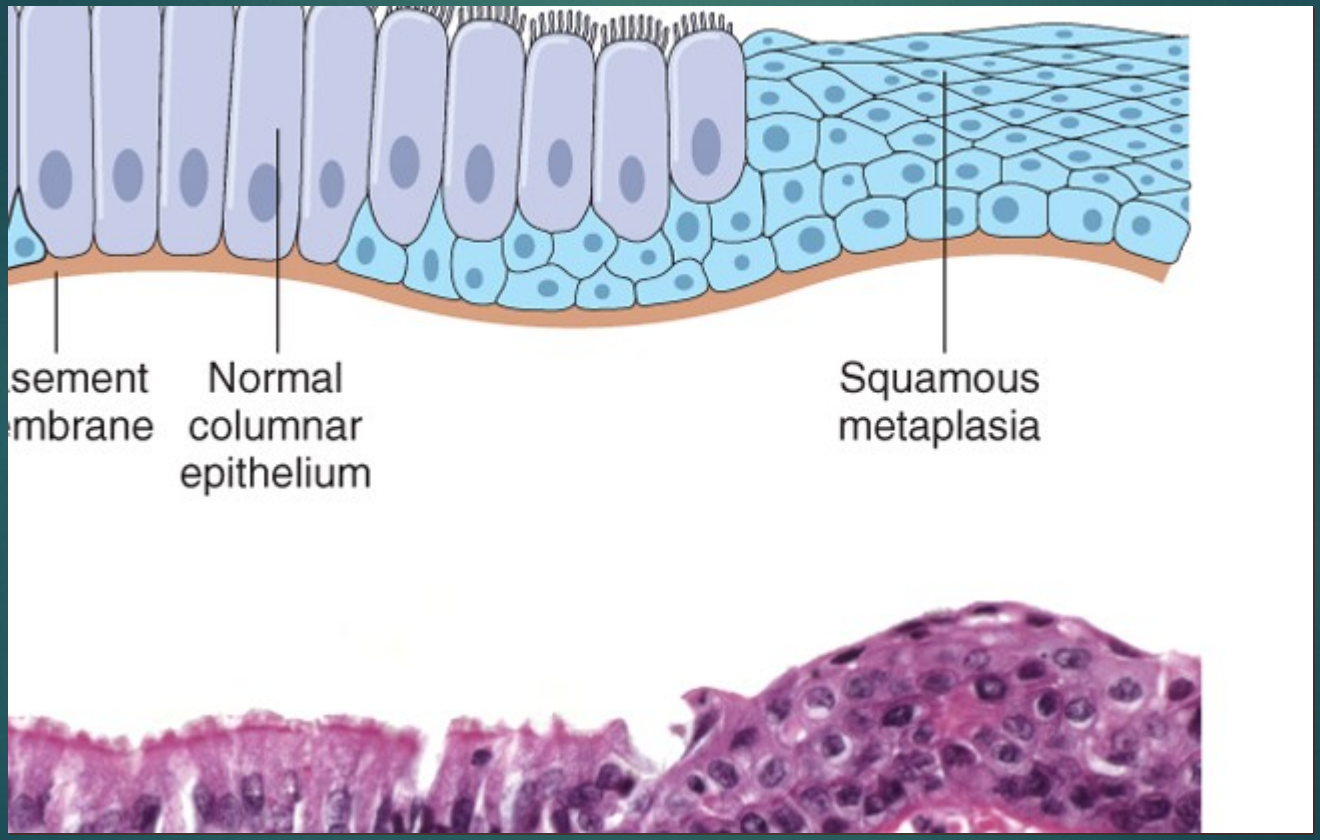
Ctd…

- ***Atrophy due to decreased blood supply***

- A decrease in blood supply cause a decrease in the delivery of oxygen & nutrients
- In ischemic tissue, where the blood supply is inadequate even to maintain the atrophic cell; cell injury or cell death may ensue.

Metaplasia

- Is an **adaptive substitution of one type of cell in to another type that is able to tolerate the stress**.
- It is **a reversible condition**
- The most common metaplasia is **columnar to squamous.**
- An example is the conversion of **columnar epithelium of the respiratory tract into squamous type in habitual cigarette smokers**.


sement
mbrane
Normal
columnar
epithelium
Squamous
metaplasia

Ctd…

- The influences that predisposes metaplasia, if persistent, may induce **malignant transformation in metaplastic epithelium**
- **Metaplasia from squamous to columnar type may also occur. Esophageal squamous epithelium is replaced by intestinal – like columnar under the influence of refluxed gastric acid**
- **Cancers may arise that are typically glandular carcinoma (adenocarcinoma)**

Ctd…

- **Connective tissue metaplasia is the formation of cartilage, bone or adipose tissue (mesenchymal tissue) in tissue that normally do not contain these elements.**
- ***Myositis ossificans*** **– bone formation in muscle after bone fracture**

Cell injury & cell death

- The cell may acquire a reversible injury or may obtain an irreversible injury & may die.
- The factor influencing cell injury & cell death depends on
- Intensity of stimulus
- Duration of the injury
- Type of injury
- Type of cell involved

Ctd…

Normal cells

(homeostasis)

stress ↓ ↓ injurious agent

↓ ↓

Adaptation → → Cell injury

enable to

adapt

Causes of cell injury

- Oxygen deprivation
- Physical agents
- Chemical agents & drugs
- Infectious agents
- Immunologic reactions
- Genetic derangements
- Nutritional imbalance

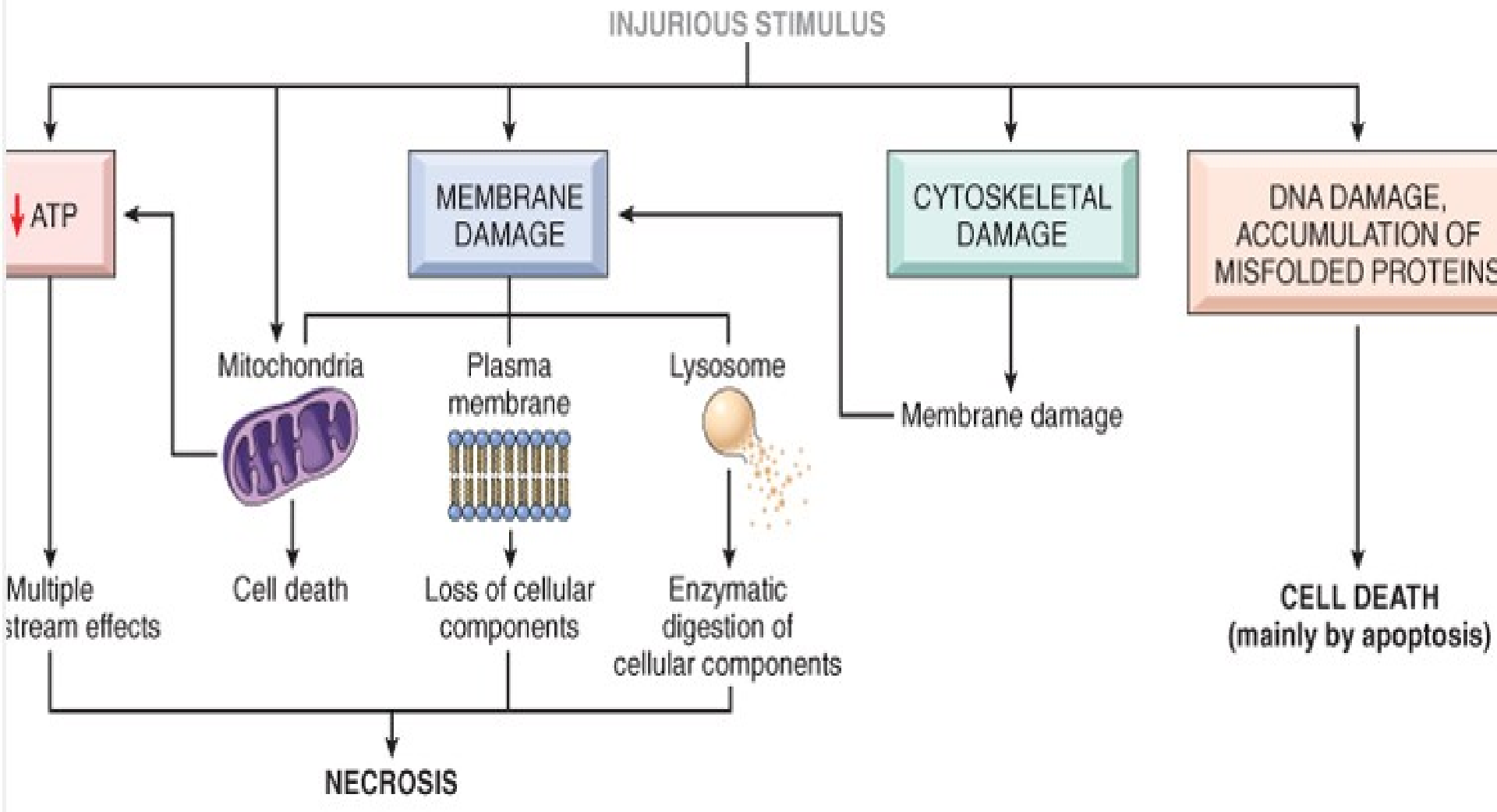
Mechanisms of cell injury

- Principles that is relevant to most forms of cell injury
  - The cellular response to injurious stimuli depends on the type of injury, its duration & its severity
  - The consequence of cell injury depend on the type, state, & adaptability of the injured cell

Ctd…

- Cell injury results from functional & biochemical abnormalities in one or more of several essential cellular components. The most important targets of injurious stimuli are:-
- ✓ Aerobic respiration involving mitochondrial oxidative phosphorylation & production of ATP
- ✓ The integrity of cell membranes
- ✓ Protein synthesis
- ✓ The cytoskeleton
- ✓ The integrity of the genetic apparatus of the cell

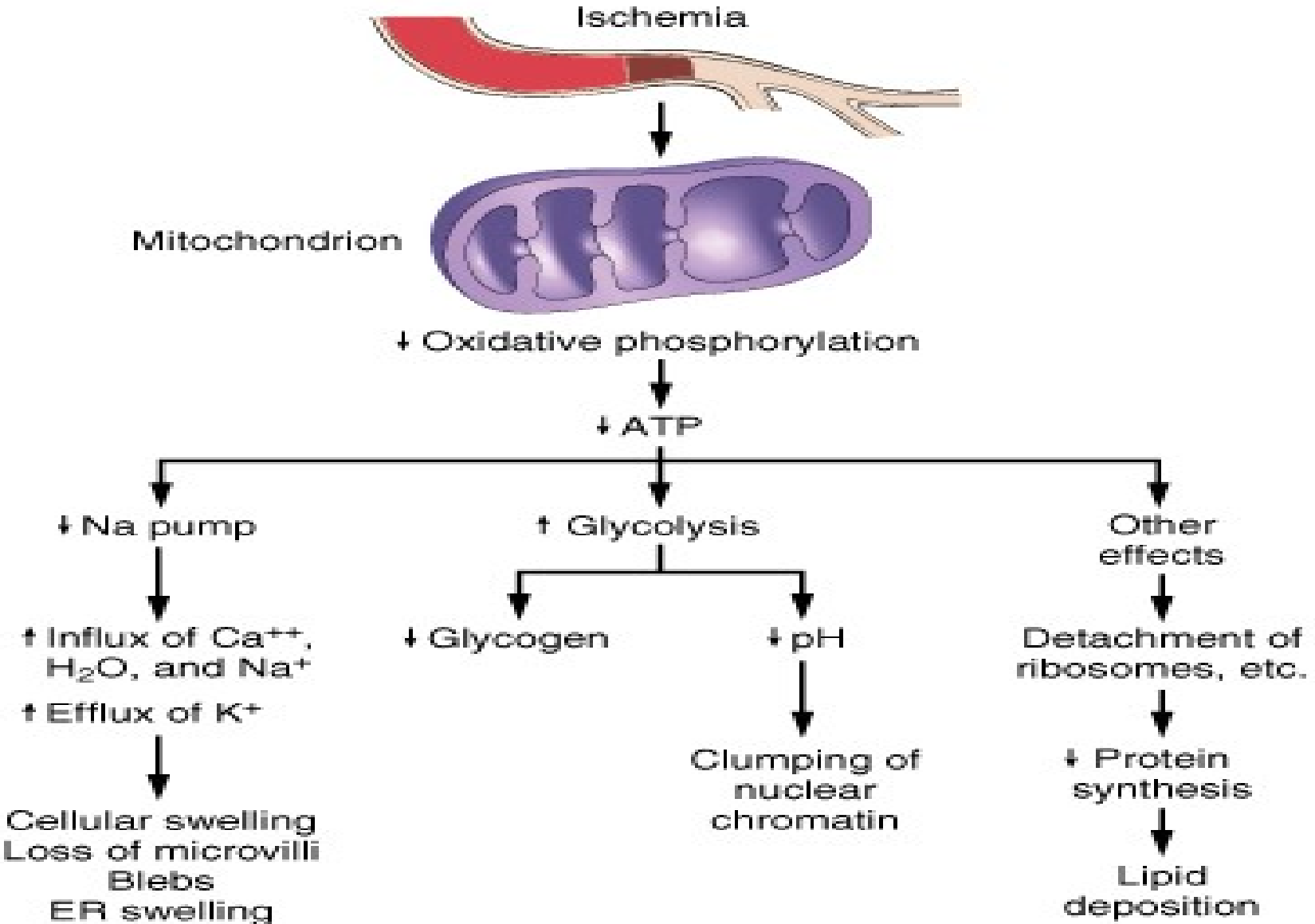
Ctd…


INJURIOUS STIMULUS
ATP
MEMBRANE DAMAGE
CYTOSKELETAL DAMAGE
DNA DAMAGE, ACCUMULATION OF MISFOLDED PROTEINS
Mitochondria
Plasma membrane
Lysosome
Membrane damage
Multiple stream effects
Cell death
Loss of cellular components
Enzymatic digestion of cellular components
CELL DEATH (mainly by apoptosis)
NECROSIS

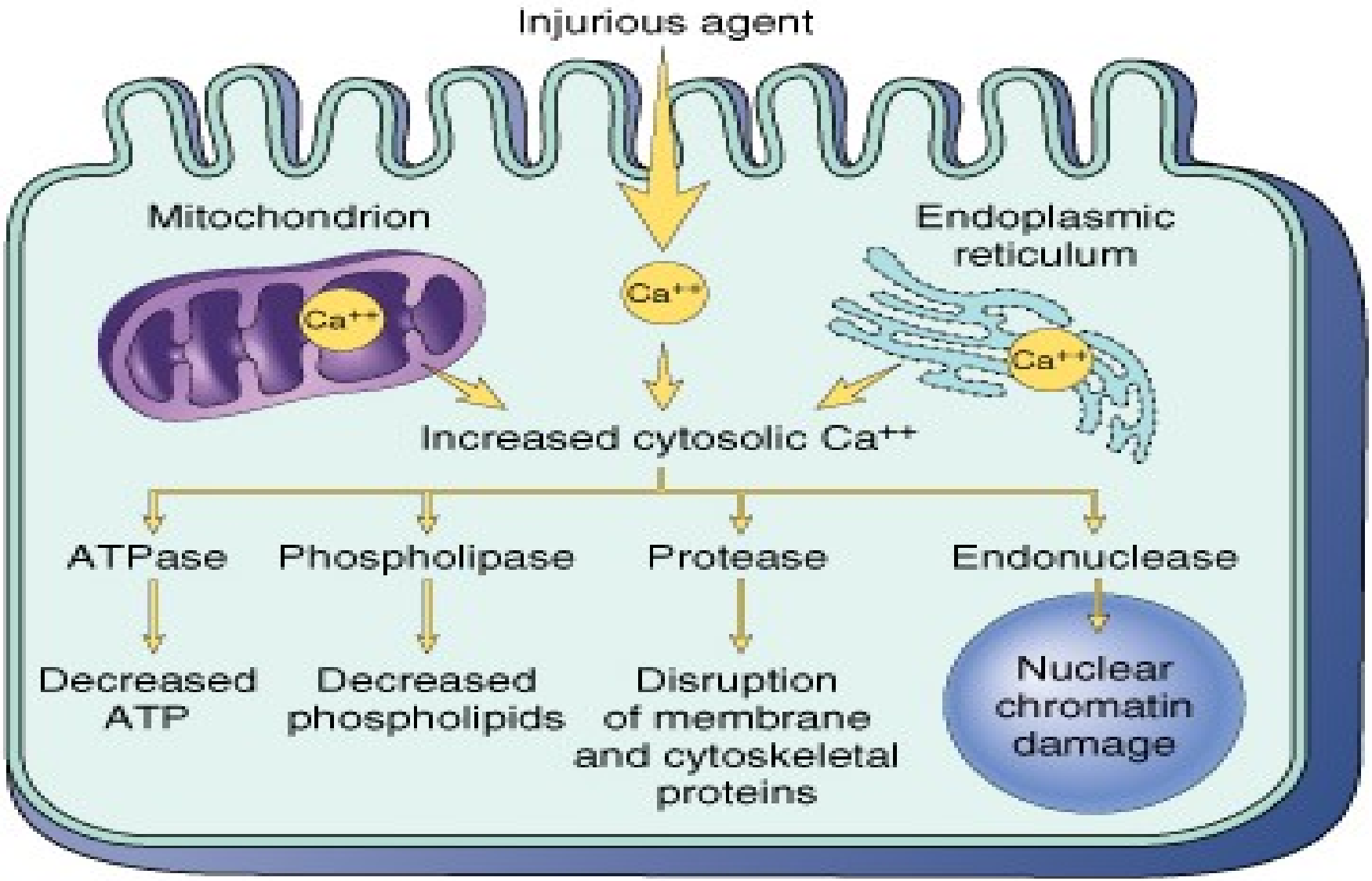
Ctd…

- Biochemical mechanisms that are responsible for cell injury induced by different stimuli:-
- ✓ Depletion of ATP
- ✓ Mitochondrial damage
- ✓ Influx of intracellular calcium & loss of calcium homeostasis
- ✓ Accumulation of oxygen-derived free radicals (oxidative stress)
- ✓ Defects in membrane permeability

Ctd…


Ischemia
Mitochondrion
↓ Oxidative phosphorylation
↓ ATP
↓ Na pump
↑ Glycolysis
Other effects
↑ Influx of Ca++, H2O, and Na+
↑ Efflux of K+
↓ Glycogen
↓ pH
Detachment of ribosomes, etc.
Clumping of nuclear chromatin
↓ Protein synthesis
Cellular swelling
Loss of microvilli
Blebs
ER swelling
Lipid deposition

Ctd…


Injurious agent
Mitochondrion
Ca++
Ca++
Endoplasmic reticulum
Ca++
Increased cytosolic Ca++
ATPase
Phospholipase
Protease
Endonuclease
Decreased ATP
Decreased phospholipids
Disruption of membrane and cytoskeletal proteins
Nuclear chromatin damage

Cell injury

- **Reversible cell injury**
- **Irreversible cell injury**

Reversible cell injury

- When cell come back to normal after removal of the injurious agent
- Two patterns can be recognized under the light microscopy

✓ ***Cellular swelling***

- First manifestation of injury
- It appears whenever the cells are incapable of maintaining ionic & fluid homeostasis & is result of loss of function of plasma membrane energy dependent ion pumps.

Ctd…

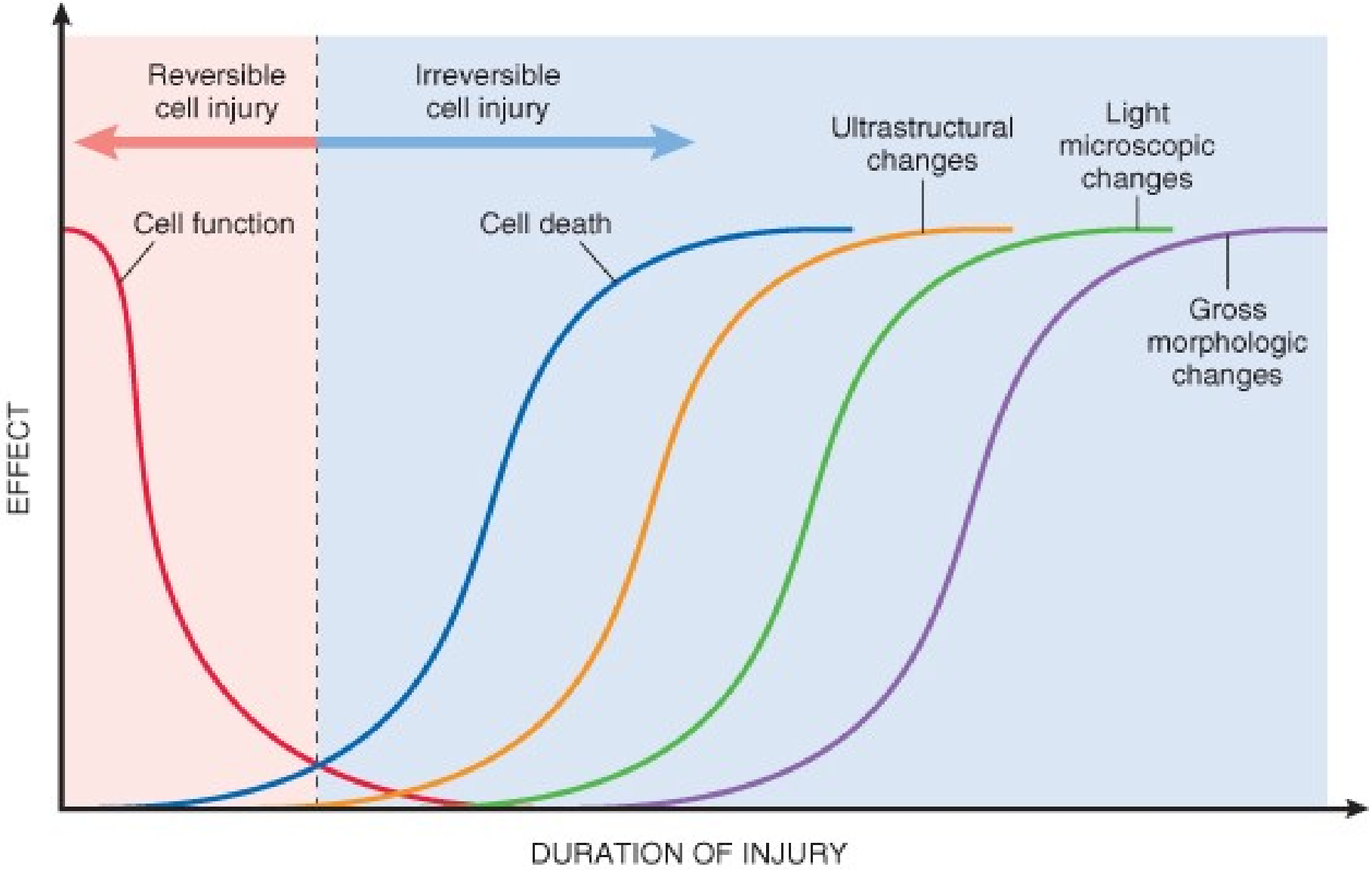
- ***Fatty change***

- **Manifested by the appearance of small & large lipid vacuoles in the cytoplasm & occurs in hypoxic & various toxic injury**
- **Principally seen in cells involved in & dependant on fat metabolism such as hepatocytes & myocardial cells**

Irreversible cell injury

- With persistent stimuli ---- cell can not recover so irreversible cell injury.
- Irreversibly injured cells undergo changes that are recognized as **cell death**.

Example


Reversible cell injury
Irreversible cell injury
Cell function
Cell death
Ultrastructural changes
Light microscopic changes
Gross morphologic changes
EFFECT
DURATION OF INJURY

Ctd…

Cell death **–** is the ultimate result of cell injury &

- ✓ Is one of the crucial event in the development of disease
- ✓ With cell death, there are marked changes with in the cell.
- ▶ There are two types of cell death:-

  Necrosis

  Apoptosis

Necrosis

- Is death of a cell or tissue
- It refers to a spectrum of morphologic changes that follow cell death in a living tissue resulting from the **progressive degenerative action of enzymes in lethally injured cells**
- It is **always pathological**

Nuclear changes

- Karyolysis – the basophilia of the nucleus fades
- Pyknosis – nuclear shrinkage & increased basophilia
- Karyorrhexis – nuclear fragmentation

TYPES OF NECROSIS

1. **Coagulative necrosis**

- Most often results from **sudden interruption of blood supply to an organ**
- It is , in early stage, characterized by general preservation of tissue architecture.

Ctd…

2. **Liquefactive necrosis**

- ✓ It is characterized by **digestion of tissue**. It shows softening & liquefaction of tissue.
- ✓ It characteristically results from **ischemic injury to the CNS**
- ✓ It also occurs in **suppurative infections characterized by formation of pus**.

Ctd…

3. **Gangrenous necrosis**

- ✓ When considerable mass of tissue undergo necrosis
- ✓ Two types gangrene
  - Dry
  - Wet

Dry gangrene

- Is associated with obstruction of the **arterial blood** supply **with out interference of the venous return**.
- Is confined to the **extremities**
- The involved part become **dry, skin wrinkle**
- The color change to **dark brown or black**
- The spread is **slow**
- **There is a line of demarcation**
- **Can be changed to wet gangrene, if bacterial infection.**

Wet gangrene

- Is primarily due to interference of the **venous return**
- There is **bacterial invasion**
- **Can affect the extremities or even the internal organs**
- The involved part is **cold, swollen & pulseless**
- The skin is **moist, foul smelling & black**
- No line of demarcation
- Spread of tissue is **rapid**
- Can be fatal

Ctd…

4. **Caseous necrosis**

- It is type of necrosis most often seen in foci of **tuberculous infection**
- The term caseous is derived from the **cheesy white gross appearance of the area of necrosis.**
- On microscopic examination, the necrotic focus appears as amorphous granular debris

Ctd…

5. **Fat necrosis**

- Focal areas of **fat destruction**, typically occurring as a result of release of **activated pancreatic lipases** in to the substance of the pancreas & the peritoneal cavity. This occurs in **acute pancreatitis**.
- The activated enzymes **liquefy fat cell membranes & the lipases split the triglyceride contained with in fat cells**. The released **fatty acids** combine with **calcium** to produce grossly visible **chalky white areas(fat saponification**)

Ctd…

- Necrosis can be followed by release of intracellular enzymes into the blood to produce **inflammation** or **dystrophic calcification.**

Apoptosis

- It is a pathway of cell death that is **induced by tightly regulated intracellular program** in which cells destined to die activate enzymes that degrade the cells **own nuclear DNA & nuclear & cytoplasmic proteins.**
- Can be **physiologic** or **pathologic**

Apoptosis in **physiologic situations**

- Programmed **destruction** of cells during embryogenesis
- Hormone dependent **involution** in the adults.
- Cell **deletion** in proliferating cell populations.
- **Death** of host cells that have served their useful purpose.
- **Elimination** of potentially harmful self reactive lymphocytes.

Apoptosis in **pathologic situations**

- Cell death produced by a variety of injurious stimuli such as **radiation & cytotoxic anticancer** drugs
- Cell injury in certain **viral diseases** such as viral hepatitis.
- Pathologic **atrophy** in parenchymal organs after **duct obstruction**
- Cell death in **tumors**

Morphology

- The following morphologic features characterize cells undergoing apoptosis
  - **Cell shrinkage**
  - **Chromatin condensation**
  - **Formation of cytoplasmic blebs & apoptotic bodies**
  - **Phagocytosis** of apoptotic cells or cell bodies usually by **macrophages.**

Mechanisms of Apoptosis

- Apoptosis is an active **enzymatic process** in which **nucleoproteins** are broken down and then the cell is fragmented.
- The fundamental event in apoptosis is the activation of enzymes called ***caspases.***

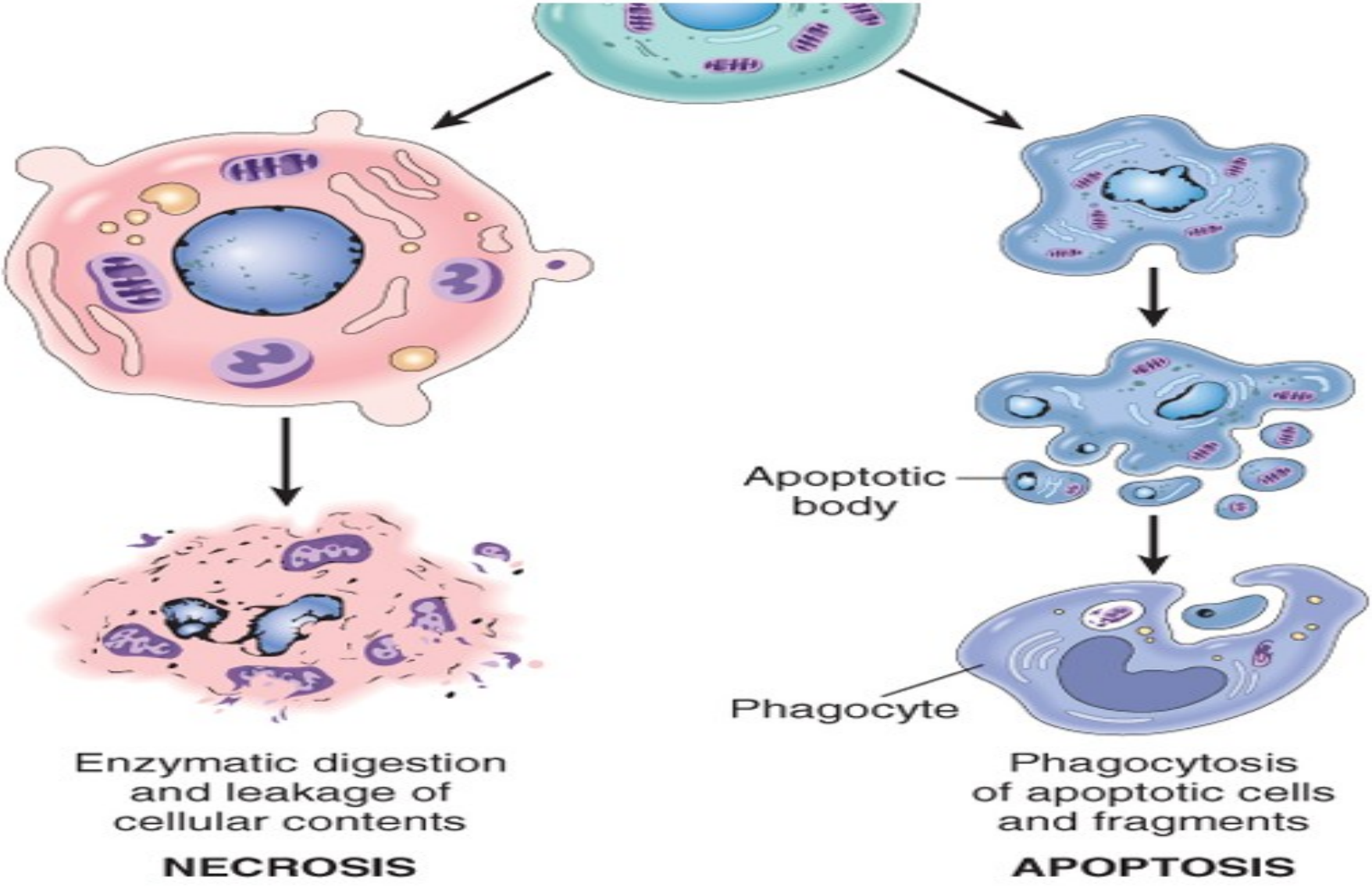
1. The Mitochondrial (Intrinsic) Pathway of Apoptosis

2. The Death Receptor (Extrinsic) Pathway of Apoptosis

Clearance of Apoptotic Cells

- Apoptotic cells undergo several changes in their membranes that promote their **phagocytosis**. In normal cells phosphatidylserine is present on the inner leaflet of the plasma membrane, but in apoptotic cells this phospholipid "**flips**" out and is expressed on the outer layer of the membrane, where it is recognized by macrophages.
- Cells that are dying by apoptosis also secrete **soluble factors** that recruit phagocytes.

Ctd…


Apoptotic body
Phagocyte
Enzymatic digestion and leakage of cellular contents
NECROSIS
Phagocytosis of apoptotic cells and fragments
APOPTOSIS

Features of necrosis & apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

Subcellular Responses to Injury

- Certain agents and stresses induce distinctive alterations involving only subcellular organelles.
- Some of these alterations occur in acute lethal injury, others are seen in chronic forms of cell injury, and still others are adaptive responses.
- **Autophagy** refers to lysosomal digestion of the cell's own **components.**

Ctd…

- Autophagy is thought to be a **survival** mechanism in **times of nutrient deprivation**, such that the starved cell lives by eating its own contents.
- Intracellular organelles and portions of cytosol are first sequestered from the cytoplasm in an ***autophagic vacuole*** formed from ribosome-free regions of the rough ER (RER).

Ctd…

- The vacuole fuses with lysosomes to form an ***autophagolysosome***, and the cellular components are digested by lysosomal enzymes.
- ***Heterophagy***, in which a cell (usually a macrophage) ingests substances from the outside for intracellular destruction.

A. Induction (Hypertrophy) of Smooth ER

- The smooth ER (SER) is involved in the metabolism of various chemicals, and cells exposed to these chemicals show hypertrophy of the ER as an adaptive response that may have important functional consequences.
- For instance, **barbiturates** are metabolized in the liver by the **cytochrome P-450** mixed-function oxidase system found in the SER.
- In addition, the products formed by this oxidative metabolism include **reactive oxygen species** (ROS), which can injure the cell.

B. Mitochondrial Alterations

- Mitochondrial dysfunction plays an important role in acute cell injury and death.
- In some non lethal pathologic conditions, there may be alterations in the number, size, shape, and presumably function of mitochondria.
- Mitochondria may assume extremely large and abnormal shapes (*megamitochondria*), as seen in hepatocytes in various nutritional deficiencies and alcoholic liver disease.
- Inherited metabolic diseases of skeletal muscle, the *mitochondrial myopathies.*

C. Cytoskeletal Abnormalities

- Abnormalities of the cytoskeleton occur in a variety of pathologic states.
- These abnormalities may be manifested as an abnormal appearance and function of cells.
- Perturbations in the organization of ***microtubules*** can cause sterility by **inhibiting sperm motility**, as well as ***defective mobility of cilia in the respiratory epithelium***, resulting in **chronic infections** due to impaired clearance of inhaled bacteria.

D. Intracellular accumulations

- ***There are three main pathways of abnormal intracellular accumulations***

1. A normal substance is produced at a normal or an increased rate, but the metabolic rate is inadequate to remove it.
2. A normal or an abnormal endogenous substance accumulates because of genetic or acquired defects in its folding, packaging, transport, or secretion.
3. An abnormal exogenous substance is deposited and accumulates because the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites.

1. Fatty Change (Steatosis)

- *Fatty change* refers to any abnormal accumulation of **triglycerides** within **parenchymal cells**.
- It is most often seen in the liver but it may also occur in heart, skeletal muscle, kidney, and other organs.
- Steatosis may be caused by
  - toxins
  - protein malnutrition
  - diabetes mellitus
  - obesity, and
  - anoxia

Ctd…

- The significance of fatty change depends on the cause and severity of the accumulation.
- When mild, it may have no effect on cellular function.
- Fatty change is reversible. In the severe form, fatty change may precede cell death, and may be an early lesion in a serious liver disease called ***nonalcoholic steatohepatitis.***

2. Cholesterol and Cholesteryl Esters

- **Cellular cholesterol metabolism is tightly regulated to ensure normal cell membrane synthesis without significant intracellular accumulation**
- **Phagocytic cells**
- Macrophages may be filled with minute, membrane-bound vacuoles of lipid, imparting a foamy appearance to their cytoplasm ***(foam cells)***.
- In hereditary and acquired hyperlipidemic syndromes, **macrophages** accumulate intracellular cholesterol; when present in the **subepithelial** connective tissue of skin or in tendons, clusters of these foamy macrophages form masses called ***xanthomas***.

3. Proteins

- Morphologically visible protein accumulations are much less common than lipid accumulations.
- Example:- the marked accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells, forming rounded, eosinophilic ***Russell bodies*****.**
- Mallory body, or "alcoholic hyalin," is an eosinophilic cytoplasmic inclusion in liver cells that is highly characteristic of **alcoholic liver disease.**

4. Glycogen

- Excessive intracellular deposits of glycogen are associated with abnormalities in the metabolism of either **glucose** or **glycogen**.
- Glycogen also accumulates within cells in a group of closely related genetic disorders collectively referred to as ***glycogen storage diseases, or glycogenoses***

5. Pigments

- Are colored substances, some of which are **normal** constitutes of cells (eg. Melanin) whereas others are **abnormal**.
- Pigments can be **endogenous** or **exogenous**

Exogenous pigments

- Accumulation of **carbon or coal dust** blacken lung tissue & involved LNs – **antracosis**. When inhaled, it is picked up by alveolar macrophages & transported into the regional LNs.
- **Tattooing** is a form of localized exogenous pigmentation of the skin. The pigments inoculated are phagocytosed by dermal macrophages.

Endogenous pigments

A. Melanin

- Is a brownish-black pigment produced by the melanocytes found in the skin.
- Increased melanin pigmentation is caused by sun tanning & certain disease

Eg. Nevus, or malignant melanoma & decreased melanin pigmentation is seen in **albinism & vitiligo**

Ctd…

B. Bilirubin

- Is a yellowish pigment, mainly produced during the degradation of **hemoglobin**.
- Excessive accumulation of bilirubin causes yellowish discoloration of the sclera, mucosa, & internal organs.
- Such a yellowish discoloration is called **jaundice**

Ctd…

C. Hemosiderin

- Is an iron-containing pigment derived from **ferritin**. It appears in tissue as a **golden brown amorphous aggregates** & is identified by its staining reaction (blue color) with the **Prussian blue dye**.
- Small amount normally found in **bone marrow, liver & spleen**.
- It can be local or systemic derangement

Ctd…

- Excess accumulation is divided into 2 types

I. **Hemosiderosis**

- When accumulation of hemosiderin is primarily within **tissue macrophages** & is not associated with tissue damage.

II. **Hemochromatosis**

- When there is more extensive accumulation of hemosiderin, often within ***parenchymal cells***, which leads to tissue damage, scarring & organ dysfunction.

6. PATHOLOGIC CALCIFICATION

- It implies the abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals.

Two types

- Dystrophic calcification
- Metastatic calcification

I. Dystrophic calcification

- When the deposition occurs in dead or dying tissues, it is called ***dystrophic calcification****; it occurs in the absence of calcium metabolic* derangements (i.e., with normal serum levels of calcium).
- Dystrophic calcification is encountered in areas of **necrosis of any type**.
- Although dystrophic calcification may be an incidental finding indicating insignificant past cell injury, it may also be a cause of organ dysfunction.
- For example, calcification can develop in aging or damaged heart valves, resulting in severely compromised valve motion

II. Metastatic Calcification

- Metastatic calcification can occur in normal tissues whenever there is **hypercalcemia**.
- The four major causes of hypercalcemia are

1. *Increased secretion of parathyroid hormone*
2. *Destruction of bone* due to the effects of accelerated turnover (e.g., *Paget disease*), immobilization, or tumors
3. *Vitamin D-related disorders* including vitamin D intoxication and *sarcoidosis* and
4. *Renal failure,* in which phosphate retention leads to ***secondary hyperparathyroidism***

Amyloidosis

- Is a pathologic **proteinaceous substance deposited between cells** in various tissue & organs of the body in a wide variety of clinical settings
- Amyloid is a beta pleated sheets of protein
- Clinical diagnosis depends on morphologic identification of this distinctive substance in appropriate **biopsy** specimen.

Ctd…

- On light microscopy & standard tissue stains, **amyloid** appears as an **amorphous, eosinophilic, hyaline**, extracellular substance with progressive accumulation, encroaches on & produces **pressure atrophy** of adjacent cells

Ctd…

- To differentiate it from other proteins, **congo red stain** is used, it imparts a pink or red color to tissue deposits under ordinary light. Under polarizing microscopy green birefringence of the stained amyloid is seen.

Classification of amyloidosis

Primary amyloidosis

- It is usually systemic distribution & is characterized by deposition of the **AL** type.
- Most pts have some form of plasma cell dyscrasia such as multiple myeloma.

Ctd…

Reactive systemic amyloidosis

- The amyloid deposits in this pattern are systemic in distribution & are composed of **AA** protein
- It occurs secondary to an **associated inflammatory condition** – tuberculosis, bronchoectasis, chronic osteomyelitis, RA.

3. Inflammation

HAVE A BREAK!



History

- **Egyptian papyrus - 3000 B.C.**
- **Celsus (Roman in 1st century A.D.)**

  Rubor - Tumor - Calor - Dolor

  redness - swelling - heat - pain
- **Virchow added functio laesa later**

What is inflammation?

- Inflammation –

  Protective response intended to eliminate the initial cause of cell injury and the necrotic cells and tissues arising from the injury.

- Inflammation is intimately associated with the **repair process** which includes parenchymal cell regeneration and scarring.

Inflammation

- Acute - minutes to days
  - Characterized by fluid and protein
  - *PMN's*
  - Exudate SG > 1.020
- Chronic - weeks to years
  - *Lymphocytes and macrophages*
- ACUTE Inflammation - PMN's (Polymorphonuclear Cells)
- CHRONIC Inflammation - Mononuclear Cells

EXUDATE

Acute inflammation

"The immediate and early response to an injurious agent"

Chronic inflammation

"Inflammation of prolonged duration (weeks or months) in which active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously"

Exudate

- ↑ vascular permeability
- high protein & cell debris
- SG > 1.020

Transudate

- normal vascular permeability
- hydrostatic pres. → plasma ultrafiltrate
- low protein (mostly albumin)
- SG < 1.012

Edema

- exudate or transudate ; interstitium or cavity

Acute inflammation major components

- Transient vasoconstriction
- Vasodilatation
- Endothelial permeability
- Extravasation of PMNs

Five classic local signs of acute inflammation

- Heat
- Redness
- Swelling
- Pain
- Loss of function

- Calor – vasodilatation
- Rubor – vasodilatation
- Tumor – vascular permeability
- Dolor – mediator release/PMNs
- Functio laesa – loss of function

Vascular changes *you need to know this*

- Transient vasoconstriction
- Vasodilation
- Exudation of protein rich fluid
- Blood stasis
- Margination
- Emigration/Transmigration

Vascular changes

Protein exits vessels :

↓ intravascular osmotic pressure

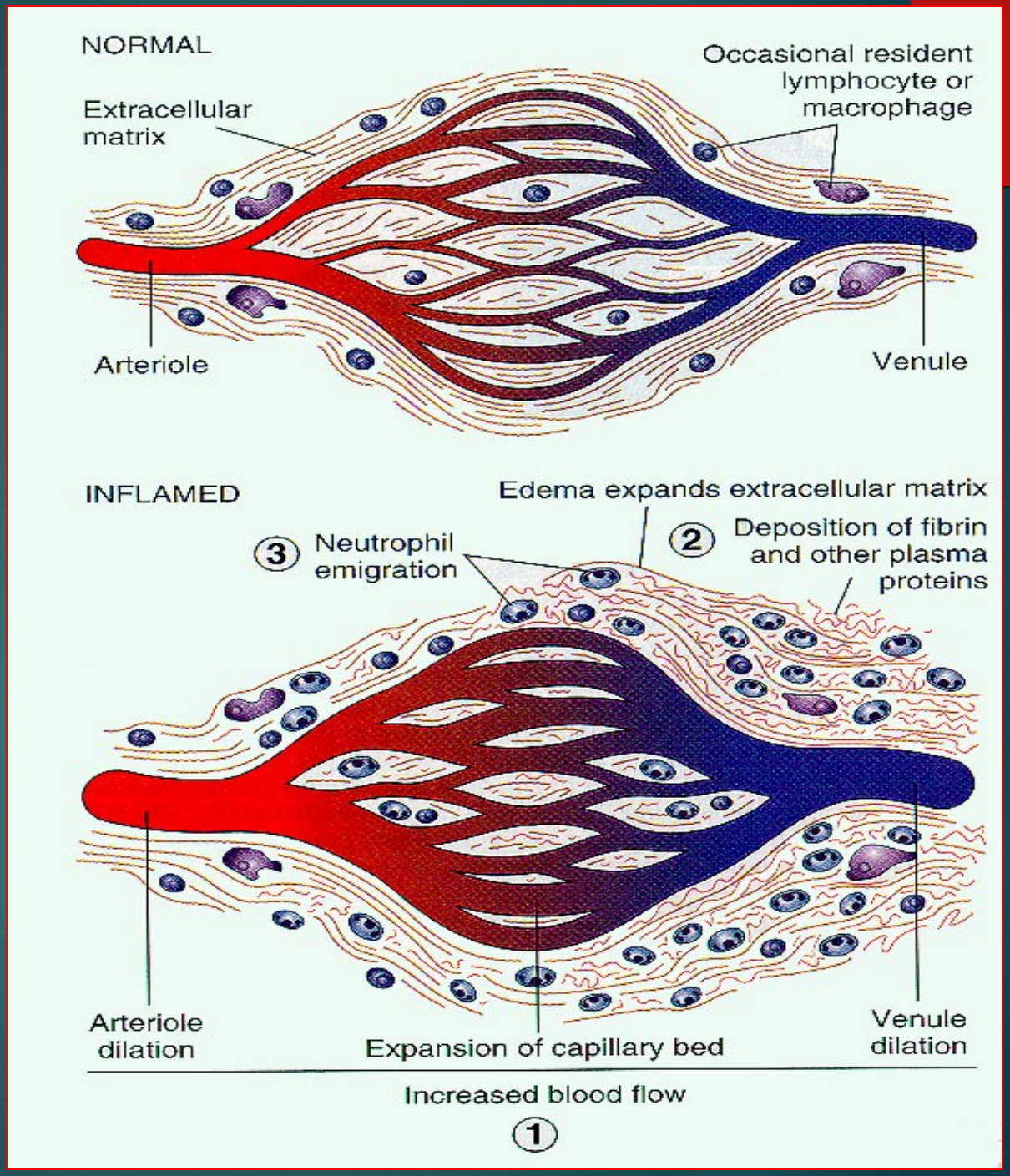
↑ intravascular hydrostatic pressure

Endothelial gaps at intercellular junctions:

*** immediate transient response**

*** histamine, bradykinin, leukotrienes, substance P**

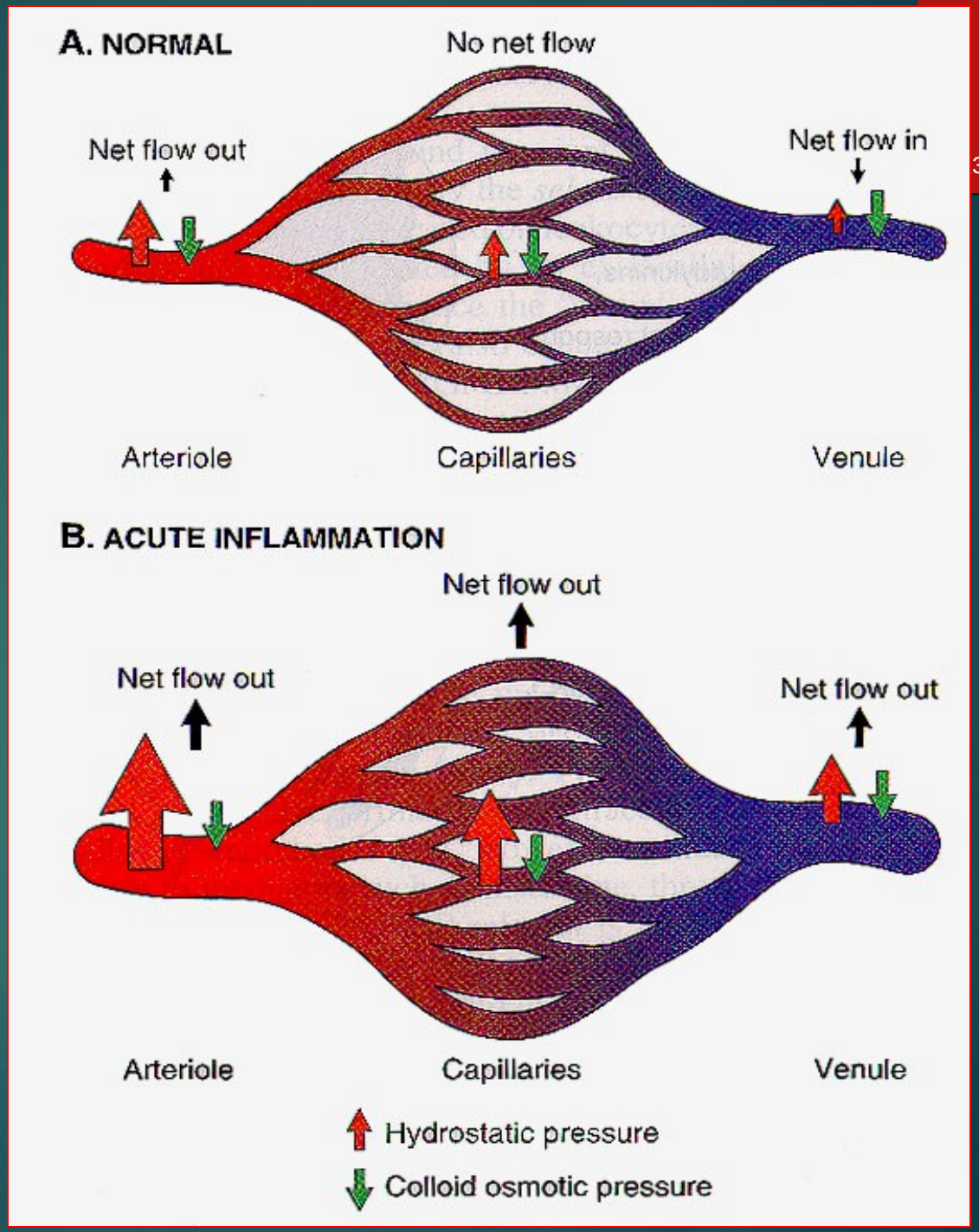
Fig 3-2


NORMAL
Occasional resident lymphocyte or macrophage
Extracellular matrix
Arteriole
Venule
INFLAMED
Edema expands extracellular matrix
2
Deposition of fibrin and other plasma proteins
3
Neutrophil emigration
Arteriole dilation
Expansion of capillary bed
Venule dilation
Increased blood flow
1

Vascular permeability

- Vasodilation – increased blood flow
- Increased intravascular hydrostatic pressure
- *Transudate* - ultrafiltrate blood plasma (contains little protein)
  - Again, this is very transient and just gets the process started. Think acute inflammation, think EXUDATE
- *Exudate* - (protein-rich with PMNs)
  - *Exudate is the characteristic fluid of acute inflammation*
- Intravascular osmotic pressure decreases
- Osmotic pressure of interstitial fluid increases
- Outflow of water and ions - *edema*

Fig 3-3


A. NORMAL
No net flow
Net flow out
Net flow in
Arteriole
Capillaries
Venule
B. ACUTE INFLAMMATION
Net flow out
Net flow out
Net flow out
Arteriole
Capillaries
Venule
Hydrostatic pressure
Colloid osmotic pressure

How do endothelial cells become permeable?

- Endothelial cell contraction
- Junctional retraction
- Direct endothelial injury (immediate sustained response)
- Leukocyte-dependent endothelial injury
- Increased transcytosis of fluid

Direct endothelial injury (immediate sustained response)

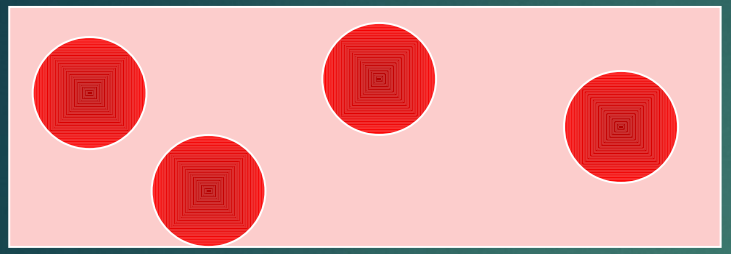
- Endothelial cell necrosis and detachment
- Result of severe injury or burn
- Occurs immediately and lasts until vessel repaired

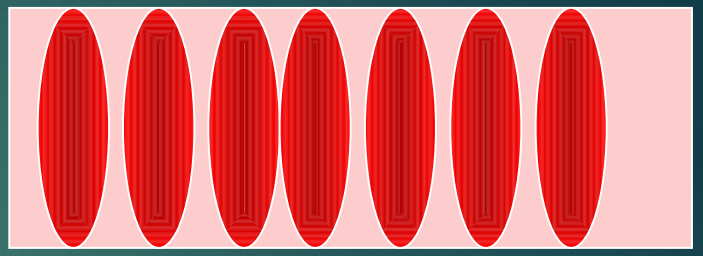
Leukocyte-dependent endothelial injury

- Occurs at sites of leukocyte accumulation
- Due to leukocyte activation which releases proteolytic enzymes and toxic oxygen

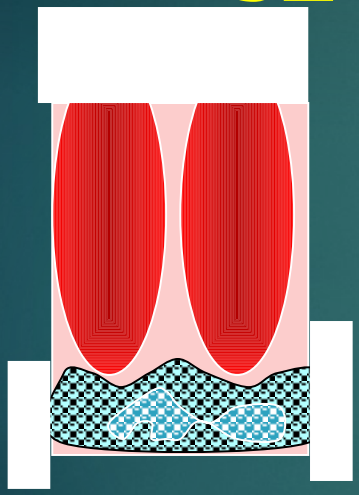
Leukocyte Cellular Events

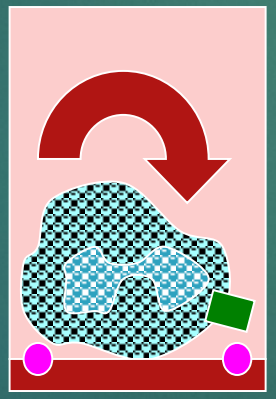
- Margination and Rolling
- Adhesion and Transmigration
- Migration into interstitial tissue

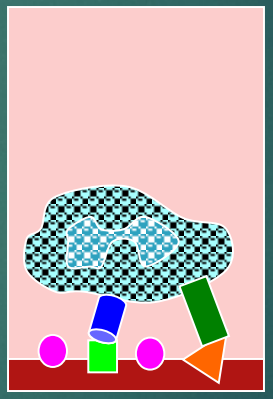


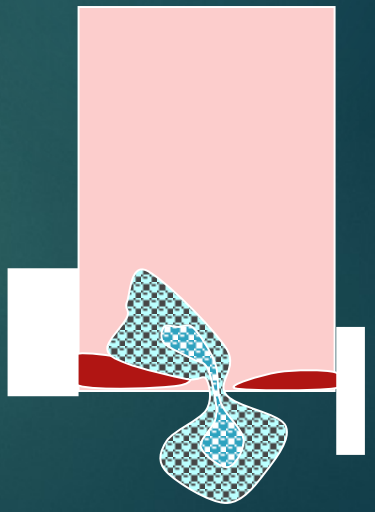


SLOWING CONCENTRATION

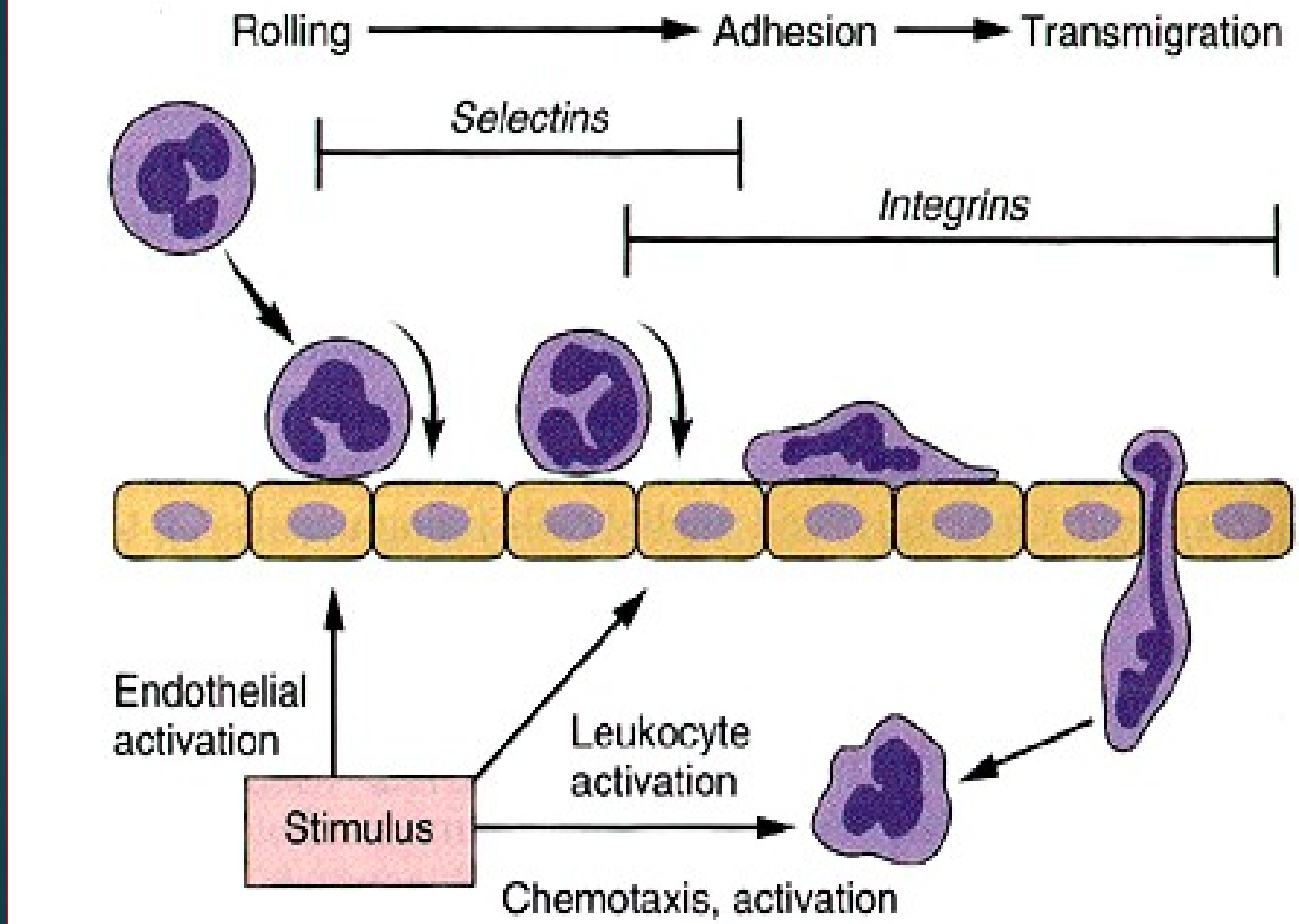


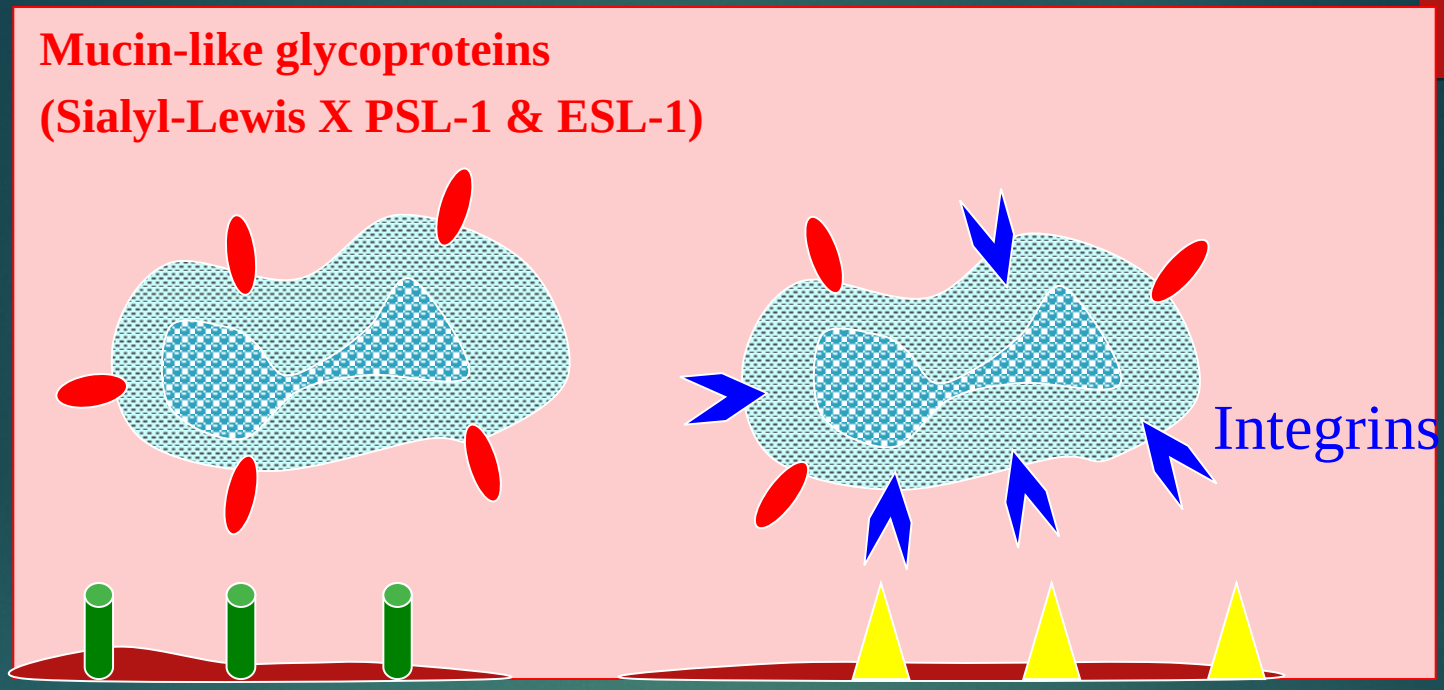






Margination Rolling Adhesion Transmigration


Rolling
Adhesion
Transmigration
Selectins
Integrins
Endothelial activation
Leukocyte activation
Stimulus
Chemotaxis, activation



Selectins

Weak and transient binding

Results in rolling

CAMS

Integrins upregulated and activated for increased affinity to CAMS

Results in firm adhesion

Margination

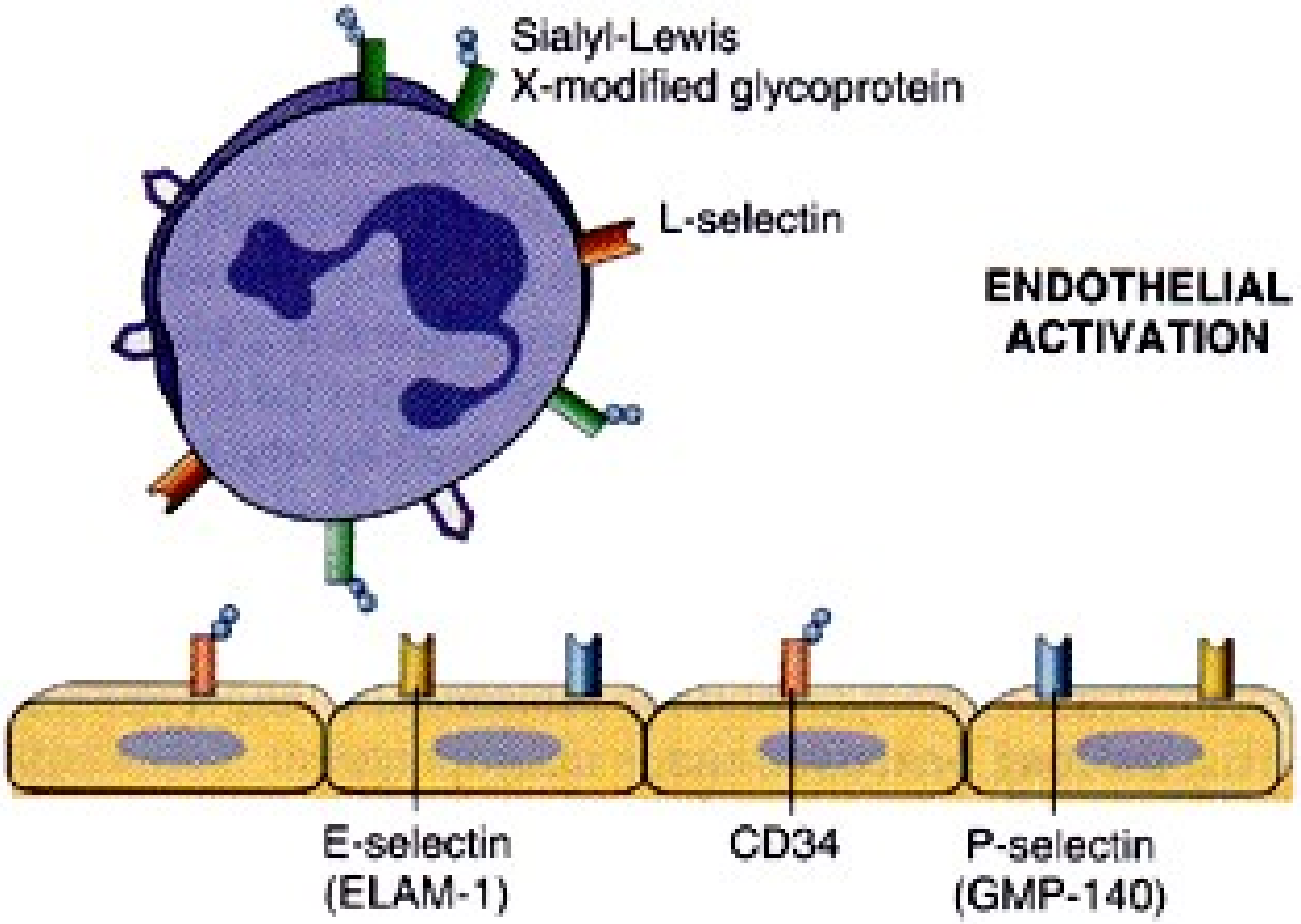
- Normal flow - RBCs and WBCs flow in the center of the vessel
- A *cell poor* plasma is flowing adjacent to endothelium
- As blood flow slows, WBCs collect along the endothelium → Margination

Endothelial Activation

- The underlying stimulus causes release of mediators which activate the endothelium causing selectins and other mediators to be moved quickly to the surface

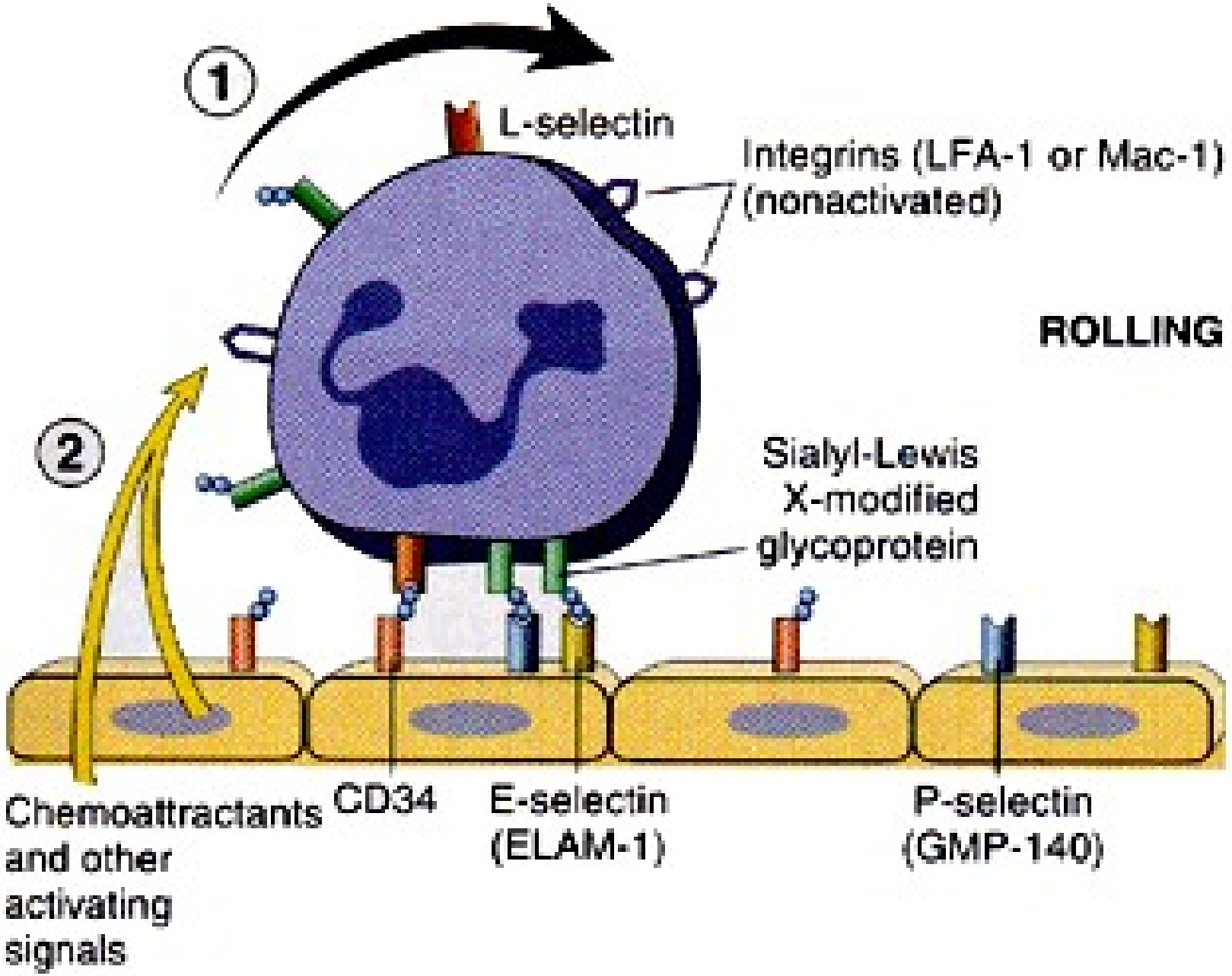
Selectins

- Selectins bind selected sugars
  - *Se*lected + *Lectins* (sugars) = Selectins
- Some selectins are present on endothelial cells (E-Selectin)
- Some selectins are present on leukocytes (L-Selectin)
- Some selectins are present on platelets (P-Selectin)
- Weak & transient binding
- Results in rolling


Sialyl-Lewis
X-modified glycoprotein
L-selectin
ENDOTHELIAL
ACTIVATION
E-selectin
(ELAM-1)
CD34
P-selectin
(GMP-140)

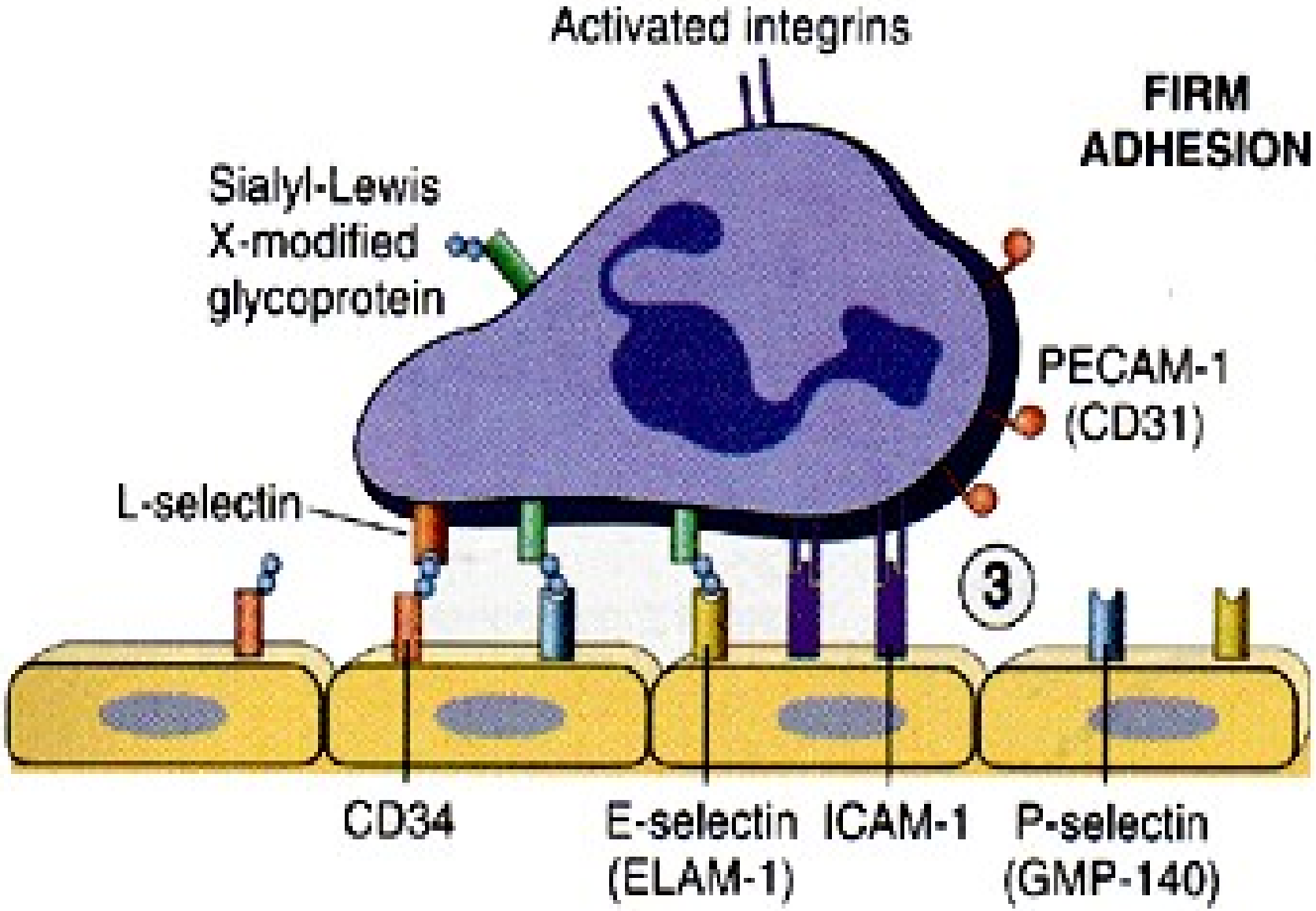
Rolling

- Selectins transiently bind to receptors
- PMNs bounce or roll along → Rolling


1
L-selectin
Integrins (LFA-1 or Mac-1)
(nonactivated)
ROLLING
2
Sialyl-Lewis
X-modified
glycoprotein
Chemoattractants
and other
activating
signals
CD34
E-selectin
(ELAM-1)
P-selectin
(GMP-140)

Adhesion

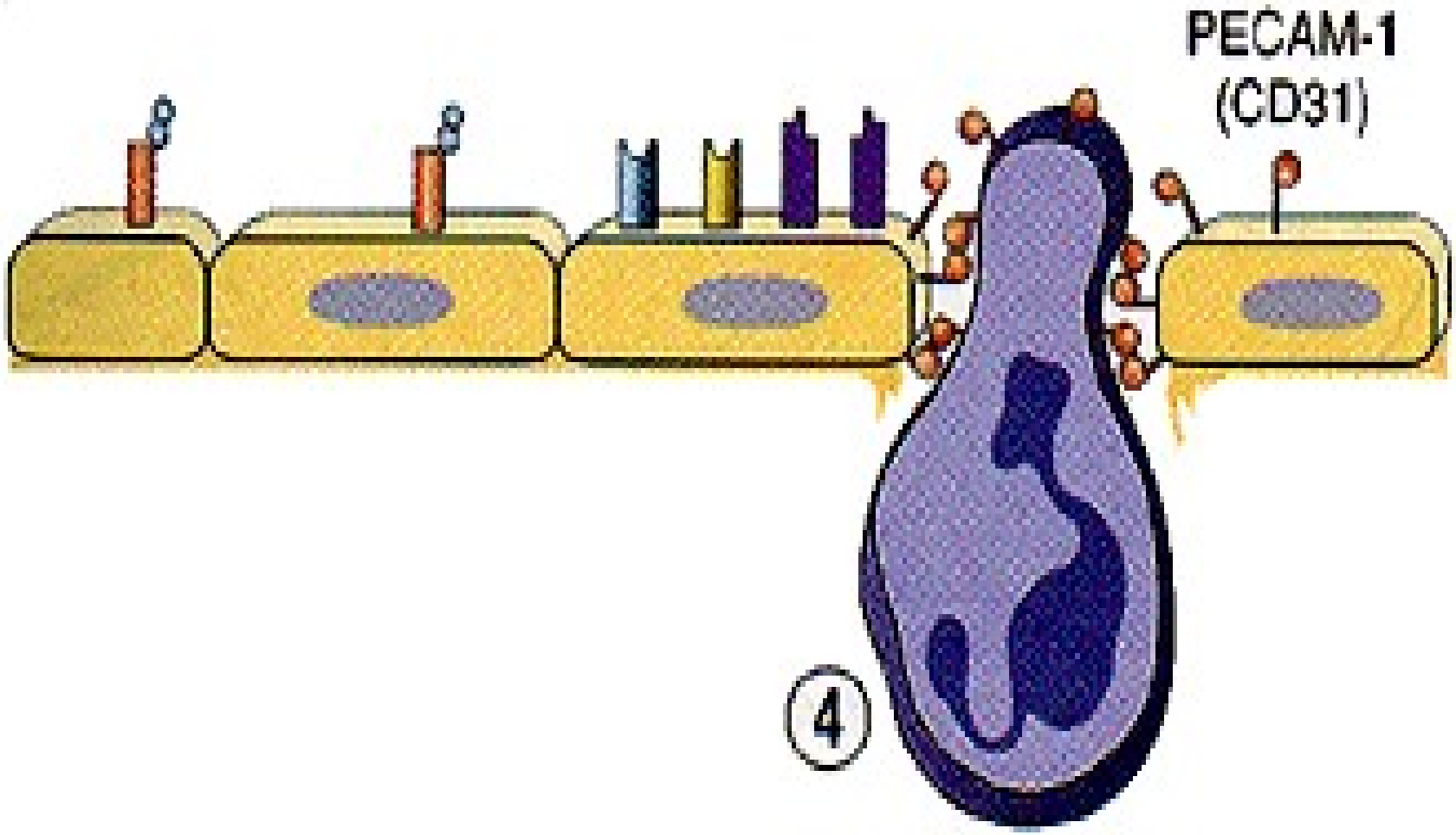
- Mediated by integrins ICAM-1 and VCAM-1


Activated integrins
FIRM ADHESION
Sialyl-Lewis X-modified glycoprotein
PECAM-1 (CD31)
L-selectin
3
CD34
E-selectin (ELAM-1)
ICAM-1
P-selectin (GMP-140)

Transmigration

- Mediated/assisted by PECAM-1 & ICAM-1 (Integrins)
- Diapedesis (cells crawling)
- Primary in venules
- Collagenases degrade BM ↑ Permeability

TRANSMIGRATION



Chemotaxis

- Movement toward the site of injury along a chemical gradient
  - Chemotactic factors include
    - Complement components (20 serum proteins)
    - Arachadonic acid (AA) metabolites
    - Soluble bacterial products
    - Chemokines, cytokines

Phagocytosis & Degranulation

- Phagocytosis (engulf and destroy)
- Degranulation and the oxidative burst destroy the engulfed particle
- Recognition & attachment
  - Opsonins coat target and bind to leukocytes
- Engulfment
- Killing/degradation
  - O_2 dep: Reactive O_2 species in lysosomes & EC
  - O_2 indep: Bactericidal permeability agents, lysozyme, lactoferrin

Leukocyte-induced tissue injury

- Lysosomal enzymes are released into the extracellular space during phagocytosis causing cell injury and matrix degradation
- Activated leukocytes release reactive oxygen species and products of arachidonic acid metabolism which can injure tissue and endothelial cells
- These events underlie many human diseases (e.g. Rheumatoid arthritis)

Disorders

Genetic	**Defect**
LAD 1	•B chain of CD11/CD18 integrins
LAD 2	•Sialylated oligosaccharide
Neutrophil-specific granule deficiency	•Absence of neutrophil-specific granules
CGD	•Defective chemotaxis
X-linked	•NADPH oxidase (membrane)
AR	•NADPH oxidase (cytoplasm)
MPO deficiency	•Absent MPO-H2O2 system
Chediak-Higashi syndrome	•Lysosomal defect
Acquired	
Thermal injury, DM, sepsis	•Chemotaxis
Dialysis, DM	•Adhesion
Leukemia, anemia, sepsis, DM, neonates, malnutrition	•Phagocytosis & microbicidal activity

Leukocyte adhesion deficiency 1 (LAD-1)

- Recurrent bacterial infections
- Inflammatory lesions lack neutrophil infiltrate
- High numbers of neutrophils in the circulation
- Neutrophils from patients can roll but do not stick
- B chain of CD11/CD18 integrin

Chediak-Higashi Syndrome

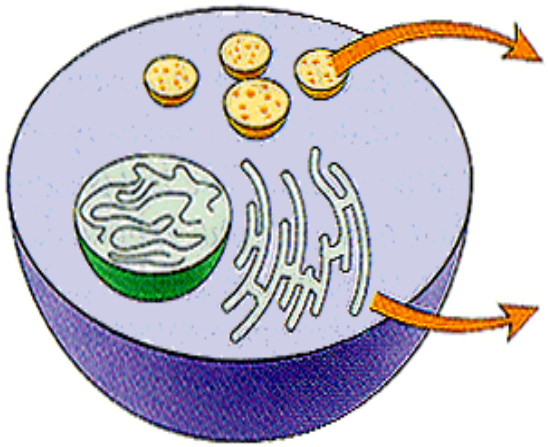
- This syndrome has been on every board test since Noah
- *Defects in phagolysosome formation*
- Defect in chemotaxis and lysosomal degranulation into phagosomes

Chronic Granulomatous Disease

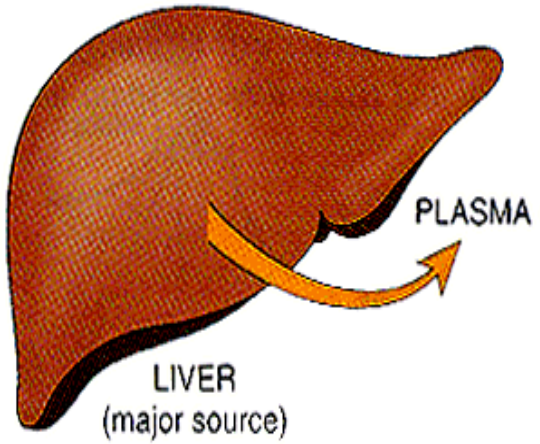
- Defect in NADPH oxidase system
- Marked decrease in ability to kill microorganisms

Chemical mediators of inflammation

- Plasma-derived
  - Circulating precursors
  - Have to be activated
- Cell-derived
  - Sequestered intracellular
  - Synthesized de novo
- Most mediators bind to receptors on cell surface but some have direct enzymatic or toxic activity
- Mediators are tightly regulated



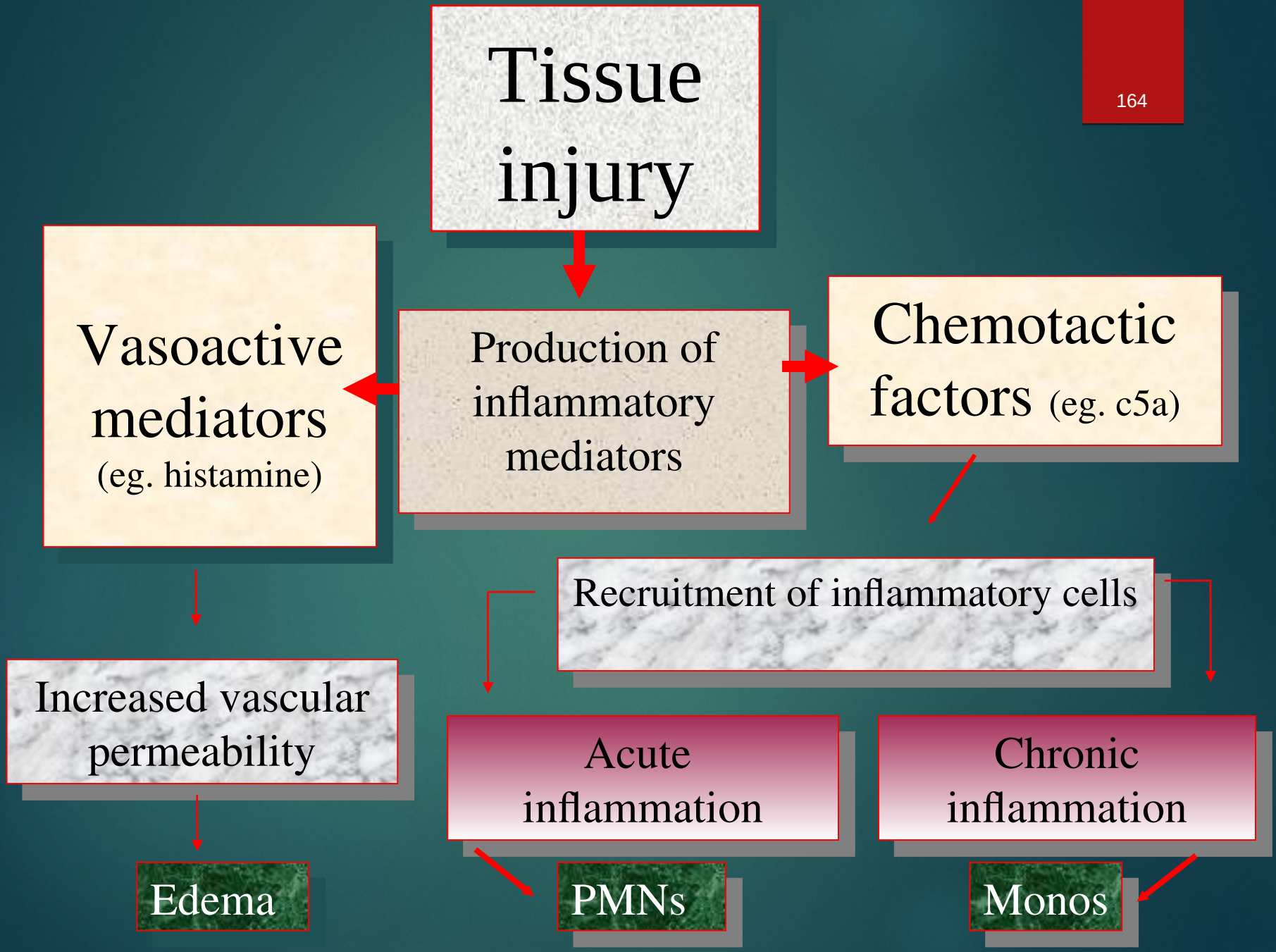
CELLULAR



PLASMA

LIVER
(major source)

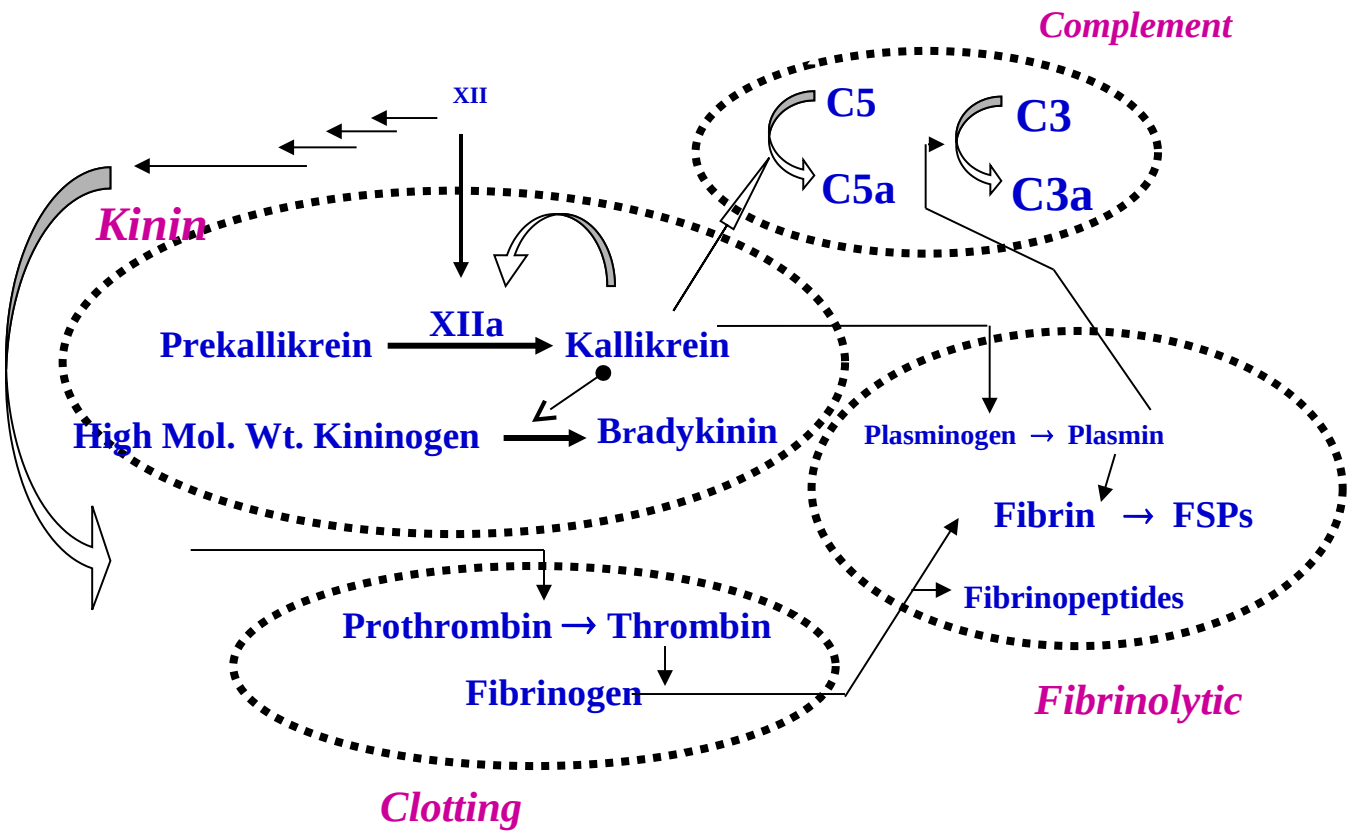
	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, EC
	Activated oxygen species	All leukocytes
	Nitric oxide	Macrophages
	Cytokines	Lymphocytes, macrophages, EC
Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	
Complement activation	C_{3a}, C_{5a}	anaphylatoxins
	C_{3b}	
	$C_{5b\text{-}9}$	(membrane attack complex)

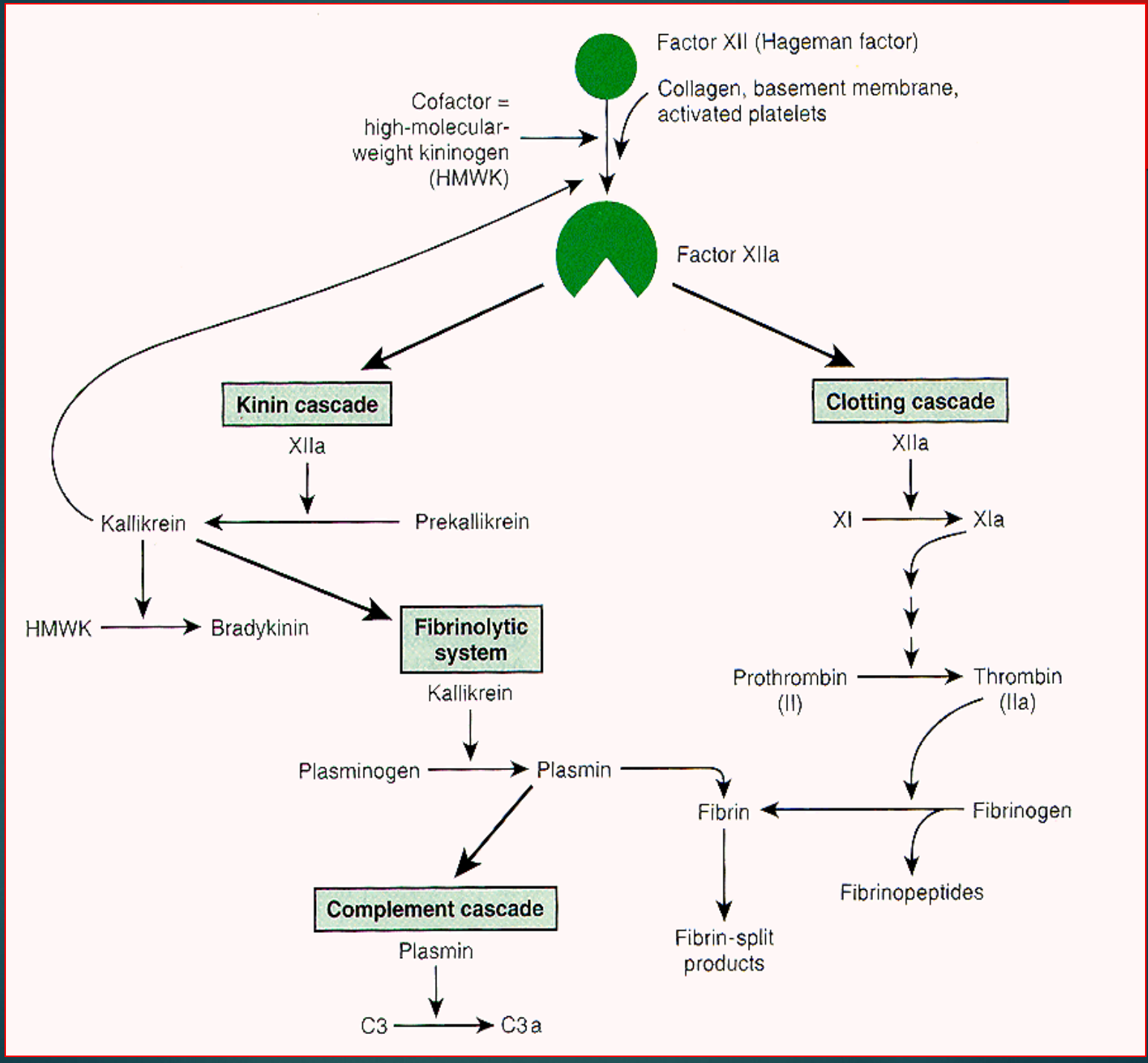

Tissue injury
Vasoactive mediators (eg. histamine)
Production of inflammatory mediators
Chemotactic factors (eg. c5a)
Recruitment of inflammatory cells
Increased vascular permeability
Acute inflammation
Chronic inflammation
Edema
PMNs
Monos

Plasma Mediator Systems - Interaction

1. **Kinin**
2. **Clotting**
3. **Complement**
4. **Fibrinolytic**

Plasma Mediator Systems - Interaction




Factor XII (Hageman factor)
Collagen, basement membrane, activated platelets
Cofactor = high-molecular-weight kininogen (HMWK)
Factor XIIa
Kinin cascade
XIIa
Kallikrein
Prekallikrein
HMWK
Bradykinin
Fibrinolytic system
Kallikrein
Plasminogen
Plasmin
Complement cascade
Plasmin
C3
C3a
Clotting cascade
XIIa
XI
XIa
Prothrombin (II)
Thrombin (IIa)
Fibrin
Fibrinogen
Fibrinopeptides
Fibrin-split products

Kinin cascade

- Leads to formation of bradykinin
- Bradykinin causes
  - Increased vascular permeability
  - Arteriolar dilatation
  - Smooth muscle contraction
- Bradykinin is short lived (kininases)
- Vascular actions similar to histamine

Complement system

- Role in immunity (C5-9 complex)
  - Membrane Attack Complex (MAC C5-9)
  - Punches a hole in the membrane

Complement system

- Role in inflammation (c3a and c5a)
  - Vascular effects
    - Increase vascular permeability and vasodilation
    - Similar to histamine
  - Activates lipoxygenase pathway of arachidonic acid metabolism (c5a)

Complement system

- Leukocyte activation, adhesion and chemotaxis (c5a)
- Phagocytosis
  - c3b acts as opsonin and promotes phagocytosis by cells bearing receptors for c3b

Vasoactive amines

- Histamine
  - Found in mast cells, basophils and platelets
  - Released in response to stimuli
  - Promotes arteriolar dilation and venular endothelial contraction
    - results in widening of interendothelial cell junctions with increased vascular permeability
- Serotonin
  - Vasoactive effects similar to histamine
  - Found in platelets
  - Released when platelets aggregate

Arachidonic Acid (AA)

- Where is it located?
  - *AA is a component of cell membrane phospholipids*
- The breakdown of AA into its metabolites produces a variety of biologic effects

Arachidonic acid metabolites

- Metabolites of AA - short-range hormones
- AA metabolites act locally at site of generation
- Rapidly decay or are destroyed

Arachidonic Acid

- AA is released from the cell membrane by phospholipases which have themselves been activated by various stimuli and/or inflammatory mediators
- AA metabolism occurs via two major pathways named for the enzymes that initiate the reactions; lipoxygenase and cyclooxygenase

AA metabolites (eicosanoids)

Cyclooxygenases synthesize

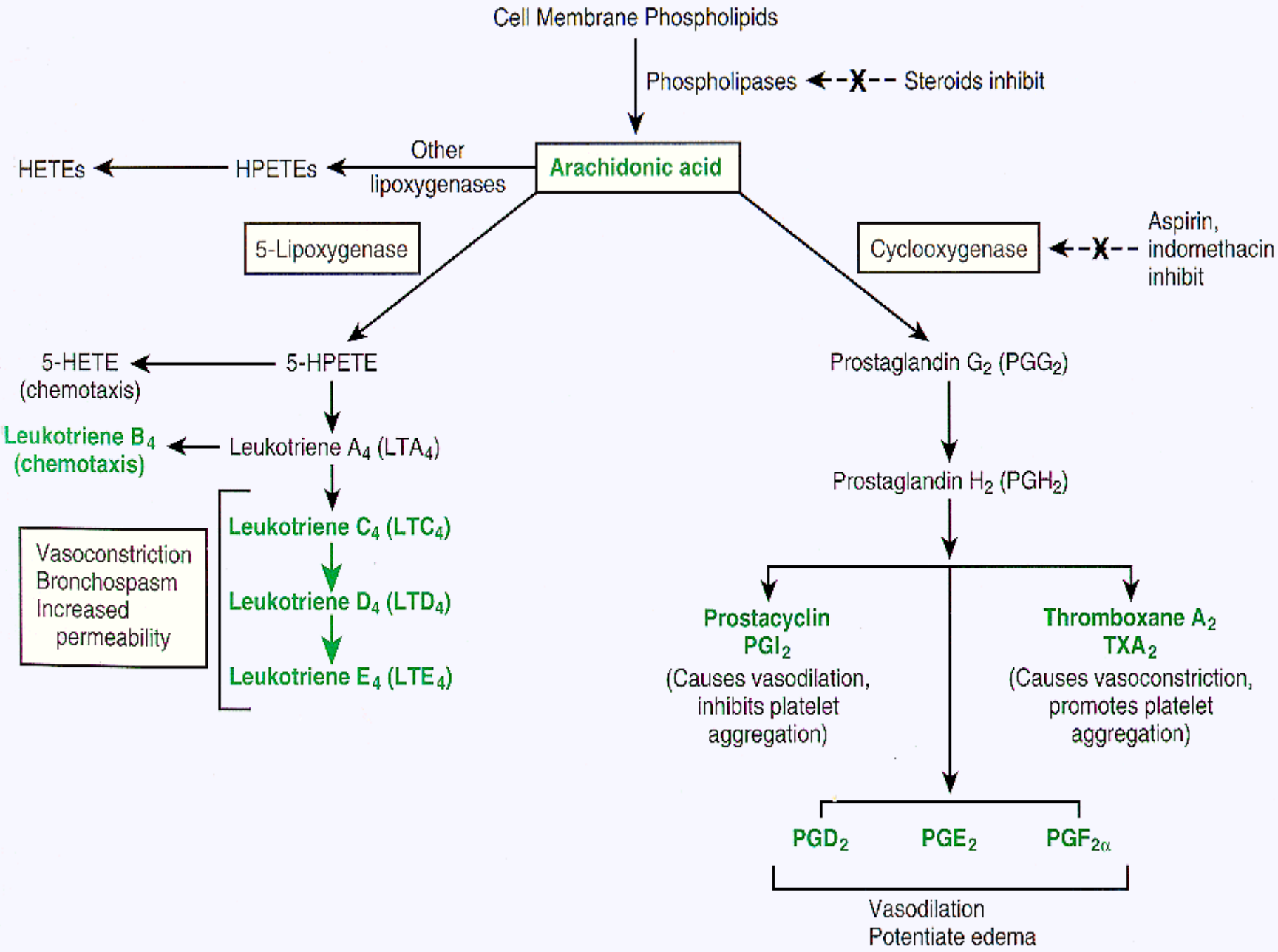
Prostaglandins

Thromboxanes

Lipoxygenases synthesize

Leukotrienes

Lipoxins


Cell Membrane Phospholipids
Phospholipases
Steroids inhibit
Arachidonic acid
Other lipoxygenases
HPETEs
HETEs
5-Lipoxygenase
Cyclooxygenase
Aspirin, indomethacin inhibit
5-HPETE
5-HETE (chemotaxis)
Leukotriene A4 (LTA4)
Leukotriene B4 (chemotaxis)
Leukotriene C4 (LTC4)
Leukotriene D4 (LTD4)
Leukotriene E4 (LTE4)
Vasoconstriction
Bronchospasm
Increased permeability
Prostaglandin G2 (PGG2)
Prostaglandin H2 (PGH2)
Prostacyclin PGI2
(Causes vasodilation, inhibits platelet aggregation)
Thromboxane A2 TXA2
(Causes vasoconstriction, promotes platelet aggregation)
PGD2
PGE2
PGF2α
Vasodilation
Potentiate edema

PGG_2

↓

PGH_2



PGI_2
Prostacyclin

PGD_2 ; PGE_2 PGF_2

TXA_2
Thromboxane

Vasodilatation

Inhibits Platelet Aggregation

Vasodilatation
Edema

Vasoconstriction

Promotes Platelet Aggregation

Arachidonic Acid Metabolites

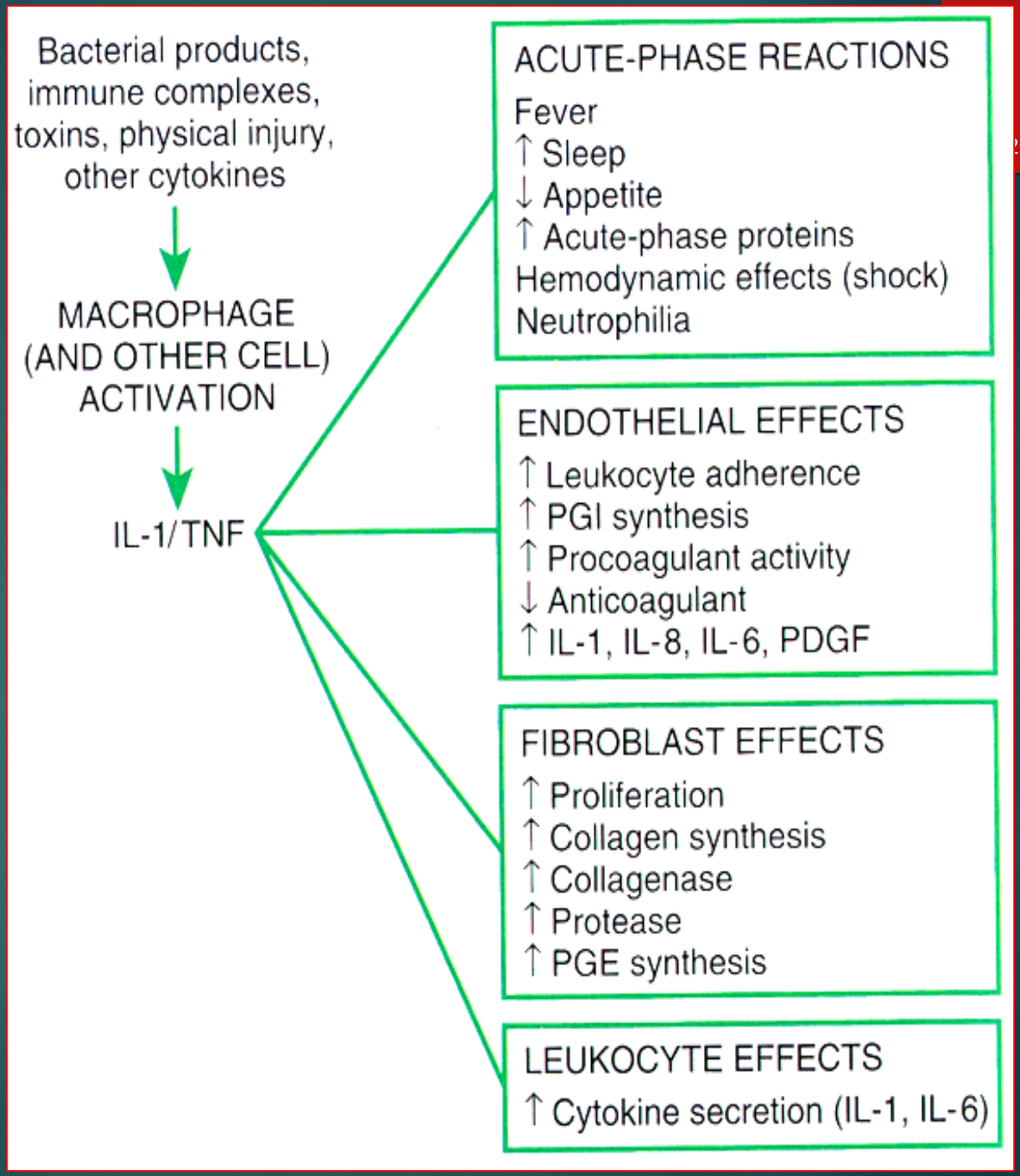
- Participate in every aspect of acute inflammation
- *Effective Anti-inflammatory agents act on AA pathways*
  - *Aspirin and Non-Steroidal Anti-inflammatory Drugs (NSAID's) - Cyclooxygenase path*
  - *Steroids act, in part, by inhibiting Phospholipase A2*

Platelet-Activating Factor (PAF)

- Another phospholipid-derived mediator released by phospholipases
- Induces aggregation of platelets
- Causes vasoconstriction and bronchoconstriction
- 100 to 1,000 times more potent than histamine in inducing vasodilation and vascular permeability
- Enhances leukocyte adhesion, chemotaxis, degranulation and the oxidative burst
- It does everything!

Cytokines

- Polypeptides that are secreted by cells
- Act to regulate cell behaviors.
- Autocrine, paracrine or endocrine effects
- These “biological response modifiers” are being actively investigated for therapeutic use in controlling the inflammatory response


Bacterial products, immune complexes, toxins, physical injury, other cytokines
MACROPHAGE (AND OTHER CELL) ACTIVATION
IL-1/TNF
ACUTE-PHASE REACTIONS
Fever
↑ Sleep
↓ Appetite
↑ Acute-phase proteins
Hemodynamic effects (shock)
Neutrophilia
ENDOTHELIAL EFFECTS
↑ Leukocyte adherence
↑ PGI synthesis
↑ Procoagulant activity
↓ Anticoagulant
↑ IL-1, IL-8, IL-6, PDGF
FIBROBLAST EFFECTS
↑ Proliferation
↑ Collagen synthesis
↑ Collagenase
↑ Protease
↑ PGE synthesis
LEUKOCYTE EFFECTS
↑ Cytokine secretion (IL-1, IL-6)

Selected Inflammatory Cells & Their Chemokines

Target Cell	Important Chemokines
Neutrophils	IL-8, Groα, β, γ, others
Monocytes	MIP-1α, MIP-1β, MCP-1,2,3
Eosinophils	Eotaxin
Lymphocytes	Lymphotaxin
Basophils	IL-8, MIP-1α, MCP-1,3, RANTES

Nitric Oxide

- NO is a soluble free radical gas
- Made by nitric oxide synthetase (NOS) in endothelium (eNOS), macrophages (iNOS), and specific neurons in the brain (nNOS)
- Broad range of functions and effects that are short range
  - **Vasodilatation by relaxing smooth muscle**
  - **↓ platelet aggregation**
  - **Inhibits mast cells**
  - **Regulates leukocyte recruitment**

Outcomes of Acute Inflammation

- Resolution
- Fibrosis
- Abscess formation
- Progression to chronic inflammation

MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

- **Serous inflammation -** characterized by the outpouring of a watery, relatively protein-poor fluid (effusion)
- depending on the site of injury, derives either from the serum or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities.
- The skin blister resulting from a burn or viral infection.

Ctd…

- **FIBRINOUS INFLAMMATION -** occurs as a consequence of more severe injuries, with a resultant greater vascular permeability allowing larger molecules (specifically, **fibrinogen**) to pass the endothelial barrier.
- Fibrinous exudates may be degraded by fibrinolysis and resulting in restoration of the normal tissue structure **(resolution).**
- However, failure to completely remove the fibrin results in the ingrowth of fibroblasts and blood vessels, leading ultimately to **scarring (organization)**
- For example, organization of a fibrinous pericardial exudate forms dense fibrous scar tissue that bridges or obliterates the pericardial space and restricts myocardial function.

Ctd…

- **SUPPURATIVE (PURULENT) INFLAMMATION -** is manifested by the presence of large amounts of purulent exudate **(pus)** consisting of neutrophils, necrotic cells, and edema fluid.
- Certain organisms (e.g., staphylococci) are more likely to induce this localized suppuration and are therefore referred to as **pyogenic.**
- **Abscesses** are focal collections of pus that may be caused by deep seeding of pyogenic organisms into a tissue or by secondary infections of necrotic foci.

Ctd…

- **ULCERATION -** refers to a site of inflammation where an epithelial surface (skin, gastric epithelium, colonic mucosa, bladder epithelium) has become necrotic and eroded, often with associated subepithelial acute and chronic inflammation.
- Can occur as a consequence of toxic or traumatic injury to the epithelial surface (e.g., peptic ulcers) or may be due to vascular compromise (as in foot ulcers associated with the vasculopathy of diabetes).

Chronic inflammation

- Difficult to define
- Inflammation of prolonged duration in which active inflammation, tissue injury and the healing proceed simultaneously.

Occurs in:

- Persistent infections - AFB, fungi, Treponemas
  - Low toxicity
  - Delayed hypersensitivity
  - Granulomatous inflammation
- Prolonged exposure to potentially toxic agents
  - Silica
  - Toxic plasma lipids → atherosclerosis
- Autoimmunity - RA, lupus

Chronic inflammation is characterized by:

- Infiltration with mononuclear cells (macrophages, lymphocytes & plasma cells)
- Tissue destruction
- Repair involving angiogenesis and fibrosis
- Macrophage is the ***prima donna*** of chronic inflammation.

Macrophage

prominent role due the large repertoire of

products it can produce when activated.

.Tox. O_2

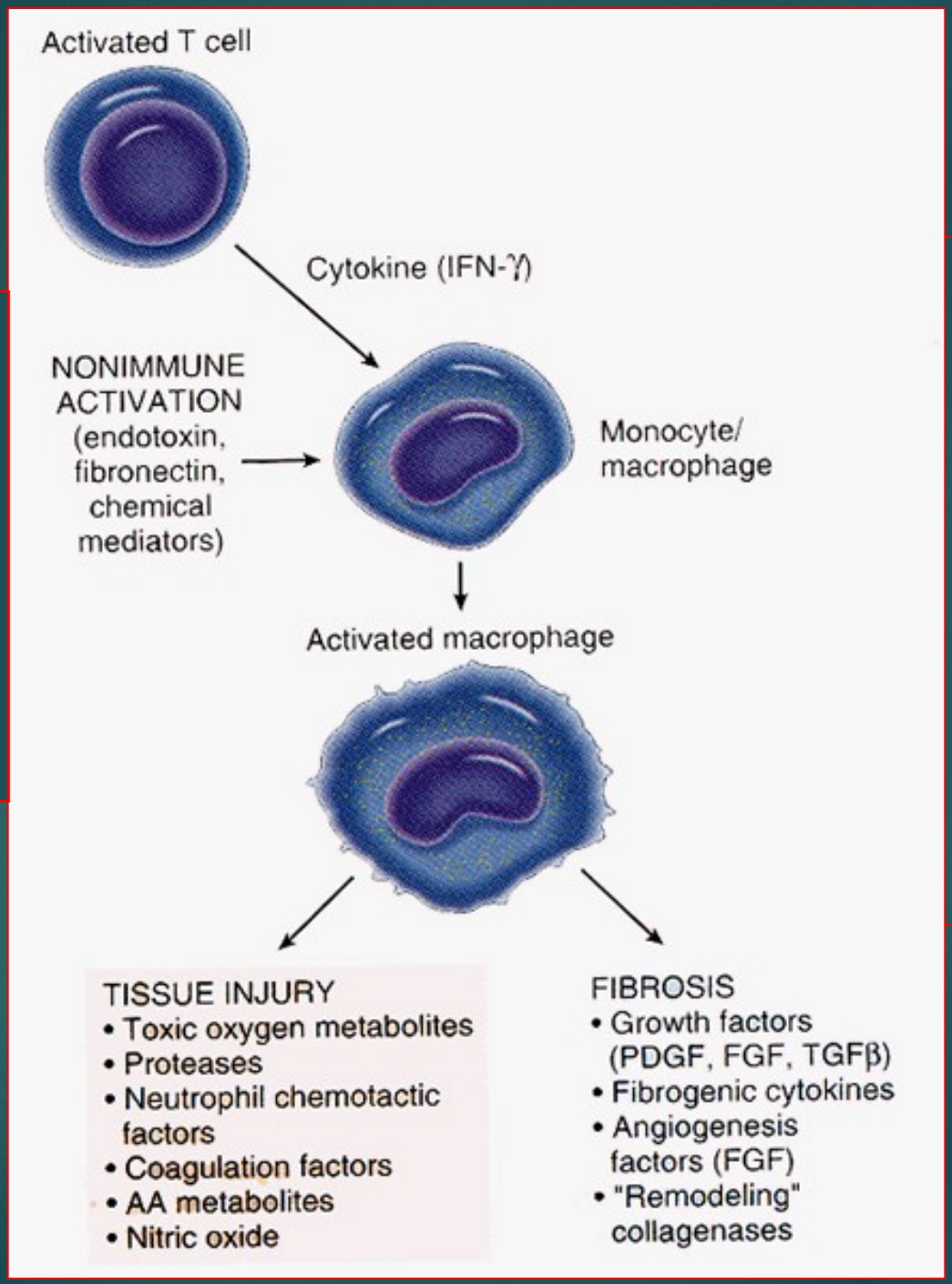
.Proteases .Collagenases .Chemotx factors

.Coag factors .AA metabolites .NO, PDGF, FGF,TGF-β

Key macrophage events

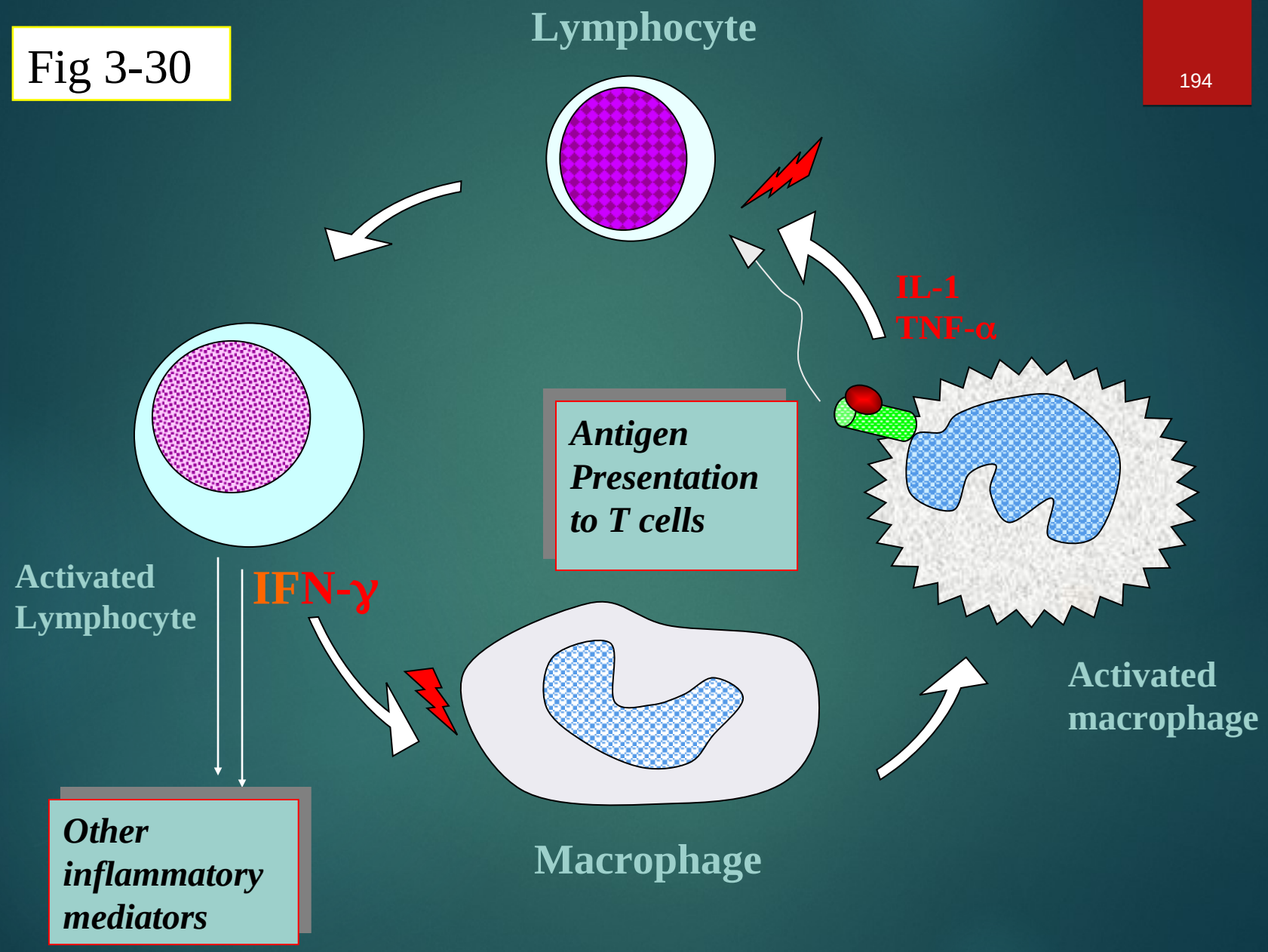
1. Recruitment from circulation
2. Local Proliferation
3. Immobilization
4. **Differentiation (microglia, kupffer, alveolar macrophage, osteoclasts**).

Fig 3-12



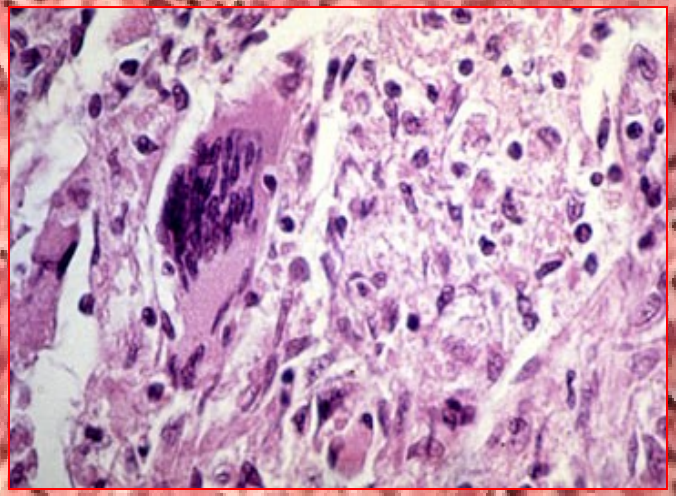
Note that the activated macrophage releases products that are similar to those released by PMNs.

Fig 3-30


Lymphocyte
IL-1
TNF-α
Antigen Presentation to T cells
Activated Lymphocyte
IFN-γ
Activated macrophage
Other inflammatory mediators
Macrophage

Granulomatous Inflammation

- **Aggregations of activated, modified (epitheliod) appearance macrophages.**
- **Granuloma – focal collection of granulomatous inflammation**
- Bacteria
  - **Tuberculosis**
  - **Leprosy**
- Parasites
  - **Schistosomiasis**
- **Fungi**
  - **Histoplasmosis**
  - **Blastomycosis**
- **Metal/Dust**
  - **Berylliosis**
  - **Silicosis**
- **Foreign body**
  - **Splinter**
  - **Suture**
  - **Graft material**
- **Sarcoidosis**



4. Repair

- Regeneration of injured tissue by parenchymal cells of the same type
- Replacement by connective tissue
- Starts as early as 24 hours
- **Granulation tissue at 3 - 5 days**
- **Four Components:**
  - **Angiogenesis**
  - **Migration and proliferation of fibroblasts**
  - **Deposition of extracellular matrix (ECM)**
  - **Remodeling (Maturation & organization of fibrous tissue)**

Proliferative Potential

- Labile cells - continuously dividing
  - Epidermis, mucosal epithelium, GI tract epithelium etc.
- Stable cells - low level of replication
  - Hepatocytes, renal tubular epithelium, pancreatic acini...etc.
- Permanent cells - never divide
  - Nerve cells, cardiac myocytes, skeletal muscle

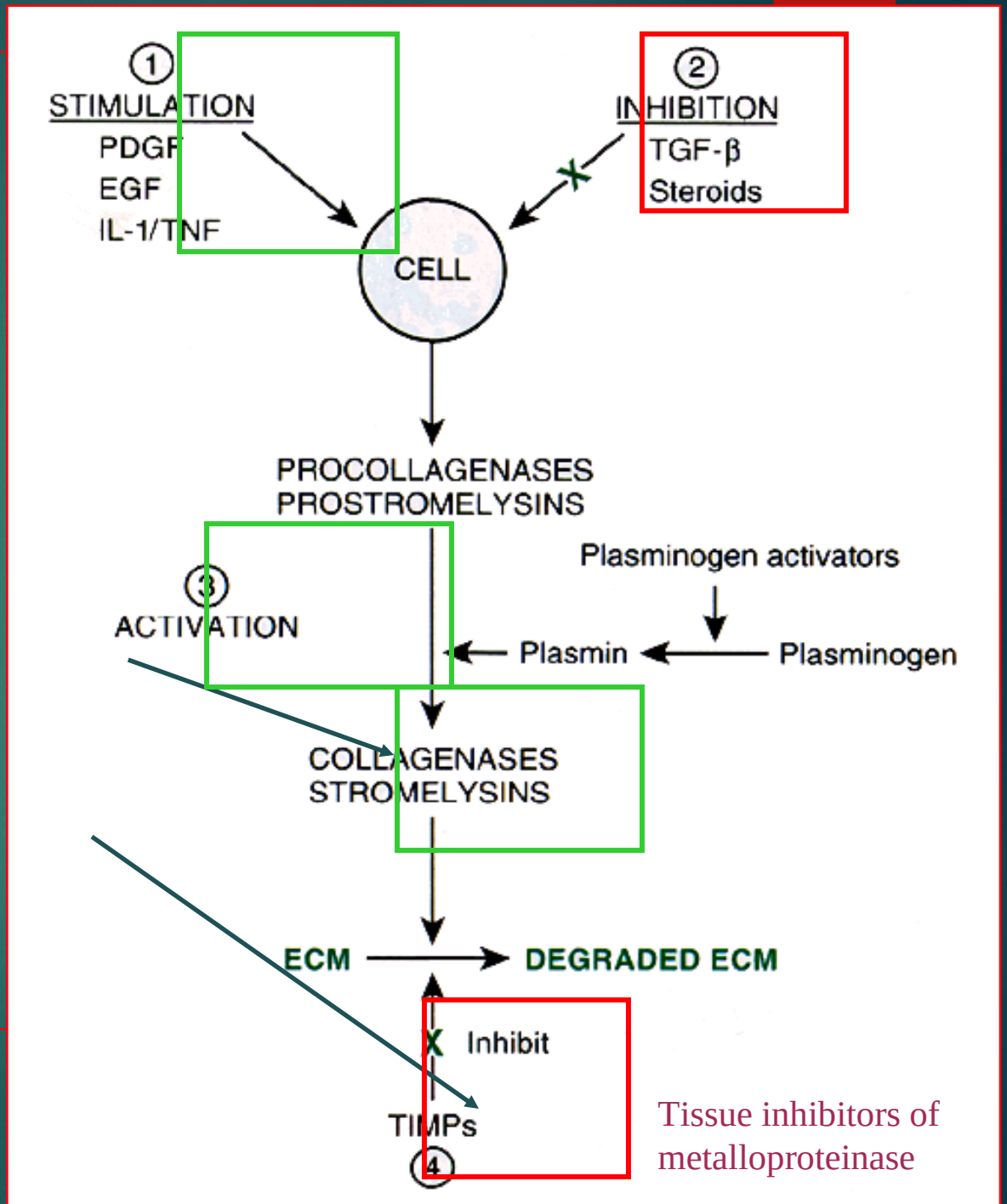
Components of the process of fibrosis

- Angiogenesis - New vessels budding from old.
- Fibrosis, consisting of emigration and proliferation of fibroblasts and deposition of ECM.
- Scar remodeling, tightly regulated by **proteases** and **protease inhibitors**

Tissue Remodeling

- Balance of deposition Vs degradation
- **Zn-dependent matrix metalloproteinases and their inhibitors**
  - **Interstitial collagenases → type I, II, III collagen**
  - **Gelatinase → type IV collagen & fibronectin**
  - **Stromelysins → variety of ECM**
  - **Membrane-bound matrix metalloproteinases (MBMMP)**
  - **Tissue inhibitors of metalloproteinase (TIMP)**

Fig 4-16 Scar remodeling is regulated by metalloproteinases and their inhibitors



Tissue inhibitors of metalloproteinase

Wound healing

- Complex but orderly phenomenon number of processes
- Induction of acute inflammatory response by an initial injury
- Regeneration of parenchymal cells
- Migration and proliferation of both parenchymal and connective tissue cells
- Synthesis of ECM proteins.
- Remodeling of connective tissue and parenchymal components to restore tissue function.
- Remodeling of connective tissue to achieve wound strength.

Healing by first intention (primary union)

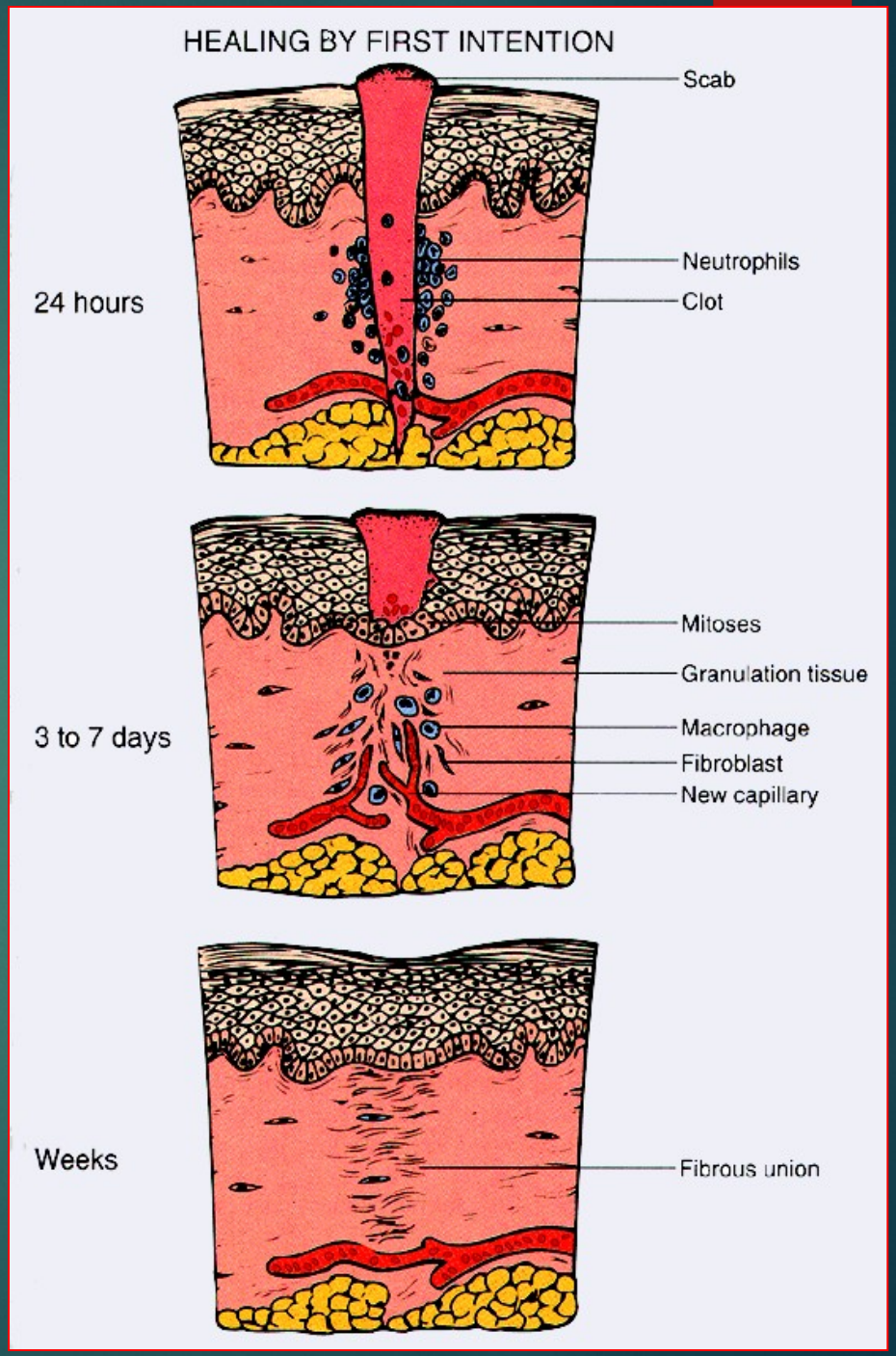
Clean, uninfected, surgical incision with sutures:

1. Blood clot forms
2. < 24 hours – PMNs appear
3. 24-48 hrs cut edges of epidermis thicken from basal cell hyperplasia, and epithelium migrates for union
4. By day 3 – PMN's replaced by macrophages.
   Granulation tissue invades & collagen at margins.

Healing by first intention (primary union)

5. Incision filled with granulation tissue. Maximal neovascularization & collagen bridges gap. Epidermis covers & is mature.
6. One week – After suture removal wound strength only 10% (compared with unwounded skin)
7. Second week – Continued collagen deposition and fibroblast proliferation. PMNs gone.
8. First month – Scar with cellular connective tissue and no inflammatory cells. Regressed vascular channels.
9. Third month – 70-80% of maximum strength.

Fig 4-17
Healing by first intention



Healing by second intention (separated)

- Large tissue defect to fill common denominator
- Differs from primary union in several ways:
  - More fibrin, more debris → more intense inflammation
  - More granulation tissue is formed
  - Wound contraction aided by myofibroblasts

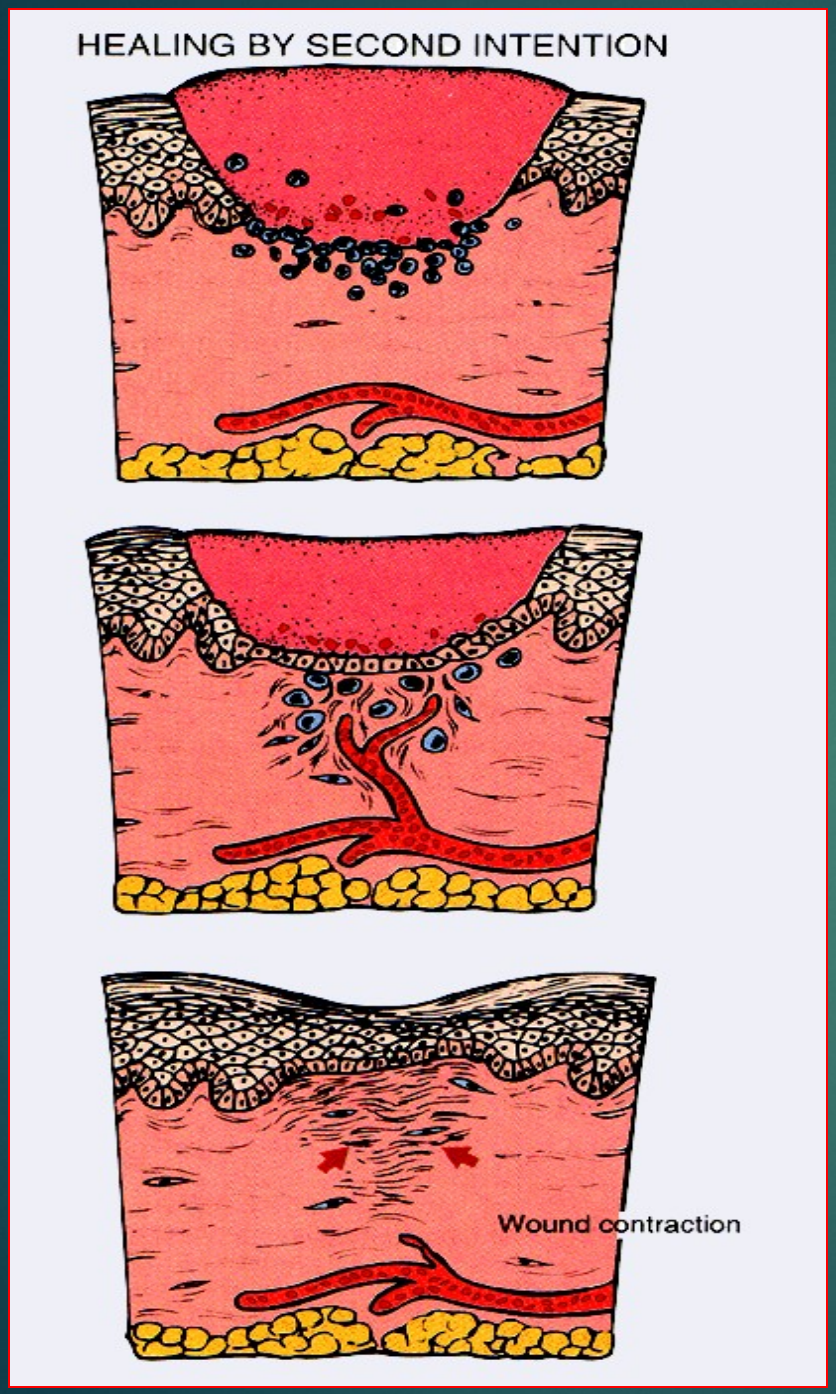


Fig 4-17
Healing by second intention:
Larger injury, abscess, infarction.
Process is similar but results in much larger scar and then primary union





Factors that influence healing

- Nutrition - vitamin C
- Metabolic status – diabetes hinders
- Circulatory status
- Hormones – steroids/glucocorticoids inhibit
- Infection
- Mechanical stress
- Foreign bodies
- Size, locations and type of the wound

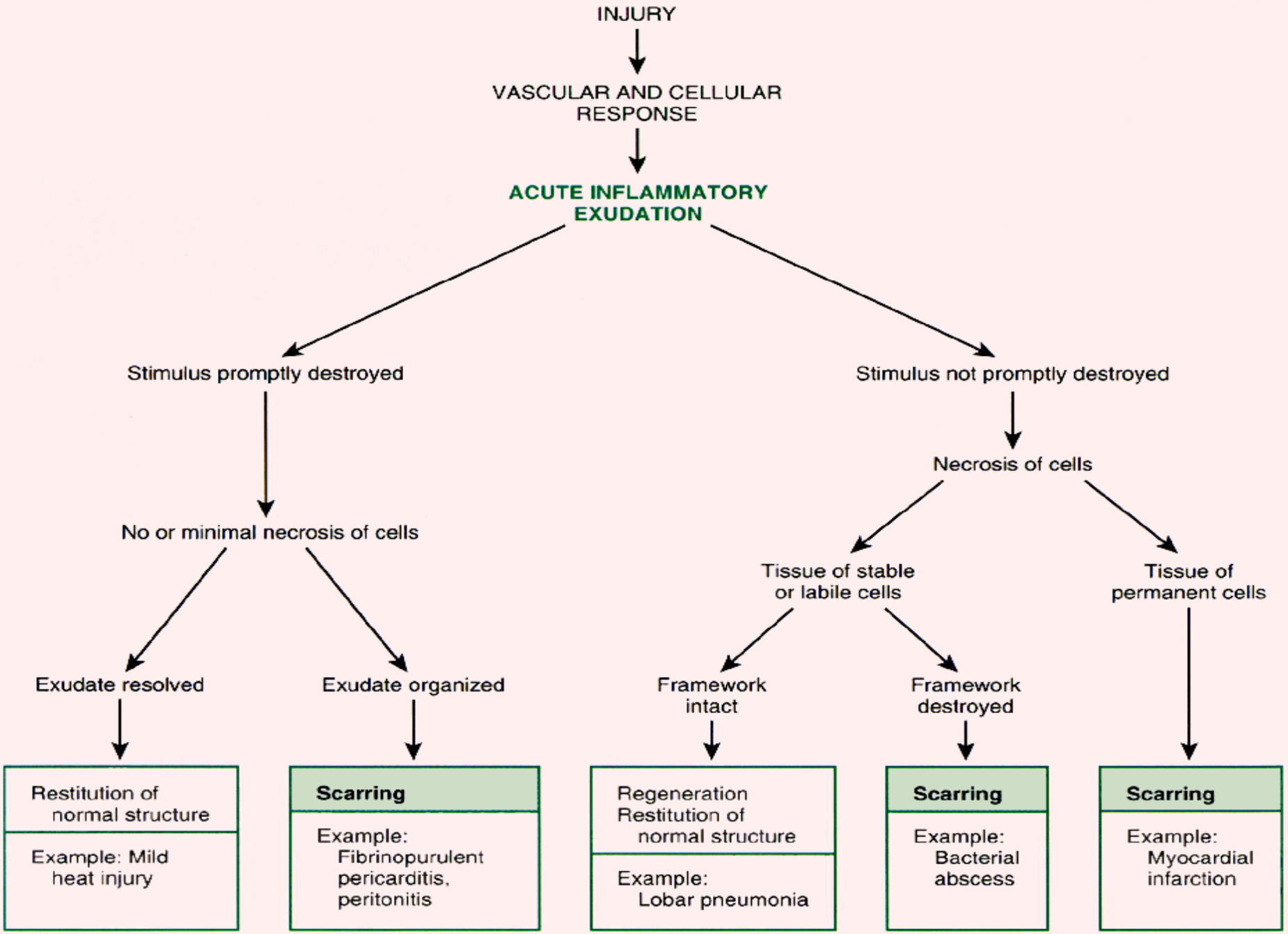
Whether a wound heals by primary or secondary union is determined by the nature of the wound, rather than by the healing process itself

Complications in cutaneous wound healing

1. Deficient scar formation
- wound dehiscence & incisional hernias
- ulceration

2. Excessive scar formation
- keloid
- Hypertrophic scar

3. Excessive contraction


INJURY
VASCULAR AND CELLULAR RESPONSE
ACUTE INFLAMMATORY EXUDATION
Stimulus promptly destroyed
Stimulus not promptly destroyed
No or minimal necrosis of cells
Necrosis of cells
Tissue of stable or labile cells
Tissue of permanent cells
Exudate resolved
Exudate organized
Framework intact
Framework destroyed
Restitution of normal structure
Example: Mild heat injury
Scarring
Example: Fibrinopurulent pericarditis, peritonitis
Regeneration Restitution of normal structure
Example: Lobar pneumonia
Scarring
Example: Bacterial abscess
Scarring
Example: Myocardial infarction

Read

- Fracture healing

5. Hemodynamic Disorders,Thromboembolic disease, and Shock

EDEMA

- Approximately 60% of lean body weight is water,
  - 2/3 is intracellular and
  - 1/3 is extracellular compartments, mostly as **interstitial fluid**
- Only 5% of total body water is in blood plasma

Ctd…

- *Edema* signifies increased fluid in the interstitial tissue spaces &
- Fluid collections in different body cavities
- *hydrothorax*
- *hydropericardium*
- *hydroperitoneum* (commonly called *ascites*)
- **Anasarca** is a severe and generalized edema with profound subcutaneous tissue swelling.

Mechanisms for edema formations

1. Increased Hydrostatic Pressure

Causes

- *Localized* increases in intravascular pressure can result from impaired venous return example, lower extremity DVT.
- *Generalized* increases in venous pressure

Eg. *CHF*

Ctd…

2. Reduced Plasma Osmotic Pressure

Albumin is the serum protein most responsible for maintaining intravascular colloid osmotic pressure

Causes

- *nephrotic syndrome*
- protein malnutrition
- diffuse liver diseases etc…

3. Lymphatic Obstruction

Impaired lymphatic drainage and consequent ***lymphedema***

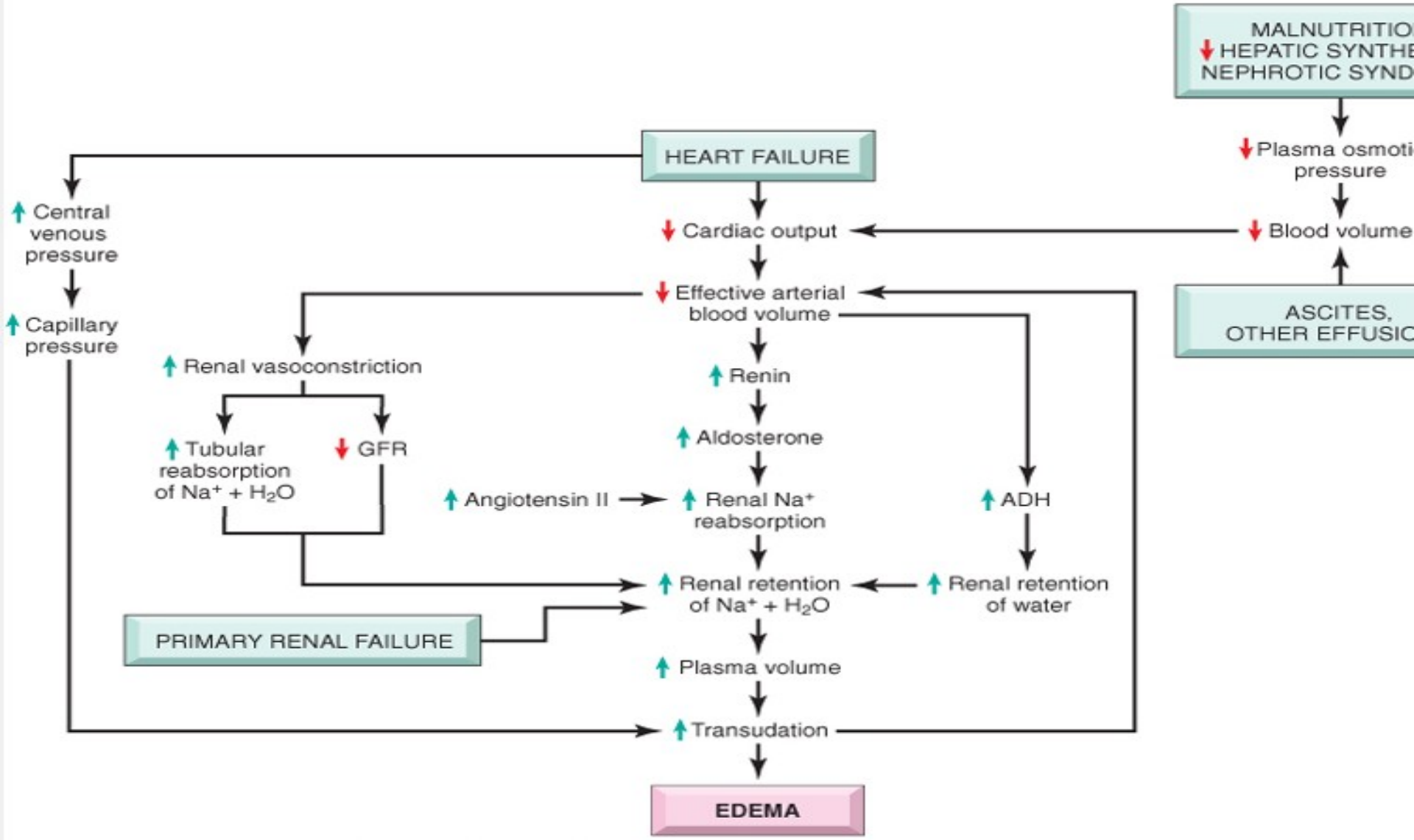
Morphology

- Most easily recognized grossly
- **Microscopically, edema fluid is reflected primarily as a clearing and separation of the extracellular matrix elements with subtle cell swelling.**
- Edema is most commonly encountered in subcutaneous tissues, lungs, and brain
- **Subcutaneous edema** can be diffuse or more prominent in regions with **high hydrostatic pressures.**

Ctd…

- Gravity-dependent distribution is referred to as **dependent edema**
- Finger pressure over significantly edematous subcutaneous tissue displaces the interstitial fluid and leaves a finger-shaped depression called **pitting edema**

Ctd…


MALNUTRITIO
HEPATIC SYNTHE
NEPHROTIC SYND
Plasma osmoti pressure
HEART FAILURE
Central venous pressure
Cardiac output
Blood volume
Capillary pressure
Effective arterial blood volume
ASCITES, OTHER EFFUSIC
Renal vasoconstriction
Renin
Aldosterone
Tubular reabsorption of Na+ + H2O
GFR
Angiotensin II
Renal Na+ reabsorption
ADH
Renal retention of Na+ + H2O
Renal retention of water
PRIMARY RENAL FAILURE
Plasma volume
Transudation
EDEMA

HYPEREMIA AND CONGESTION

- The terms *hyperaemia* and *congestion* both indicate a local increased volume of blood in a particular tissue.
- **Hyperaemia** is an *active process* resulting from augmented blood flow due to **arteriolar dilation**. The affected tissue is redder than normal because of engorgement with oxygenated blood.

- **Congestion** is a *passive process* resulting from **impaired venous return out of a tissue**. It may occur systemically or local. The tissue has **a blue-red** colour ***(cyanosis)***

HEMORRHAGE

- is extravasation of blood from vessels into the extravascular space.
- An increased tendency to haemorrhage (usually with insignificant injury) occurs in a wide variety of clinical disorders collectively called ***hemorrhagic diatheses.***
- can be external or can be confined within a tissue; any accumulation is referred to as a ***hematoma.***
- Minute (1- to 2-mm) haemorrhages into skin, mucous membranes, or serosal surfaces are called ***petechiae***

Ctd…

- Slightly larger (3- to 5-mm) hemorrhages are called ***purpura***
- Larger (1- to 2-cm) subcutaneous hematomas (**bruises**) are called ***ecchymoses***
- Large accumulations of blood in one or another of the body cavities are called *hemothorax, hemopericardium, hemoperitoneum,* or *hemarthrosis.*
- **Clinical significance of hemorrhage depends on the volume and rate of blood loss & site of bleeding.**

HEMOSTASIS AND THROMBOSIS

Normal Hemostasis

- is the result of a set of well regulated processes that accomplish two important function:-
  - maintain blood in a fluid, clot-free state in **normal vessel**
  - induce a rapid & localized hemostatic plug at a site of **vascular injury**.
- **Thrombosis** is inappropriate activation of normal hemostatic process such as formation of a blood clot (thrombus) in an injured vasculature or after minor injury.

Ctd…

- Both haemostasis & thrombosis are regulated by

  - Vascular wall
  - Platelets
  - Coagulation cascade

Hemostasis after injury is achieved by

1. vasoconstriction
2. platelet plug – primary hemostatic plug.
3. blood clot as result of blood coagulation – secondary hemostatic plug.
4. fibrous formation to close permanently.

Endothelium:-

- Endothelial cells modulate both antithrombotic & prothrombotic function

Antithrombotic properties

Antiplatelet

- An intact endothelium prevents platelets & plasma coagulation factors from coming in contact with the highly **thrombogenic subendothelial ECM**
- Endothelial **prostacyclin** & **NO** inhibits **platelets** from adhering to uninjured endothelium.

Ctd…

Anticoagulant effect

- Heparin like molecules act indirectly by interacting with antithrombin III to inactivate thrombin, factor Xa & other coagulation factors.
- Thrombomodulin act indirectly by binding to thrombin, converting it from procoagulant to an anticoagulant capable of activating protein C. **protein C** inhibits clotting by proteolytic cleavage of factors Va & VIIIa

Fibrinolytic effect

- Endothelial cells synthesize **tissue type plasminogen activator (t-PA)** promoting fibrinolytic activity.

Ctd…

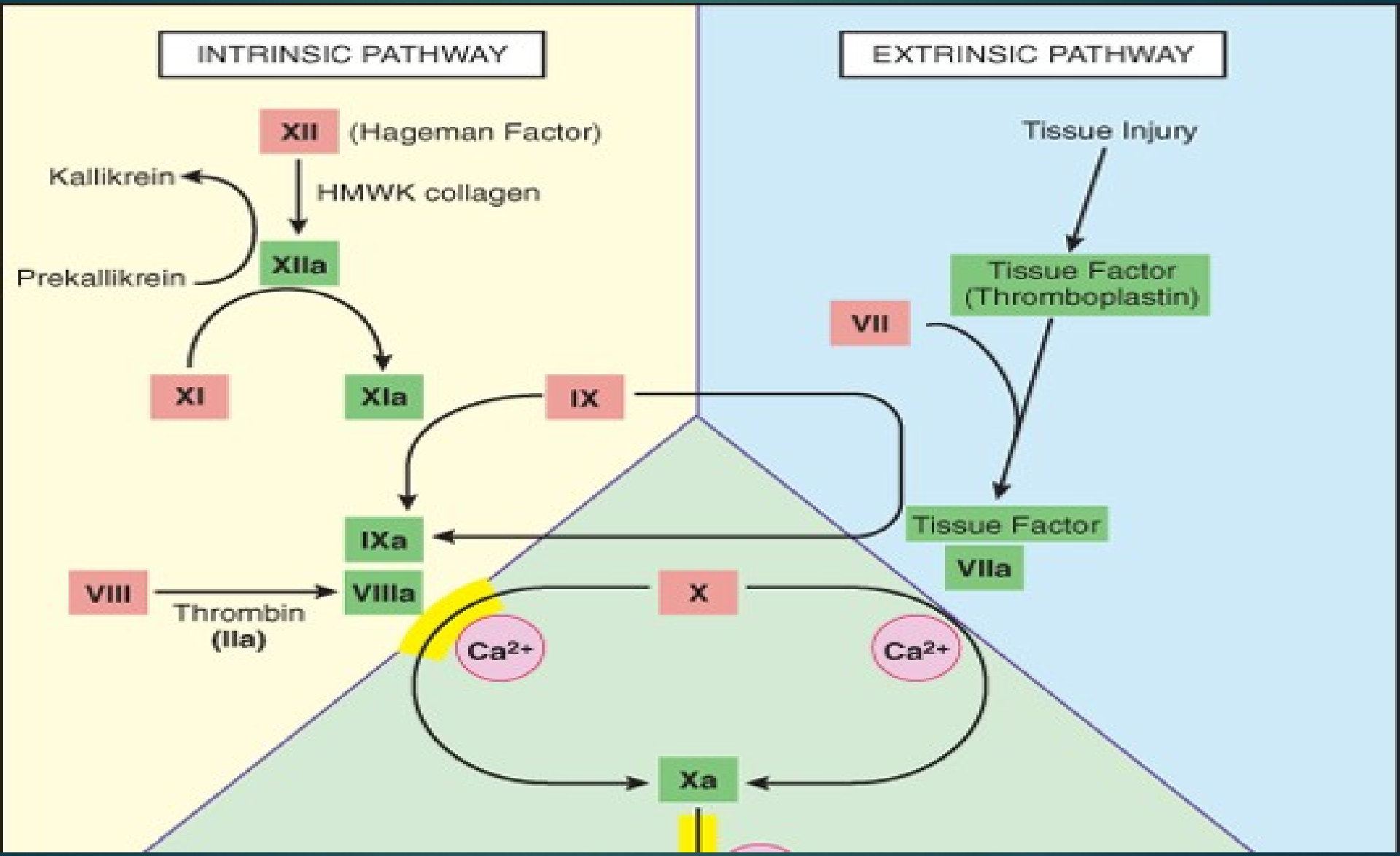
Prothrombotic properties

- **Platelet effects** – endothelial injury leads to **adhesion of platelets** to the underlying ECM which is facilitated by endothelial production of **von willebrand factor**. It binds platelet to collagen & other surfaces.
- **Procoagulant effects** – endothelial cells are induced to synthesize **tissue factor** which activates the **extrinsic clotting cascade**.
- **Antifibrinolytic effects** - endothelial cells secrete **inhibitors of plasminogen activators** (PAIs) which depress fibrinolysis.

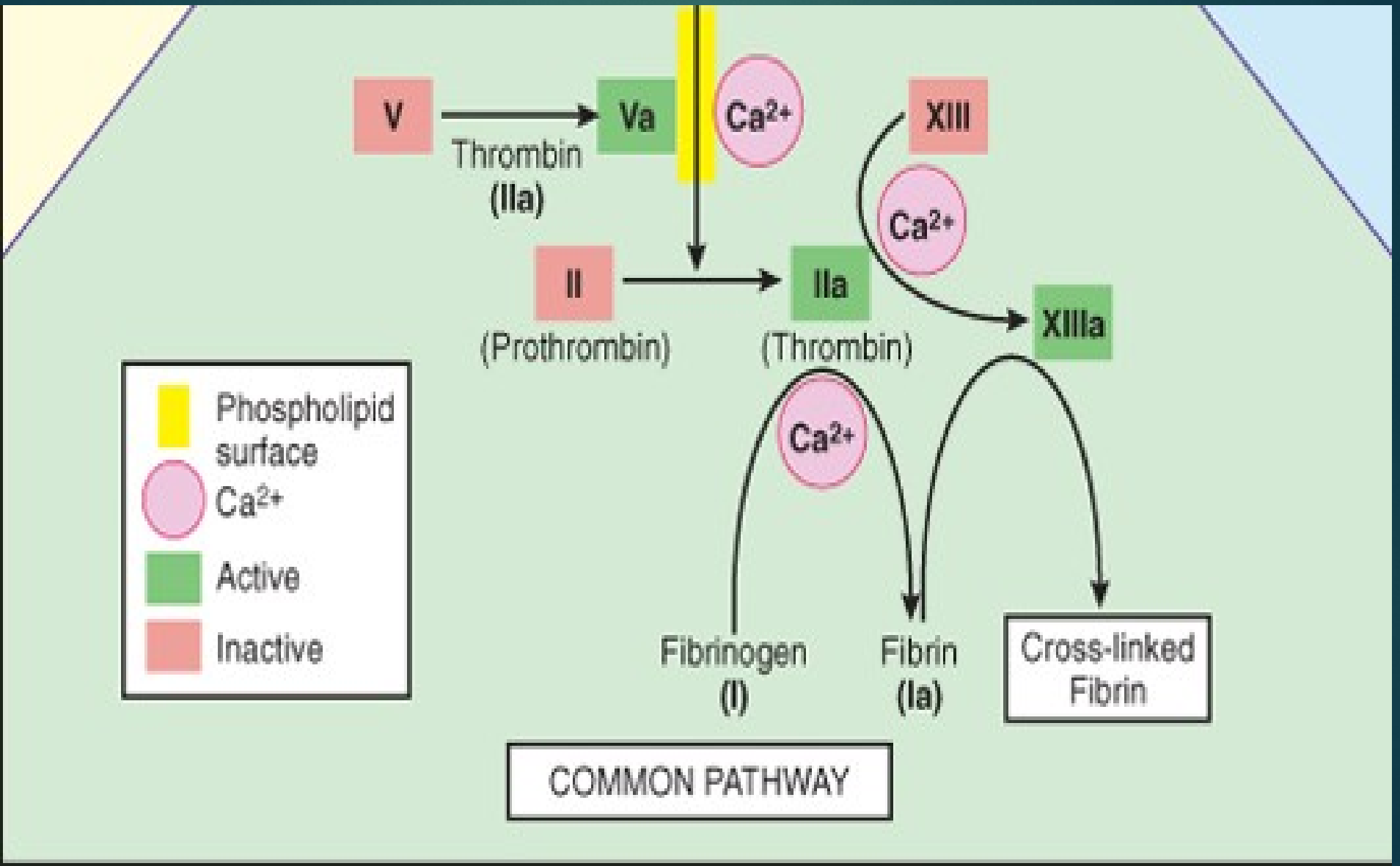
Coagulation cascade

- The coagulation cascade is a series of enzymatic conversions, turning inactive proenzymes into activated enzymes & resulting in the formation of **thrombi**.
- Thrombin then converts the soluble plasma protein fibrinogen in to the **insoluble fibrous protein fibrin**
- It either uses **intrinsic or extrinsic** pathways

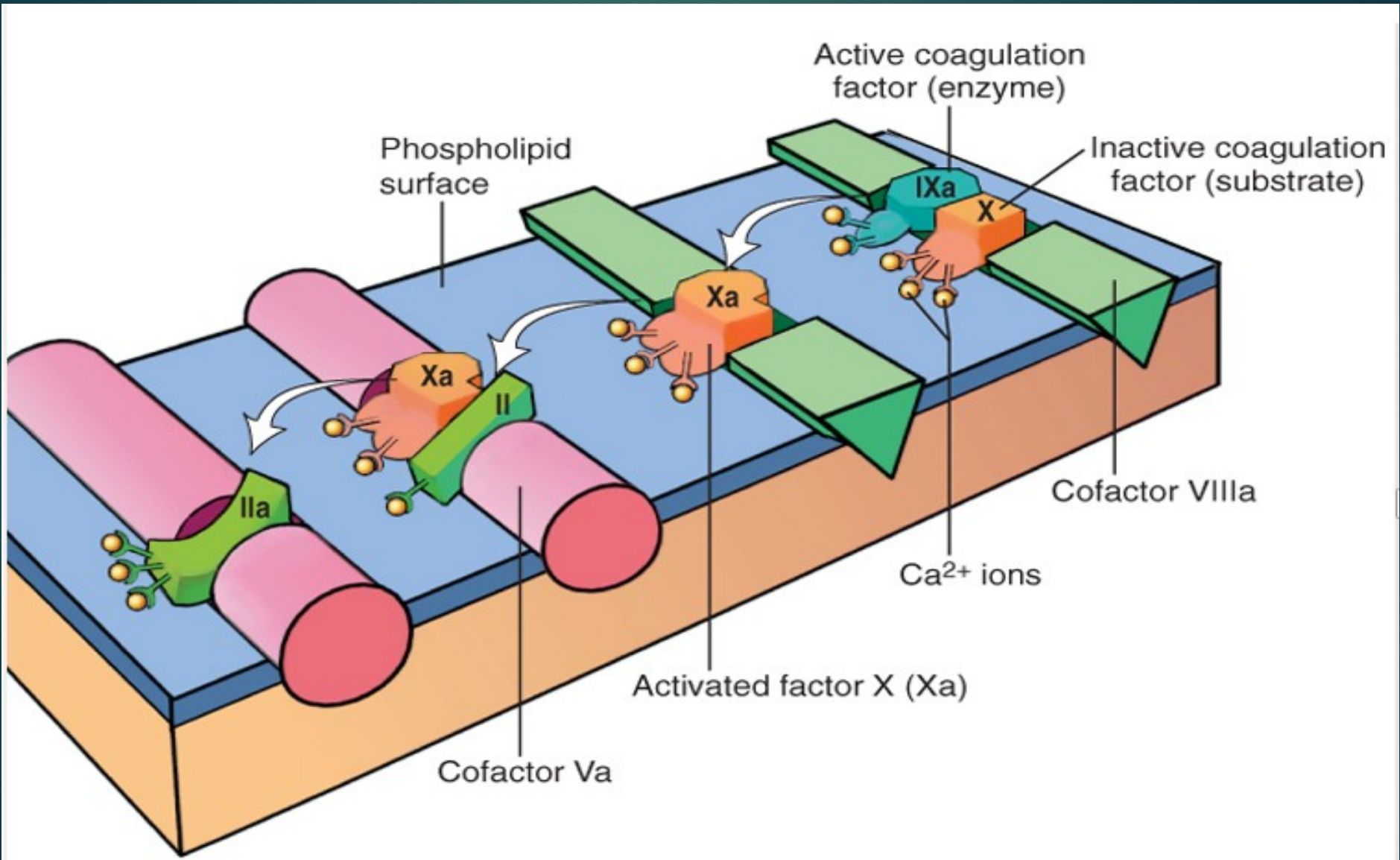
Ctd…


INTRINSIC PATHWAY
EXTRINSIC PATHWAY
XII
(Hageman Factor)
Kallikrein
HMWK collagen
Prekallikrein
XIIa
Tissue Injury
Tissue Factor
(Thromboplastin)
VII
XI
XIa
IX
IXa
Tissue Factor
VIIa
VIII
Thrombin
(IIa)
VIIIa
X
Ca2+
Ca2+
Xa

Ctd…


V
Thrombin
(IIa)
Va
Ca2+
XIII
Ca2+
II
(Prothrombin)
IIa
(Thrombin)
XIIIa
Phospholipid surface
Ca2+
Active
Inactive
Ca2+
Fibrinogen
(I)
Fibrin
(Ia)
Cross-linked Fibrin
COMMON PATHWAY

Sample

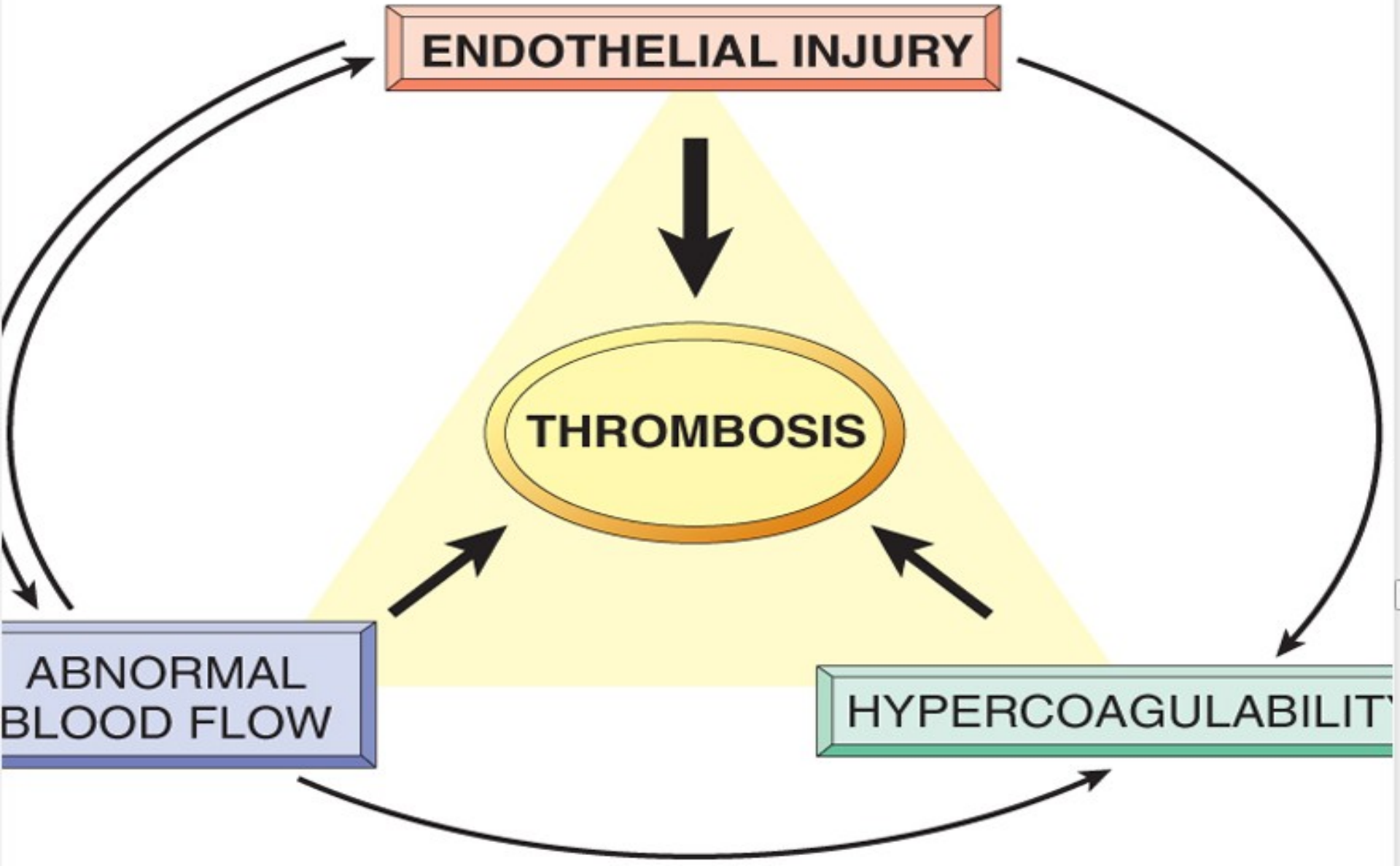

Active coagulation factor (enzyme)
Phospholipid surface
Inactive coagulation factor (substrate)
IXa
X
Xa
Xa
II
IIa
Cofactor VIIIa
Ca2+ ions
Activated factor X (Xa)
Cofactor Va

THROMBOSIS

- Three primary factors predispose to thrombus formation – "**Virchow triad"**

1. Endothelial injury
2. Stasis or turbulence of blood flow
3. Blood hypercoagulability

Ctd…


ENDOTHELIAL INJURY
THROMBOSIS
ABNORMAL
BLOOD FLOW
HYPERCOAGULABILIT

Endothelial injury

- it is particularly important for thrombus formation occurring in heart or in arterial circulation.
- physical loss of endothelium will lead to exposure of subendothelial ECM, adhesion of platelets, release of **tissue factor** & local depletion of **prostacyclin** but dysfunctional endothelium also may lead to **thrombosis**

Eg. Endocardial injury, ulcerated atherosclerotic artery.

Stasis or turbulence of blood flow

- turbulence results in arterial & cardiac thrombosis by causing endothelial injury or dysfunction
- stasis is major factor in development of venous thrombosis

E.g. Aortic or arterial aneurism – stasis

Myocardial infarction - stasis

Mitral valve stenosis- Turbulence

Hyper viscosity syndrome (polycytemia)

Hypercoagulability

- It is defined as any alteration of the coagulation pathways that predispose to thrombosis.
- The cause can be primary (genetic) or secondary (acquired).

Secondary causes

- **High risk**
  - immobilization
  - myocardial infarction
  - atrial fibrillation
  - tissue damage (surgery, fracture, burn..
  - cancer
  - prosthetic cardiac valves
  - DIC
  - Antiphospholipid antibody syndrome

Ctd…

- **Low risk**
  - Cardiomyopathy
  - nephrotic syndrome
  - hyperestrogenic state
  - oral contraceptive use
  - smoking

Morphology of thrombi

- Thrombi may develop any where in the CVS
- A thrombus both microscopically or grossly has apparent laminations called **lines of zahin**. This is produced by an alternating pale layers containing platelets admixed with some fibrin & a darker layer containing red cells
- Most common sites of **arterial thrombi** in descending order are

  - **Coronary artery**
  - **Cerebral artery**
  - **Temporal artery**

  - Bacterial or fungal infections may cause valvular damage of the heart as it occurring in **infective endocarditis** lead to the development of **thrombotic mass or vegetation.**
  - Sterile vegetation in hypercoagulable state with no infection called non bacterial thrombotic endocarditis

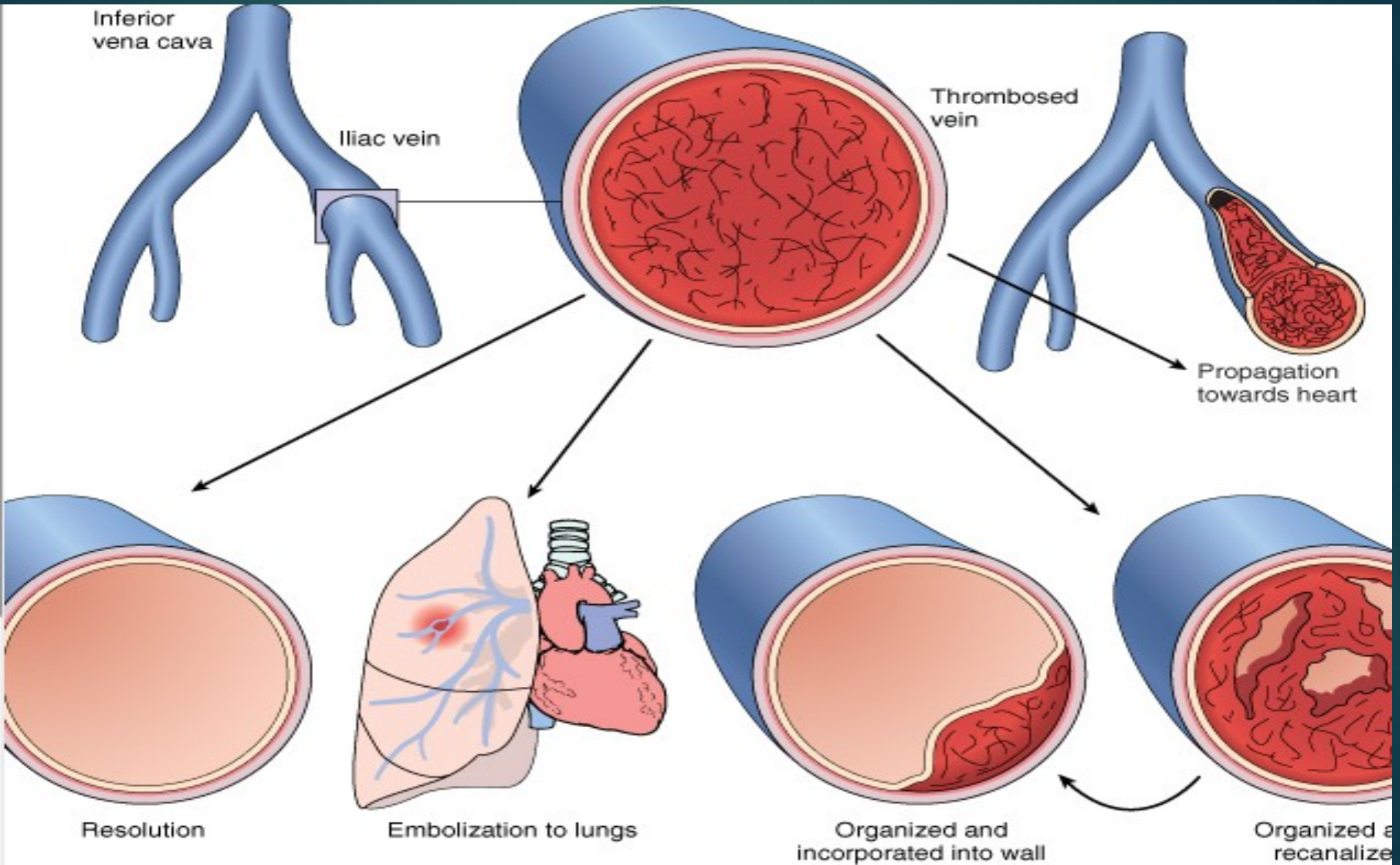
Fate of thrombus

- **propagation**
- **embolization**
- **dissolution**
- **organization & recanalization**

Clinical correlations

- **Thrombi are significant clinically in that:**
  - **cause obstruction of arteries & veins**
  - **they are possible source of emboli**

Fate of thrombosis



Venous thrombosis (phlebothrombosis)

- affects veins of the lower extremity in **90% of cases**

1. superficial venous thrombosis

- **usually occur in saphenous system particularly when there are varicosities.**
- **cause local edema, pain, & tenderness, become symptomatic but rarely embolize**
- **local edema due to impaired venous drainage, predispose the involved overlying skin to infection after slight trauma developing a condition known as varicose ulcer**

Ctd…

2. Deep venous thrombosis

- Are more serious as they may emboli

- Usually starts in deep veins within the calf muscles.

- Although they may cause local pain &edema, unlike superficial vein thrombosis, they are entirely **asymptomatic in approximately 50%of patient**, since deep veins obstruction rapidly offset of relived by **collateral bypass channels**.

Conditions associated with DVT

- Trauma, surgery, burns result in

a) Reduced physical activity leading to stasis

b) Injury to vessels

c) Release of procoagulant substance from the tissue

- Pregnancy & puerperal state increase coagulation factors & reduced synthesis of antithrombotics.
- Malnutrition, debilitating conditions & wasting diseases such as cancer. DVT due to these conditions known as **MARANTIC thrombosis**

Ctd…

- Migrating thrombophlebitis which affects various veins throughout the body is usually of obscure etiology, but sometimes associated with cancer particularly **pancreatic cancer**. It is also known as TROSSEAU syndrome

Arterial & cardiac thrombosis

- Atherosclerosis is major initiator of thrombosis related to abnormal vascular flow & loss of endothelial integrity
  - Myocardial infarction is related to dyskinetic contraction of the myocardium as well as damage to the adjacent endocardium & cardiac thrombi can arise.
- RHD may result in atrial mural thrombi due to mitral valve stenosis followed by left atrial dilation.
  - In addition to obstructive features, arterial thrombi may embolize to any tissue, but particularly common in the **brain, kidney, spleen** because of their large volume of in flow of blood.

Disseminated intravascular coagulation (DIC)

- It is an acute or chronic thrombohemorragic disorder occurring as a result of progressive activation of coagulation pathway beyond physiologic set point secondary to a variety of diseases resulting in failure of all components of hemostasis.
- It is also called **consumption coagulopathy**

Etiology & pathogenesis

- DIC is not a primary disease but coagulopathy that occurs in the course of variety of **clinical condition**
- It may result from pathologic activations of extrinsic &/or intrinsic pathways of coagulation or impairment of clot inhibiting influences

Two mechanisms that trigger DIC

- **Release of tissue factor or thromboplastin**
- **Wide spread injury to the endothelial cells**

Major disorders associated with DIC

Acute

Obstetric conditions

- Placenta abruption
- Septic abortion
- Retained dead fetus
- Amniotic fluid embolism
- Toxemia

Ctd…

Infections

- Gm –ve sepsis
- Meningococcemia
- Malaria

Burn, accidental trauma

Chronic

- Neoplasm
- Chronic illness

Clinical course

- The consequences of DIC are **two fold**:-
- **First**, widespread deposition of fibrin with in the microcirculation. This may lead to ischemia of more severely affected or more vulnerable organs & hemolytic anemia resulting from fragmentation of red cells as they squeeze through narrowed microcirculature **(microangiopatic hemolytic anemia)**
- **Second**, **hemorrhagic diathesis** may dominate the clinical picture because of consumption of platelets & clotting factors & increase in **fibrinolysis**

EMBOLISM

Definition

- Is a detached intravascular solid, liquid or gaseous mass that is carried by blood to sites distant from its point of origin
- 99% source is thrombus
- Rare forms of emboli includes fat globules & bubbles of air, amniotic fluid, infected foreign material, bits of bone marrow, platelets aggregation, fragment of material from ulcerating atheromatous plaque or fragments of a tumor.

Ctd…

- Emboli lodge in vessels too small to permit further passage, resulting in a partial or complete vascular occlusion. The potential consequence of this is the ischemic necrosis of distal tissue known as **infarction**
- Depending on site of origin, emboli may lodge in the pulmonary or systemic circulations

Pulmonary thromboembolism

- In more than 95% instance venous emboli originate from **deep leg vein thrombosis**
- The effect of pulmonary embolism depends on the size of the embolus & on the state of pulmonary circulation.
- More pulmonary emboli i.e 60%-80% are clinically silent b/c they are very small.

Systemic thromboembolism

- Refers to emboli traveling with in arterial circulation
- Most (80%) arise from intra cardiac mural thrombi, 2/3 of which are associated with left ventricular wall infarcts & another quarter with dilated left atria secondary to rheumatic VHD
- Remainder from aortic aneurysm, thrombi on ulcerated atherosclerotic plaques or fragmentation of valvular vegetation.

Ctd…

- Unlike venous emboli, which tend to lodge primarily in one vascular bed (lung), arterial emboli can travel to a wide variety of sites.
- The major sites for arteriolar embolization are the lower extremities (75%) & the brain (10%), with the rest in the intestines, kidney & spleen

Crossed embolism

- Crossed or paradoxical embolism occurs in the presence of patent foremen ovale when an embolus is transferred from the right to the left side of the heart, then to the systemic circulation.

Fat embolism

- Usually follows fracture of bones & other types of tissue injury, globules of fat frequently enter the circulation.
- Although traumatic fat embolisms occur, usually it is asymptomatic in most cases & fat is removed.
- Fat embolism syndrome is characterized by pulmonary insufficiency, neurological symptoms, anemia &thrombocytopenia

Infarction

- Is an area of ischemic necrosis caused by occlusion of either the arterial supply or venous drainage in a particular tissue.
- Nearly 99% of all infarcts result from thrombotic or embolic events & almost all result from arterial occlusion.

Other mechanisms include

- Local vasospasm
- Expansion of atheroma due to hemorrhage in to the atheromatous plaque
- External compression of the vessels eg. Trauma
- Twisting of vessels as in sigmoid volvulus
- Entrapment of vessels in hernial sacks ...

- Infarction caused by **venous thrombosis** is more likely to occur in organs with single venous out flow channels eg. **Testis or ovaries**

Factors that determine the size & development of an infarct

A. The nature of vascular supply

- The presence of dual blood supply as it occur in the lung, liver, hand & forearm may also offset the occurrence of infarction rapidly unlike renal & splenic circulation, which have end arterial supply

Ctd…

B. Rate of development occlusion; slowing developing occlusion are less likely to cause infarction since they provide time for the development of collaterals.

C. Vulnerability /susceptibility to hypoxia

D. Oxygen content of blood

Types of infarcts

- Infarcts are classified depending on:

A) The basis of their color (reflecting the amount of Hemorrhage)

1) Hemorrhage (red)

2) White (anemic)

B) The presence or absence of microbial infection

1) Septic

2) Bland

Red infarcts

- It occurs
  - venous occlusion as in ovarian torsion
  - In loose tissues such as lung which allow blood to collect in infarcts zone.
  - Tissues with dual circulation (eg, lung), permitting flow of blood from unobstructed vessel in to necrotic zone
  - In tissues that were previously congested b/c of sluggish blood flow
  - When blood flow is established to a site of previous arterial occlusion & necrosis

White infarcts

It occurs

- In arterial or in solid organs such as heart, spleen, kidney, where the solidity of the tissue limits the amount of hemorrhage that can percolate or seep in to the area of ischemic necrosis from the nearby capillaries.

SHOCK

- A state in which the failure of the circulatory system to maintain adequate cellular perfusion resulting in widespread reduction in **delivery of oxygen & other nutrients to tissues**
- Regardless of the underlying pathology, shock constitutes **systemic hypoperfusion** owing to reduction either in cardiac out put or in the effective circulating blood volume. The end results are **hypotension followed by impaired tissue perfusion & cellular hypoxia.**

1. Hypovolumic shock

- Reduction in circulating blood volume which result in reduction in **preload** lead to inadequate left ventricular filling, reflecting as a decreased in left & right Ventricle end diastolic volume & pressure, culminating in decreased cardiac out put
- Causes include:-

hemorrhage, fluid loss from burns, diarrhea & vomiting

2. Cardiogenic shock

- It results from myocardial pump failure (severe depression of **cardiac performance)**

Causes

A. Myopathic

- Acute myocardial infarction i.e usually occur if ≥ 40% left ventricle mass & more on right ventricle is involved by infarction.
- Myocarditis
- Dilated / hypertrophic cardiomyopathy
- Myocardial depression in septic shock

Ctd…

B. Mechanical

→ Intracardiac

- Left ventricle out flow obstruction eg. Aortic stenosis
- Reduction in forward cardiac out put eg. AR, MR
- arrhythemia

→ Extracardiac

- it is an obstructive shock
- pericardial tamponade
- tension pneumothorax
- acute massive pulmonary embolism
- severe pulmonary HTN

3. Distributive shock

- refers to a group of shock subtypes caused by profound peripheral vasodilatation despite normal or high cardiac out put.

cause

- Septic shock
- Anaphylactic shock
- Neurogenic shock

Septic shock

Sepsis

- **definition**: is a systemic response to severe infection mediated via macrophage derived cytokines that target end organ receptors in response to infection or SIRS that has suspected or proven microbial etiology
- **Septic shock**: a kind of shock caused by systemic microbial infection, most commonly by Gm negative infection (endotoxic shock) but can also occur with Gm +ve or fungal infections.

Or

- Sepsis with

- Hypotension

- Organ dysfunction

- Unresponsive to fluid administration

Pathogenesis of septic shock

- It has a mortality rate over 50% ranking the first among causes of death in ICU
- It results from spread & expansion of an initially localized infections like pneumonia in to the blood stream
- Most causes of septic shock (≈70%) caused by endotoxin producing Gm –ve bacilli, hence the term **endotoxic shock**. Endotoxins are bacterial wall LPS released when cell walls are degraded. LPS contains a core of toxic fatty acid (lipid A) & a complex polysaccharide coat unique to each bacterial species.

Ctd…

- LPS bind with CD14 molecules on leucocytes, especially monocytes & macrophages, endothelial cells & others. Depending on the dosage of LPS-protein complex, initiation of a cascade of cytokine mediated events take place
- The mononuclear phagocytes respond to LPS by producing TNF which intern induces IL-1 synthesis. TNF & IL-1 both act on endothelial cells to produce further cytokines like IL-6, IL-8 & secondary effectors like NO & PAF

Generally high levels of all of the above result in

- Systemic vasodilatation
- Diminished myocardial contractility
- Wide spread endothelial injury & activation, **alveolar capillary damage – ARDS**
- Activation of the coagulation system result in DIC

Neurogenic shock

Neurogenic shock

- Shock may occur in setting of anesthetic accident or spinal cord injury due to loss of vascular tone & peripheral pooling of blood.

Anaphylactic shock

- It is initiated by a generalized IgE mediated hypersensitivity response, is associated with systemic vasodilation & increased vascular permeability

Stages of shock

- Uncorrected shock passes through 3 important stages;

  1. **An initial non progressive phase**:
     - It is also called a period of early compensatory period, during which a compensatory mechanisms are activated & perfusion of vital organs maintained.

  Mechanisms

i. A variety of neurohumoral mechanisms operate

- A decrease of a cardiac output will stimulate peripheral & central bar receptors with subsequent intense sympathoadrenal stimulation

Ctd…

- The net effect is

  → Tachycardia, ↑HR→ ↑CO

  → Peripheral vasoconstriction →↑ABP, is a major auto compensatory response

  →Renal conservation of fluid

ii. The fall in renal perfusion stimulate the renin – aldosterone secretion mechanism

2. Progressive stage

- Characterized by tissue hypoperfusion with onset of worsening circulatory & metabolic imbalances including acidosis.

  - There is a wide spread tissue hypoxia.

  - Anaerobic glycolysis results in excessive lactic acid production. The lactic acid reduces tissue PH & blunts vasomotor response. Anoxic injury to endothelial cells results in DIC.

  - Clinically, the patient may become confused & the urine output declines

3. An irreversible stage

- A stage at which, even if hemodynamic disorders are corrected, survival is not possible
- Widespread cell injury is caused by lysosomal enzyme leakage
- Myocardial contractile function worsens due to nitric oxide synthesis
- If ischemic bowel allows intestinal flora to inter the circulation, endotoxic shock may be superimposed
- At this point, the pt has complete renal shut down due to acute tubular necrosis

Morphology

- All organs affected in sever shock. The cellular & tissue change induced by shock are essentially those of hypoxic injury so manifest as organ dysfunction

Heart

- Focal or widespread coagulation necrosis
- May manifest subendocardial necrosis
- Myocardial infarction

Ctd…

Brain

- Its dysfunction occur when cerebral auto regulation or compensatory mechanism fail. As cerebral & coronary auto regulation try to maintain normal level of blood pressure at DPB near to 50mmHg, below which auto regulation is lost. The brain manifests as boundary zone (border zone) infarction

Kidney

- Exhibits extensive tubular ischemic injury, i.e, acute tubular necrosis. Manifested as oligouria, anuria & electrolyte disturbance

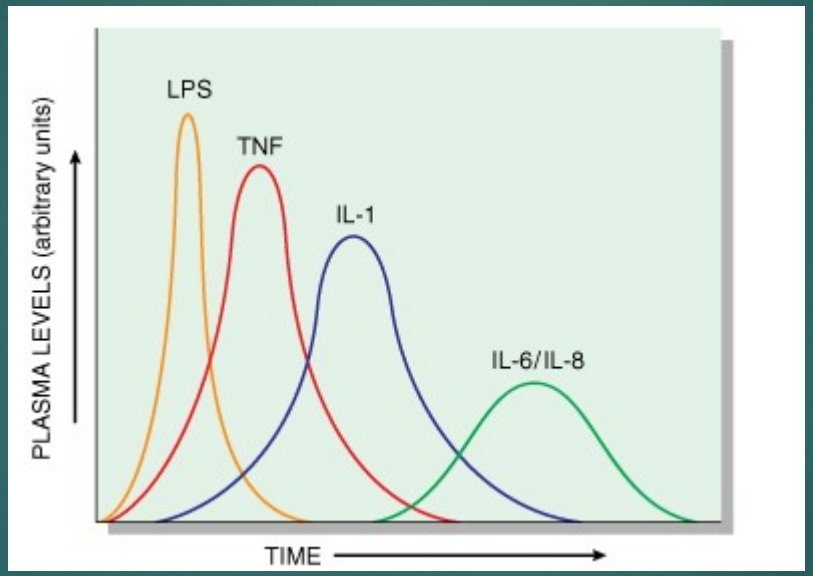
Ctd…

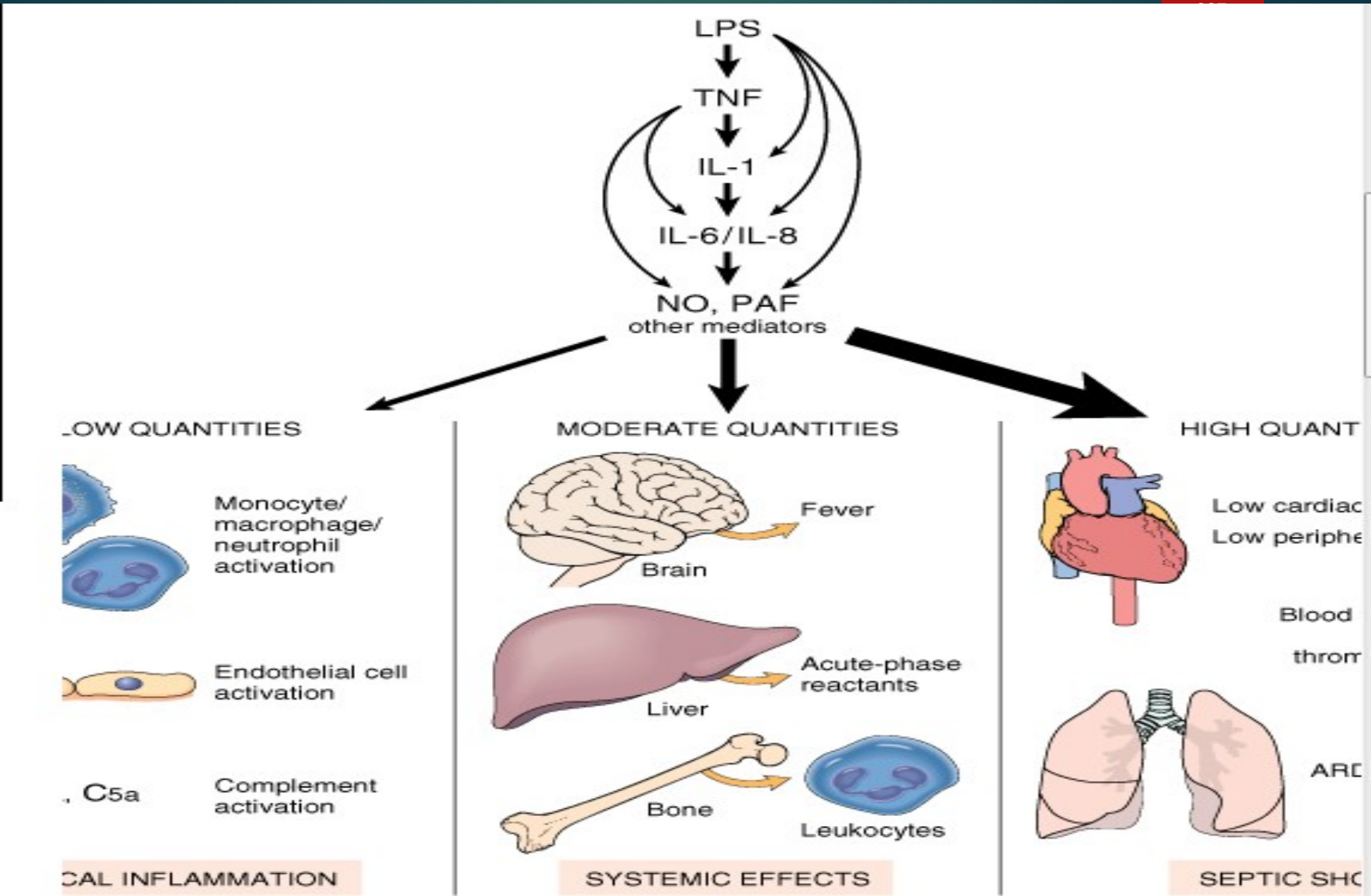
Lung

- In established shock pulmonary function may deteriorate rapidly due to a combination of causes:
- Alveolar collapse
- Pulmonary edema
- & leucocytes accumulation as a result of infection. Infection causes inflammation with exudation of protein cause fibrin to alveolar space. This features collectively known as shock lung or ARDS

Clinical course of shock

- Pt may manifest as having, a weak & rapid pulse, tachypnea & cool, clammy, cyanotic skin. In septic shock, skin initially is warm & fleshed because of peripheral vasodilatation. The pt may present with confusion, restlessness, decrease in urine out put, coma & death.
- The prognosis varies with the origin of shock & its duration. 80-90% of young pts with hypovolumic shock survive where as cardiogenic shock & septic shock carry mortality rate up to 75%.


LPS
TNF
IL-1
IL-6/IL-8
PLASMA LEVELS (arbitrary units)
TIME


LPS
TNF
IL-1
IL-6/IL-8
NO, PAF
other mediators
LOW QUANTITIES
Monocyte/
macrophage/
neutrophil
activation
Endothelial cell
activation
, C5a
Complement
activation
CAL INFLAMMATION
MODERATE QUANTITIES
Fever
Brain
Acute-phase
reactants
Liver
Bone
Leukocytes
SYSTEMIC EFFECTS
HIGH QUANT
Low cardiac
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Blood
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6. NEOPLASIA

Neoplasia

- Literally means "**new growth**"
- It is defined as

"Abnormal mass of tissues, the growth of which exceeds & is uncoordinated with that of the normal tissue & persists in the stimulus which evoked the change"

Nomenclature

- All tumors have **two basic components**
- ✓ **Proliferating neoplastic cells that constitute their parenchyma**
- ✓ **Supporting stroma made up of connective tissue & blood vessels**
- The nomenclature of tumors are based on the **parenchyma component.**
- **The growth & evolution of neoplasms are critically dependent on their stroma**

Neoplasms are named based upon two factors

- **On the histologic type : mesenchymal & epithelial**
- **On behavioral patterns : benign & malignant**

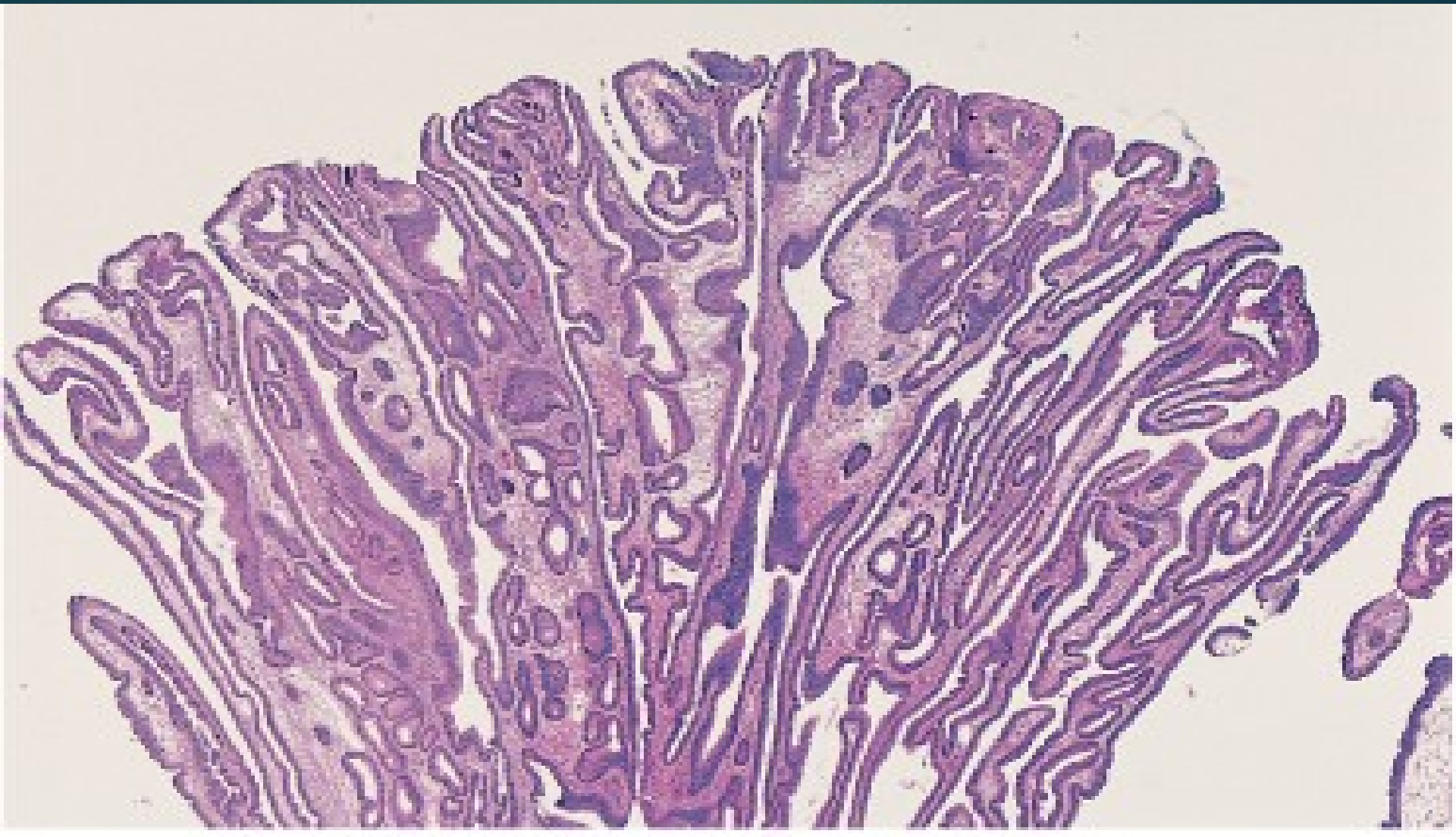
Ctd…

- Benign tumor of mesenchymal cells are designated by attaching the suffix –**oma** to the cell of origin.
- Malignant tumor arising in mesenchymal tissue are usually called **sarcoma**
- Benign epithelial tumors are variously classified, some based on their cell of origin, others on microscopic architecture & on their macroscopic pattern

Ctd…

- **Adenoma** – term applied for benign epithelial neoplasm that form glandular pattern.
- **Papillomas** – benign neoplasms producing microscopically or macroscopically visible finger like projection or warty projection from epithelial surface.
- Benign tumors that form large cystic masses are referred as **cystadenoma**

Papilloma



Ctd…

- Some tumors produce papillary patterns that protrude in to cystic spaces are called **papillary cystadenoma**
- When tumor produces macroscopically visible projection above a mucosal surface, called **polyp.**
- Malignant neoplasms of epithelial cell origin are called **carcinomas**

Ctd…

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Synovium		Synovial sarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma

Ctd…

Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Urothelial papilloma	Urothelial carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma

Ctd…

Tumors of melanocytes	Nevus	Malignant melanoma
More Than One Neoplastic Cell Type-Mixed Tumors, Usually Derived from One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer-Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Ctd…

- **Teratoma** – are made up of a variety of parenchymal cell types representative of more than one germ layer
- They arise from totipotent cells, so mostly are found in gonads.
- **Choristoma** – an ectopic rest of normal tissue
- **Hamartoma** – a mass of disorganized but mature specialized cells or tissue indigenous to the particular site.

Characteristics of benign & malignant neoplasms

A. Differentiation & anaplasia

- Differentiation refers to the extent to which parenchymal cells resemble comparable normal cells both morphologically & functionally
- In general, benign neoplasms are well differentiated. Malignant neoplasms in contrast, range from well differentiated, moderately differentiated to poorly differentiated type.
- Malignant neoplasm composed of undifferentiated cells are said to be **anaplastic**, literally anaplasia means to form **backward**

Morphological changes which mark anaplasia

- **Pleomorphism** – both cells & nuclei show variation in size & shape
- **Abnormal nuclear morphology** – nuclei contain abundant chromatin & are extremely dark staining, high nuclear cytoplasmic ratio 1:1
- Large nucleoli with mitosis
- Tumor giant cells
- Necrosis

Dysplasia

- Disordered cell growth which result in altered cell structure
- Changes may vary in size, Shape & appearance
- Smokers often have dysplastic changes in their respiratory tract
- Is an abnormal condition but can be reversible if stimulus is withdrawn
- Has potential to undergo neoplastic change

Characteristics ctd…

B. Rate of growth

C. Local invasion

D. Metastasis

- Tumor implants discontinuous with the primary tumor

Pathway of spread

A. Transcoelomic spread

- Seeding of body cavities & surfaces
- It may occur whenever a malignant neoplasm penetrates in to a natural “open field”
- Most often involved is the peritoneal cavity but other cavities – pleura, pericardial, subarachinoid & joint space may be affected
- It is often characteristics of ovarian carcinoma.

Ctd…

B. **Lymphatic spread**

- **Lymphatic route is the most common pathway for the initial dissemination of carcinomas.**
- The pattern of lymph node involvement follows the natural routes of drainage.

Ctd…

Hematogenous spread

- It is typical for sarcoma but also seen with carcinoma
- **Liver & lung** are most frequently involved in hematogenous spread.

Epidemiology

Geographic factor

- Specific differences in incidence rates of cancers are seen world wide
- For example

  Stomach carcinoma – Japan

  Lung cancer – USA

  Skin cancer – Newzeland & Australia

  Liver cancer – Ethiopia

Ctd…

Environmental factor

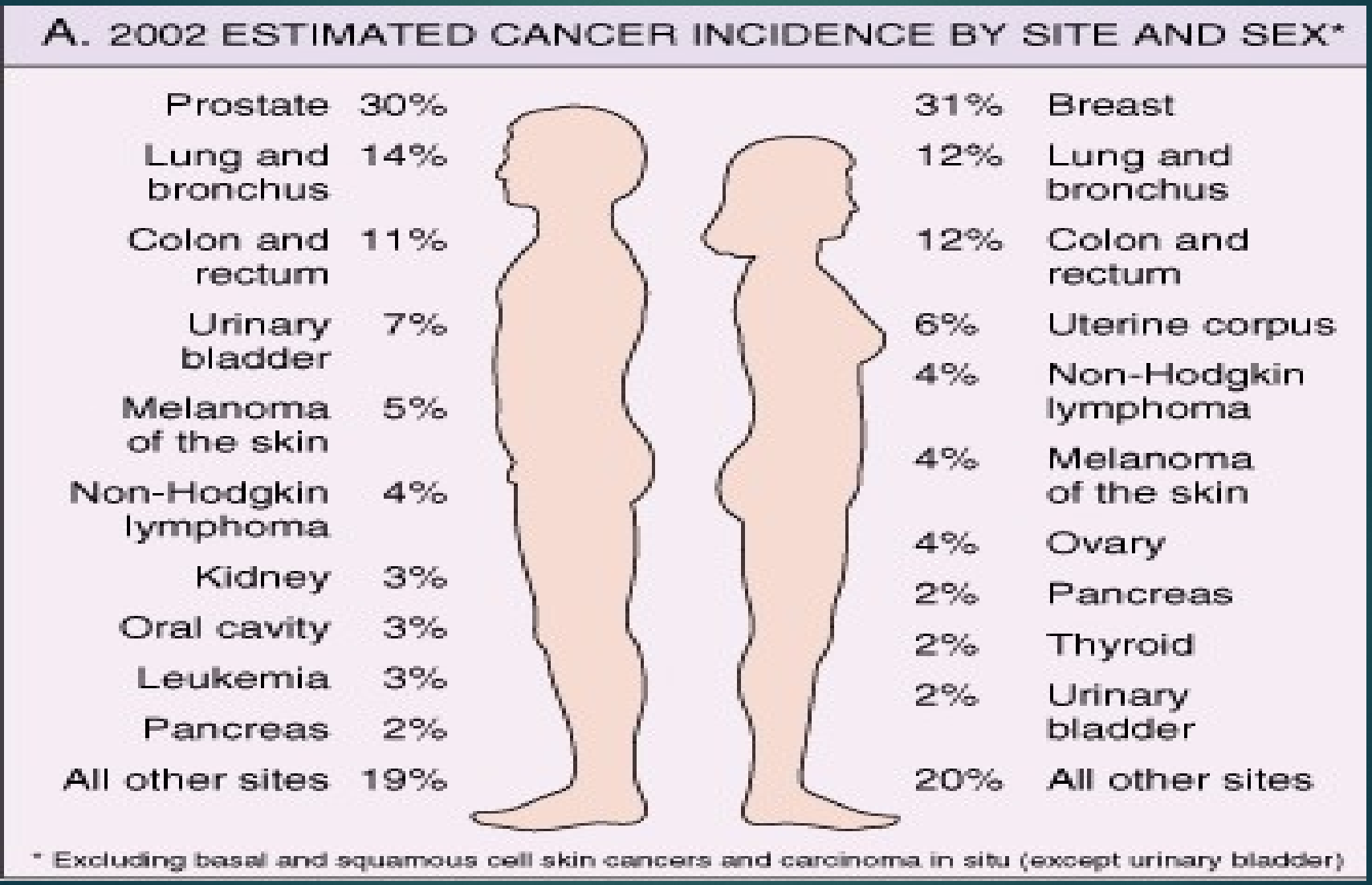
- Asbestosis – lung ca, mesothelioma, esophagus & gastric ca
- Vinyl chloride – angiosarcoma of liver
- Benzene – leukemia
- Cigarette – bronchogenic ca
- Venereal infection – cervical ca

Ctd…

Age

- Most cancer in adult occur in those over 55yrs of age
- Children under 15 yrs of age however, are susceptible to acute leukemia, CNS tumors, neuroblastoma, wilm’s tumor, retinoblastoma, rhabdomyosarcoma & etc…

Epidemiology. . .



Ctd…

- ***Genetic predisposition***
- It can be divided in to
- **Autosomal dominant inherited cancer syndromes**
- It includes several well defined cancers in which inheritance of **a single mutant gene greatly increases** the risk of developing a tumor eg. **Familial retinoblastoma**

Ctd…

- **Defective DNA repair syndrome**
- A group of cancer predisposing conditions is collectively characterized by defects in DNA repair & resultant DNA instability
- This conditions include xeroderma pigmentosum, ataxia- telangectasia & Bloom syndrome

Familial cancers

- Cancers may occur at higher frequency in certain families without a clearly defined pattern of transmission
- These includes **carcinoma of colon, breast, ovary & brain, melanoma**
- **Features that xize familial cancers include early age at onset, tumors arising in two or more close relatives of the index case & some times, multiple or bilateral tumors.**

Ctd…

- Nonhereditary predisposing conditions
- Precancerous conditions
  - These are non neoplastic conditions with well defined association with cancer.

Ctd…

- **Regenerative, hyperplastic & dysplastic proliferations are fertile soil for the origin of malignant neoplasm**
  - Endometrial hyperplasia – endometrial ca
  - Cervical dysplasia – cervical ca
  - Bronchial dysplasia – bronchogenic ca
  - Regenerative nodules – liver ca

Ctd…

- Certain non- neoplastic disorders may predispose to cancers
  - Chronic atrophic gastritis – gastric ca
  - Solar keratosis of skin – skin cancer
  - Chronic ulcerative colitis – colonic ca
  - Leukoplakia – squamous cell ca

? Does benign tumor become a malignant tumor????

Molecular basis of cancer

- The fundamental principles in cancer genetics include
- **Non- lethal genetic damage** lies at the heart of carcinogenesis. Such genetic damage (mutation) may be acquired by the action of env'tal agents such as chemicals, radiation or viruses or it may be inherited in the germ line.

Ctd…

- A tumor is formed by the clonal expansion of a single precursor cell that has incurred the genetic damage (tumors are monoclonal).

Regulator gene

- The three class of normal regulator genes are the principal targets of genetic damage

1. The growth promoting proto-oncogenes

- Proto-oncogenes activation give rise to oncogenes (cancer causing genes)

2. Growth inhibiting tumor suppressor genes

- Its physiologic role is to regulate cell growth however, the inactivation of tumor suppressor genes is the key event in cancer genesis.

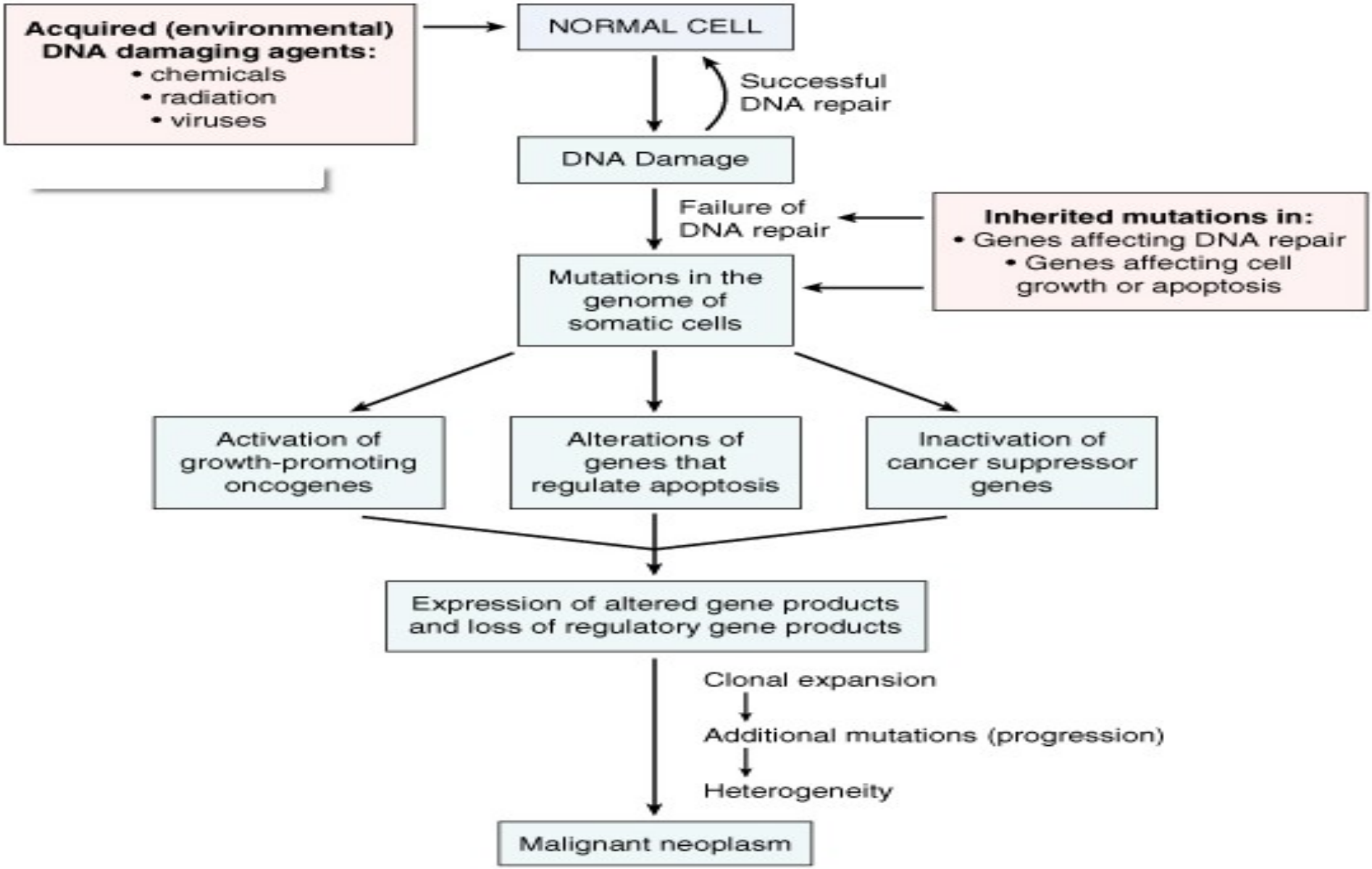
Ctd…

3. Genes that regulate programmed cell death (apoptosis)

4. Genes that regulate DNA repair

- These genes affect cell proliferation or survival indirectly by influencing the ability of the organism to repair non lethal damage in other genes. It predisposes to mutation & to neoplastic transformation

Ctd...


Acquired (environmental) DNA damaging agents:
• chemicals
• radiation
• viruses
NORMAL CELL
Successful DNA repair
DNA Damage
Failure of DNA repair
Inherited mutations in:
• Genes affecting DNA repair
• Genes affecting cell growth or apoptosis
Mutations in the genome of somatic cells
Activation of growth-promoting oncogenes
Alterations of genes that regulate apoptosis
Inactivation of cancer suppressor genes
Expression of altered gene products and loss of regulatory gene products
Clonal expansion
Additional mutations (progression)
Heterogeneity
Malignant neoplasm

Carcinogenesis

- A large number of agents cause genetic damages & induce neoplastic transformation of cells. They fall in to three categories
- **Chemical carcinogens**
- **Radiant energy**
- **Oncogenic viruses & some other microbes**

Chemical carcinogenesis

- Fall in to two categories
- Direct acting compound – these do not require chemical transformation for their carcinogenicity
- Indirect-acting compounds or procarcinogenes – require metabolic conversion to produce ultimate carcinogens capable of transforming cells .

These includes

- Direct acting alkylating agents
- Therapeutic agents such as cyclophosphamide used as anticancer agents have been documented to induce lymphoid neoplasms & leukemia
- Polycyclic aromatic hydrocarbons
- These agents represent some of the most potent carcinogens
  - Eg. They are produced in the combustion of tobacco & contribute to the cause of lung & bladder ca.

Ctd…

- Aromatic amines & Azo dyes
- Nitrosamines & amides
- Naturally occurring carcinogens
  - **Eg. Aflatoxin B1 is a potent hepatic carcinogen → Aspergillus flavus**

Radiation carcinogenesis

- Radiation energy whether in form of UV sun light or ionizing electromagnetic (X rays & gamma rays) & particulates (ß, α, protons & neutrons) radiation can transform & induce neoplasm in both humans & experimental animals

Viral & microbial carcinogesis

- Large groups of DNA & RNA viruses have proved to be oncogenic & there is an association between infections by the **bacterium H. pylori & gastric lymphoma**

DNA oncogenic viruses

Includes

- HPV
- EBV
- HBV

HPV

- Definitely causes benign squamous papilloma (warts) - type 1,2,3,4,7
- It also implicated in the genesis of squamous cell ca of cervix & anogenital region – type 16,18 & also 31,33,35,51 found in 85% SCC)
- Also linked to the causation of oral & laryngeal ca.

EBV

- Participates in the pathogenesis of four tumors
- ✓ African form Burkitt's lymphoma
- ✓ B- cell lymphomas in immuno suppressed individuals
- ✓ Some cases of Hodgkin's disease
- ✓ Nasopharyngeal carcinoma

HBV

- Strong epidemiologic association prevails b/n HBV & HCC

RNA oncogenic virus

- Only one retrovirus is firmly implicated in the causation of cancer & it is Human T cell leukemia/lymphoma virus type 1 (HTLV-1).

Helicobacter pylori

- There is an association b/n gastric infection with H. pylori as a cause of gastric lymphoma. The strong link is with **B cell lymphoma of stomach**
- Treatment of bacteria with antibiotics results in regression of the lymphoma in most cases.

Clinical features of tumors

- Both benign & malignant neoplasms may cause problems because of

1. Location & impingement on adjacent structures
2. Functional activities such as hormone synthesis
3. Bleeding & secondary infection when they ulcerate through adjacent natural surfaces
4. Initiation of acute symptoms caused by either rupture or infarction

Local & hormonal effects

- Eg. Pituitary adenoma being located in critical location can cause serious endocrinopathies
- Analogously cancers arising with or metastatic to an endocrine organ may cause an endocrine insufficiency by destroying the gland

Effects of tumor ctd…

- Benign neoplasms of endocrine origin may produce manifestations by elaborations of hormones
- Eg. A benign B-cell adenoma of pancreatic islets less than 1cm in diameter may produce sufficient insulin to cause fatal hypoglycemia
- Neoplasms in the gut may cause obstruction as they enlarge

Cancer cachexia

- Cachexia is a progressive loss of body fat & lean body mass accompanied by profound weakness, anorexia, & anemia.
- The origin of cancer cachexia is obscured
- ✓ Reduced food intake
- ✓ TNF produced by macrophages & possibly by some tumor cells is the mediator of wasting syndrome that accompanies cancer. Other cytokines such as IL-1 & IFN α can synergize with TNF α

Paraneoplastic syndrome

- It is an aggregate of symptom complexes in cancer – bearing pts that can not readily be explained either by the local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose
- It occurs in about 10% of pts with malignant disease.

Ctd…

- **The endocrinopathies** are frequently encountered paraneoplastic syndromes because the cancer cells are not of endocrine origin, the functional activity is referred as **ectopic hormone production**
- **Cushing syndrome is the most common endocrinopathy**. 50% of pts have carcinoma of lung, chiefly the small cell type. It is caused by excessive production of **corticotropin**

Grading & staging of cancers

- Grading denotes the level of differentiation.
- Staging expresses the extent of tumor spread & forecast the clinical gravity of cancer.

Ctd…

- Grading of cancer is based on the degree of differentiation of tumor cells & number of mitoses with in the tumor & presumably correlates to aggressive character of the neoplasm
- Cancers are classified in to grades I to IV with increasing anaplasia. Criteria for individual grades vary with each form of neoplasm

Ctd…

- **The staging of cancers is based on the size of primary lesions, its extent of spread to regional lymph nodes & the presence or absence of blood born metastasis.**

Ctd…

- Two major staging system are currently in use
- **Union internationale centre cancer (UICC)** which utilizes the so called **TNM system**
- The **TNM** staging varies for each specific form of cancer but there are general principles
- With increasing size, the primary lesion is xized as T1 to T4. T0 is added to indicate an insitu lesion
- N0 for no nodal involvement whereas, N1-N3 would denote involvement of an increasing number & range of nodes
- M0 signifies no distant metastasis whereas M1 or sometimes M2 indicates presence of metastasis

Ctd…

- The American joint committee (AJC) employs a some what different nomenclature & divides all cancers into stages to IV, incorporating within each of these stages the size of the primary lesion as well as the presence of nodal spread & the distant metastasis

Ctd…

- **The staging of** neoplastic disease has assumed great importance in the selection of the best form of **therapy** for the pt. indeed staging has proved to be of greater clinical value than grading.

Laboratory diagnosis of cancer

- Histologic & cytologic methods

Several sampling approaches are available

1. Biopsy
2. FNA
3. Cytologic smears

- PAP smear
- Fluid cytology
  - Advanced techniques
    - Immunohistochemistry
    - Molecular diagnosis
    - Flow cytometry
    - Tumor markers

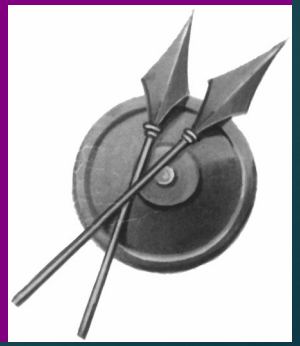
7. Selected metabolic diseases

- Thyroid and it’s disorders
- Diabetes Mellitus

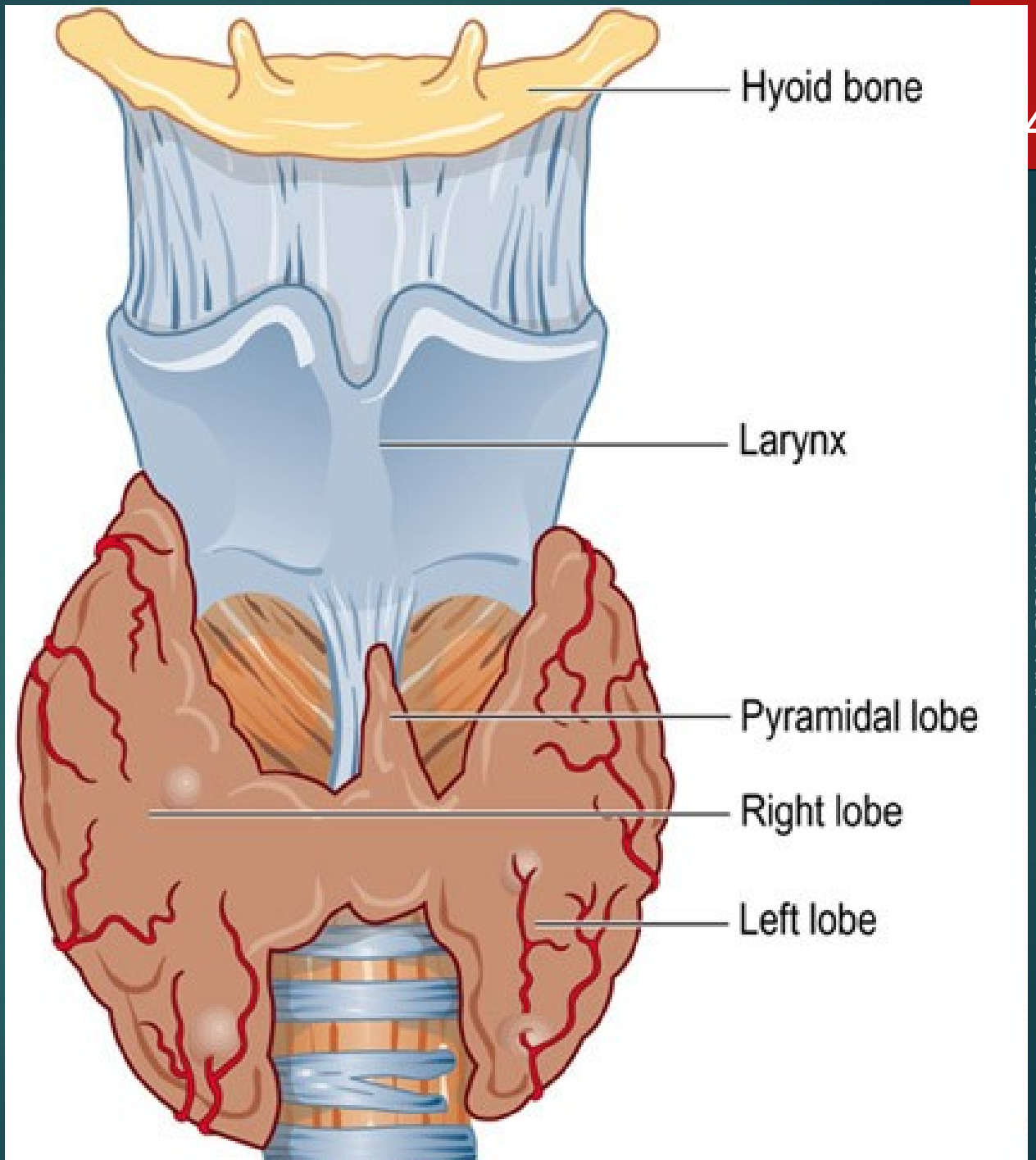
THYROID GLAND

THE THYROID GLAND

- "Thyreos" Greek for Shield.
- Morphology:
  - Largest Endocrine gland: 15 – 25 Gms in weight.
- Anatomy:
  - Has two lobes connected by an Isthmus
  - Is richly vascular; 4 -6ml/g/min
  - Has sympathetic innervation



THYROID GLAND

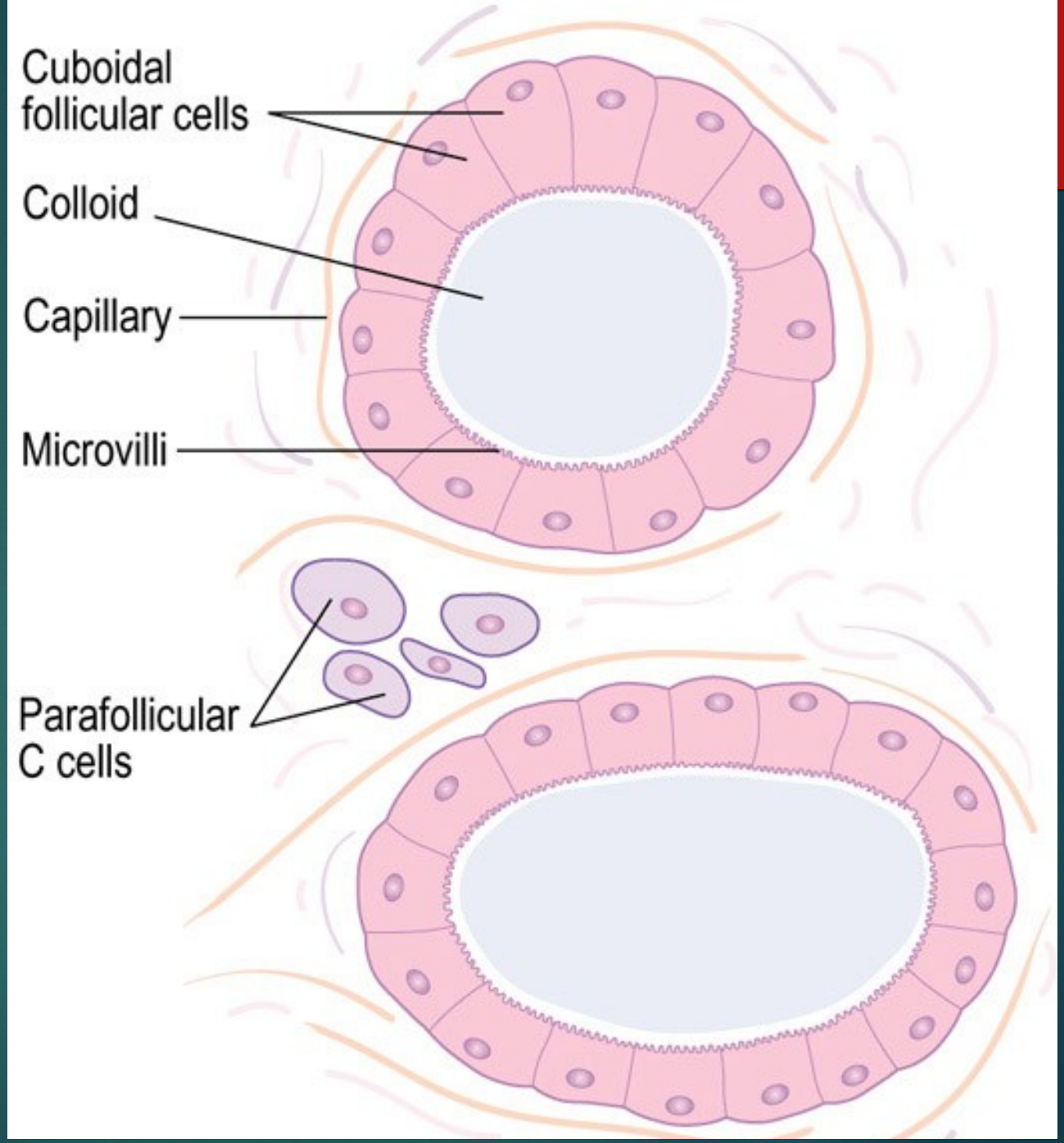


THYROID GLAND

- **EMBRYOLOGY:**
  - Begins development in the **4thwk of IUL**
  - Hormones secreted from the **12th week**.
  - Fetal Thyroid Hormones useful for:
    - Normal Fetal Bone maturation.
    - Normal development of the CNS.

THYROID GLAND

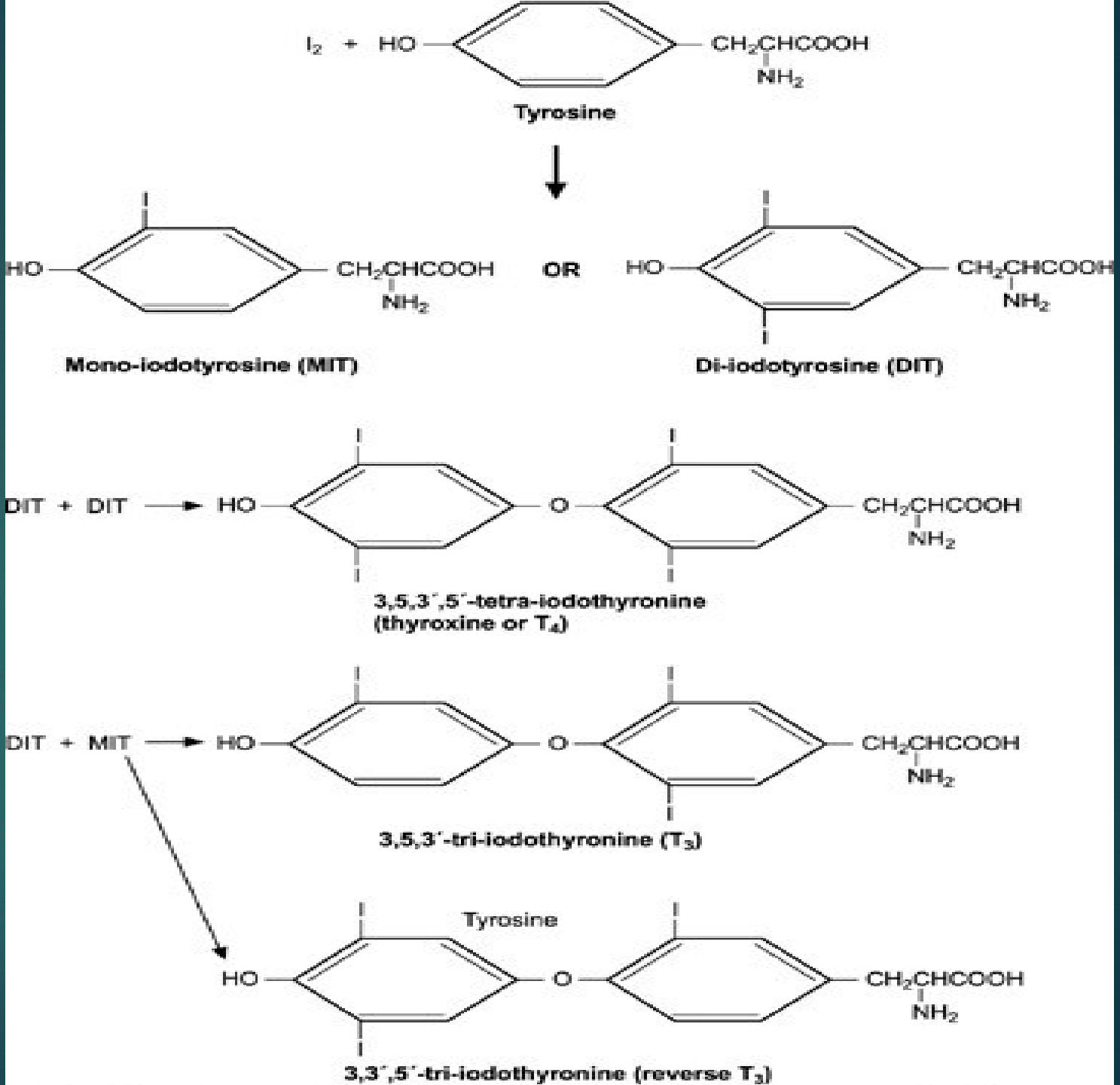
- **HISTOLOGY:**
  - 3 Million spherical follicles
  - 50 - 500µ in diameter
  - Each follicle has clear viscid protein colloid called Thyroglobulin
  - The Parafollicular ‘C’ cells secrete (Thyro) Calcitonin.


Cuboidal
follicular cells
Colloid
Capillary
Microvilli
Parafollicular
C cells

BIOSYNTHESIS OF THYROID HORMONES

- IODINE UPTAKE & TRAPPING
- IODINATION & COUPLING
  - Tyrosine + Iodine = Mono Iodo Tyrosine (MIT)
  - MIT + MIT = Di Iodo Tyrosine (DIT)
  - MIT + DIT = Tri Iodo Tyrosine T_3
  - DIT + DIT = Tetra Iodo Thyronine (T_4)

IODINATION&COUPLING



BIOSYNTHESIS OF THYROID HORMONES

NOMA
7/5/202

- COUPLED HORMONES COMBINE WITH THYROGLOBULIN, COLLOID.
- ARE FREED BY PROTEOLYSIS
- THE FREE THYROID HORMONES ARE THEN RELEASED INTO THE BLOOD

TRANSPORT OF THYROID HORMONES



- 60% : THYROXIN BINDING GLOBULIN (TBG)
- 30% : THYROXIN BINDING PRE ALBUMIN (TBPA)
- 10% : ALBUMIN

MAD:ENDOPHYSIOL: THYROID PARA
2022

EFFECTS OF THYROID HORMONES: **Metabolic**

- CALORIGENESIS:
  Heat Production.
- REGULATION:
  - Transport:
    - Ions
    - Water
  - Intermediary metabolisms:
    - CHO
    - Fats
    - Proteins
- ↑ BMR

EFFECTS OF THYROID HORMONES:

NOMA
7/5/202

Developmental

- REGULATION:
  - Growth in **Homeotherms**
  - Metamorphosis in **Poikilotherms**.
- CONTROL:
- Protein Synthesis.

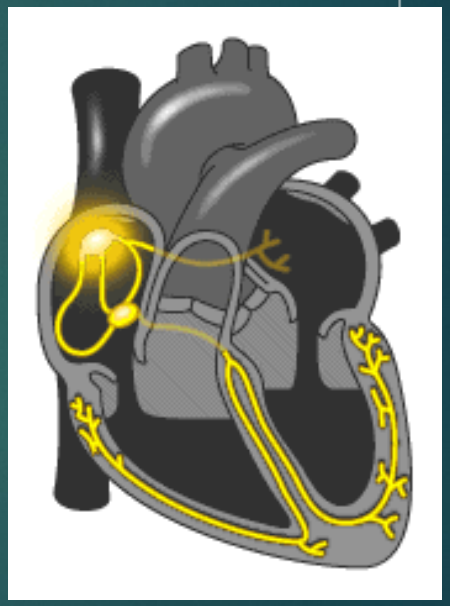
CALORIGENESIS: Heat Production

- How?
- By increasing Oxygen consumption in:
  - Heart
  - Gastric Mucosa
  - Smooth Muscles
  - Kidneys
  - Liver
  - Skeletal Muscles.



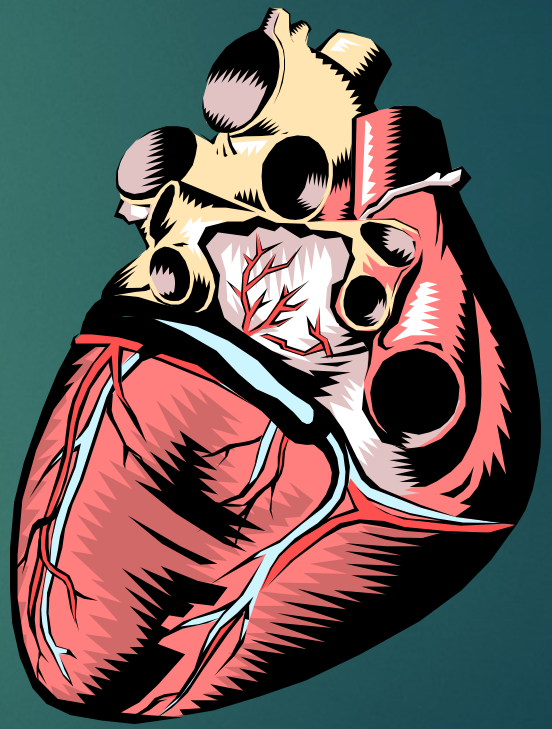
CALORIGENESIS: Heat Production

- No response to Thyroxine in
  - **T**: Testes
  - **U**: Uterus
  - **L**: Lymph nodes
  - **S**: Spleen
  - **A**: Anterior Pituitary
- Results:
  - Tachycardia
  - ↑ Sensitivity to Adrenal Lipolysis.

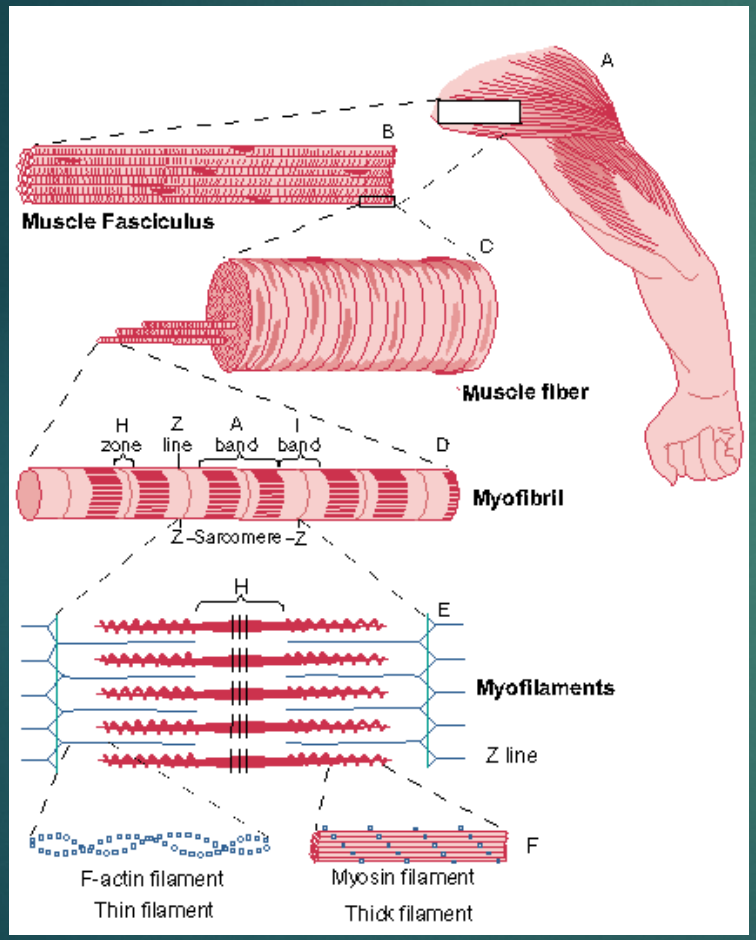


THYROID HORMONES: PHYSIOLOGIC ACTIONS

- ON THE HEART:
- POSITIVE CHRONO & IONOTROPIC EFFECT
  - ↑ No & affinity of β adrenergic receptors
  - ↑ Response to Catecholamines
  - ↑ Proportion of alpha Myosin heavy chains



THYROID HORMONES: PHYSIOLOGIC ACTIONS

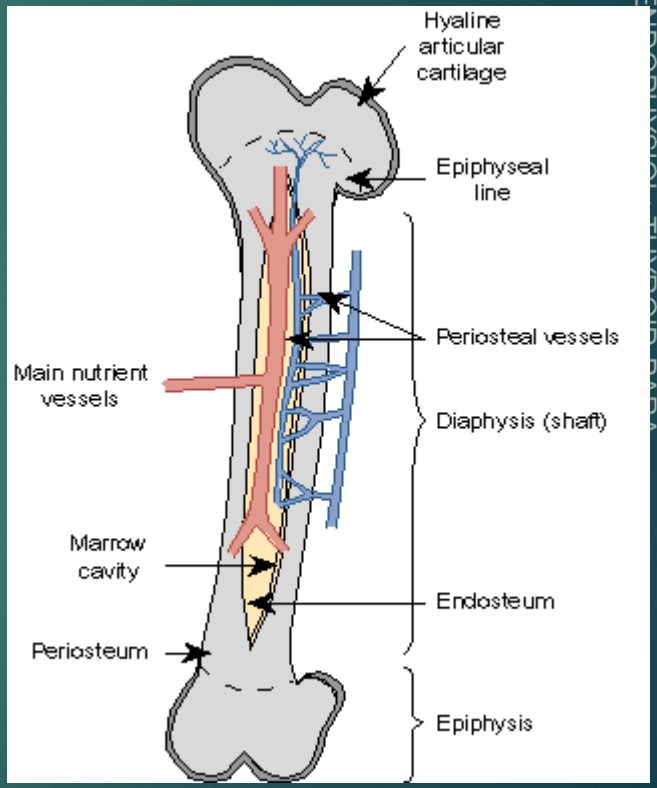


- ON THE ADIPOSE TISSUE:
  - Thyroid hormones are catabolic.
  - They cause Lipolysis.
- ON MUSCLES:
  - Catabolic
  - Protein lysis.

NOMAD:ENDOPHYSIOL:THYROID PARA
/5/2022

THYROID HORMONES: PHYSIOLOGIC ACTIONS

- ON THE BONE:
  - Developmental effect:
  - Normal growth & development.



MAD:ENDOPHYSIOL_THYROID_PARA
2022

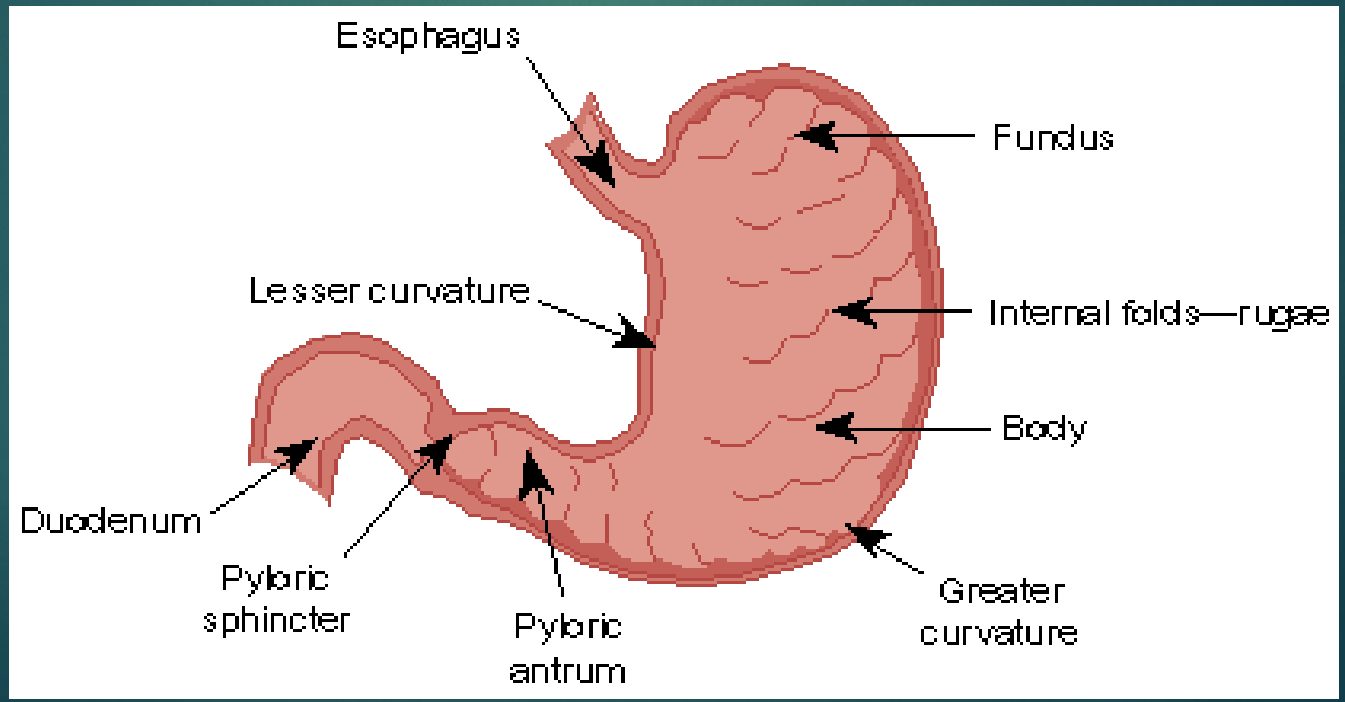
THYROID HORMONES: PHYSIOLOGIC ACTIONS



- ON THE NERVOUS SYSTEM:
  - DEVELOPMENTAL
  - Promotes normal development

THYROID HORMONES: PHYSIOLOGIC ACTIONS

- ON THE GUT:
  - METABOLIC EFFECT:
  - ↓ CHO Absorption



THYROID HORMONES: PHYSIOLOGIC ACTIONS

- ON LIPOPROTEINS:
  - METABOLIC EFFECT:
  - LDL Receptor formation.
- OTHER:
- CALORIGENESIS
- ↑ BMR:
  - ↑ Oxygen consumption in most tissues except **T**estes, **U**terus, **L**ymph nodes, **S**pleen & **A**nterior Pituitary.

THYROID HORMONES: METABOLIC EFFECTS

- CARBOHYDRATES:
  - ↑ GLUCOSE PRODUCTION BY:
    - ↑ Glycogenolysis
    - ↑ Gluconeogenesis
    - ↑ Hunger - ↑ Intake of food
  - ANTI INSULIN EFFECT:
    - ↑ Catabolism of Insulin
    - ↓ Secretion of Insulin

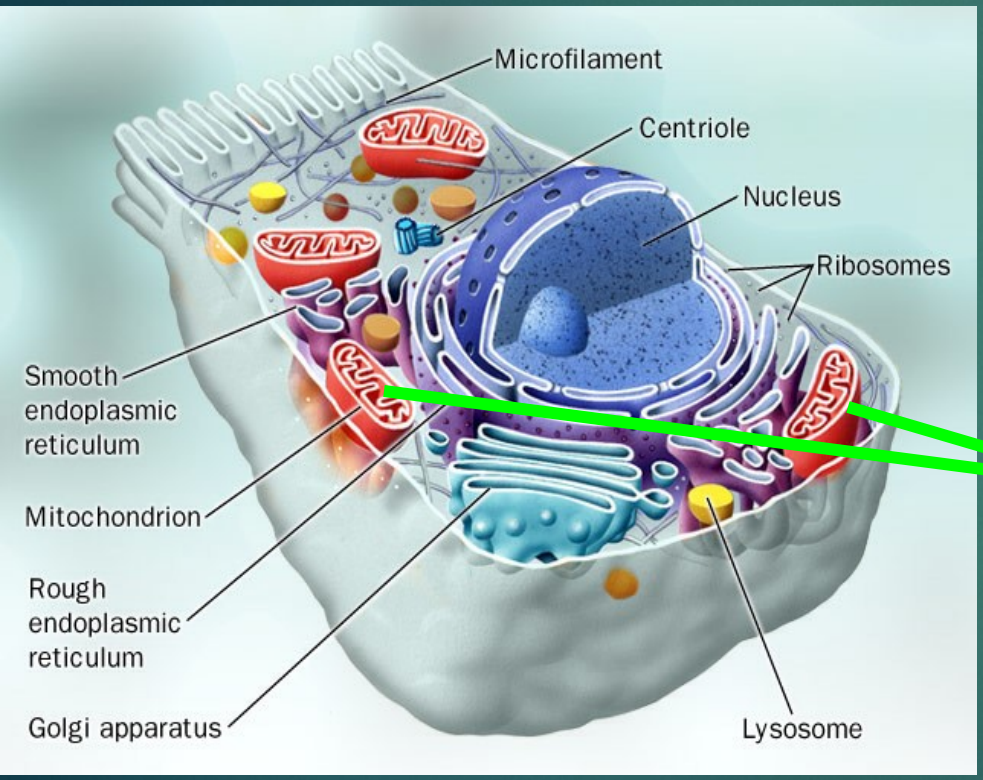
THYROID HORMONES: METABOLIC EFFECTS

- LIPIDS:
  - ↑ Synthesis
  - ↓ Lysis
  - Hypothyroidism:
    - S. Cholesterol: 400 – 700 mg%
  - Hyperthyroidism:
    - S. Cholesterol: 100 – 150 mg%

THYROID HORMONES: METABOLIC EFFECTS

- PROTEINS:
  - ↑ Anabolism
- VITAMINS:
  - Converts β Carotene to Vit A & Retinene.
- MUCOPOLYSACCARIDES:
  - Metabolism disturbed in Hypothyroidism
  - Causes ‘Myxedema’: Dry Coarse Puffy skin.

THYROID HORMONES: METABOLIC EFFECTS



- BMR:
  - Increases by 60 to 100 %
  - How?

  By increasing the size and number of Mitochondria.

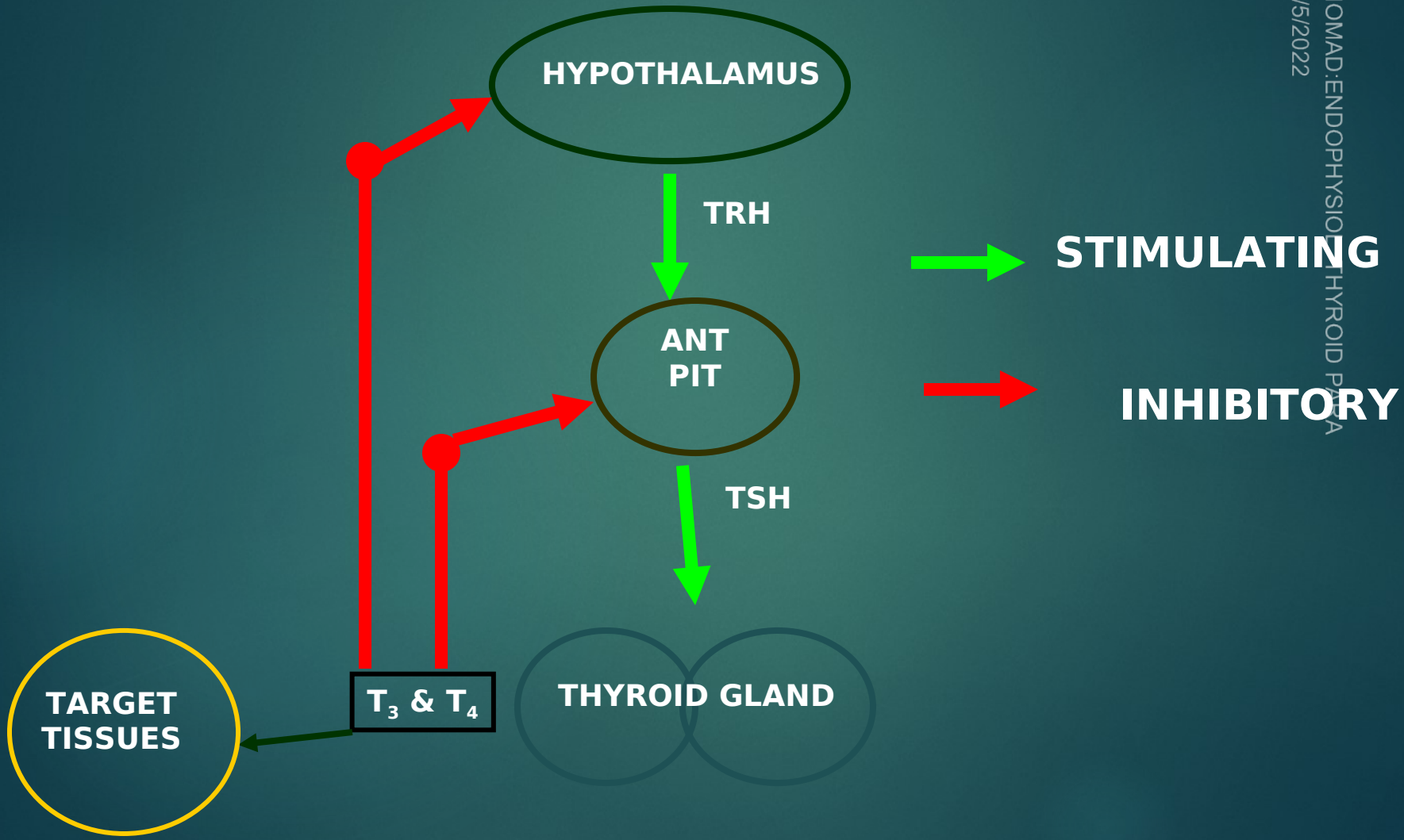
HAVE A BREAK!



Learning restarts...



THYROID HORMONES: A NEGATIVE FEEDBACK REGULATION



APPLIED ASPECTS

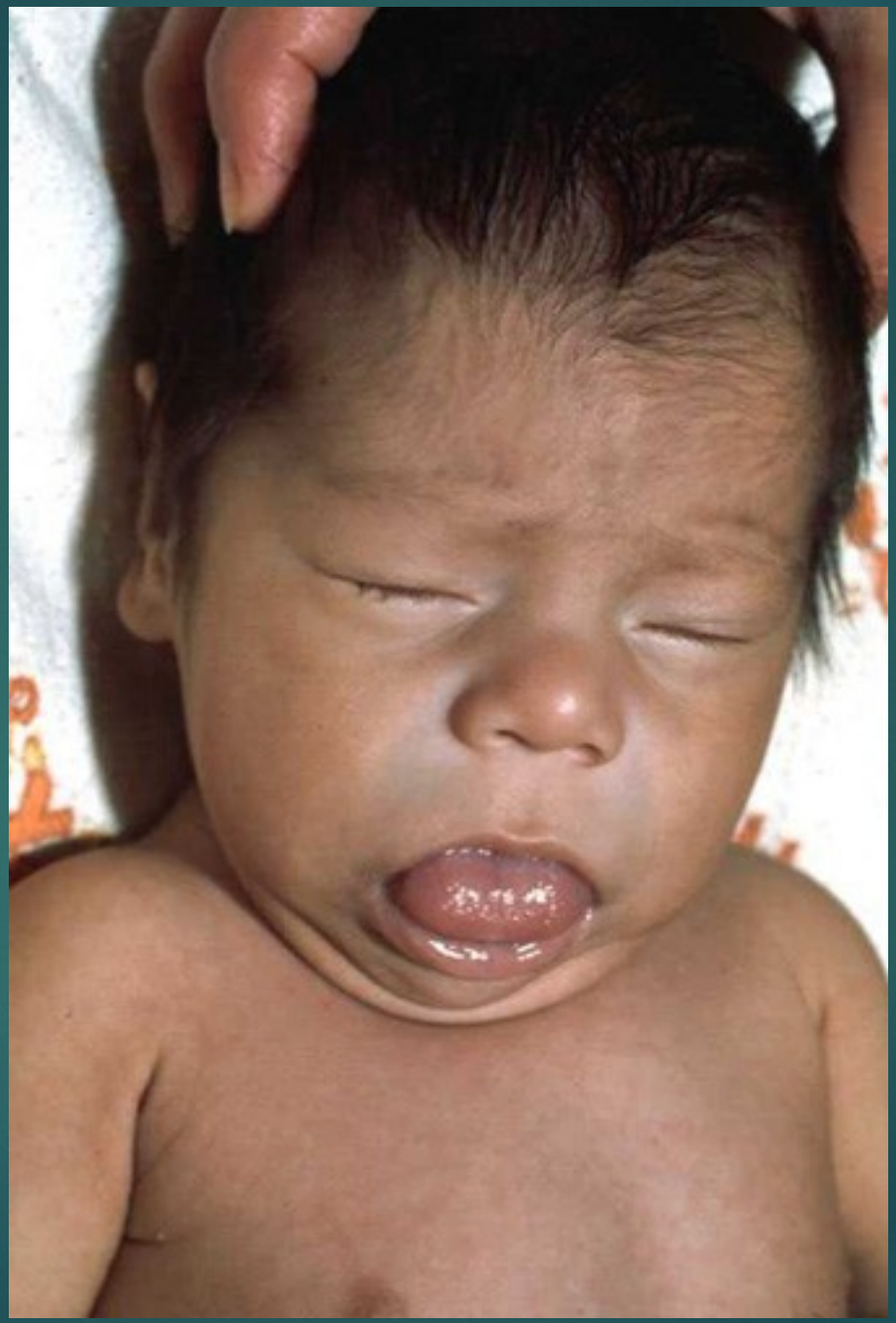
- EUTHYROIDISM: Normal thyroid status
- HYPOTHYROIDISM:
  - In infancy: Cretinism (Thyroid dwarfism)
  - In adults: Myxedema, Hypothyroidism
- HYPERTHYROIDISM:
  - Thyrotoxicosis

HYPOTHYROIDISM

- CHILDREN: CRETINISM:
  - Congenital Hypothyroidism
  - Dwarfism
  - Mentally Subnormal: MR
  - Enlarged, Protruding tongue
  - Pot bellies.



CRETINISM



PROTRUDING TONGUE

HYPOTHYROIDISM: ADULTS

- MYXEDEMA:
- CAUSES:
  - Primary: Thyroid diseases
  - Secondary: Pituitary or Hypothalamic cause.



MAD:ENDOPH
2022

MYXEDEMA: CLINICAL FEATURES

- Low BMR: - 40
- Coarse & Sparse Hair
- Dry & Yellow skin
  (Carotenemia)
- Poor Cold toleration
- Voice: Husky & slow



Tele diagnosis

MYXEDEMA: CLINICAL FEATURES

- ↓ Plasma Cholesterol
- Slow mentation
- Poor memory
- Severe mental symptoms:
  Myxedema madness

  Depression



HYPOTHYROIDISM: TREATMENT

- Very effective treatment available.
- **Replacement** of the deficient Thyroxine by **Oral tablets**.
- Brand name **Eltroxin**
- This causes **all** the **clinical features** to **disappear**.



HYPERTHYROIDISM

- Also called Thyrotoxicosis
- Hyperphagia + Weight loss
- Heat Intolerance
- ↑ Pulse Pressure
- Sleeping Pulse Rate >90/min



HYPERTHYROIDISM



- Nervousness, Anxiety
- Fine Tremor: Paper test
- Warm, soft skin
- Sweating
- ↑ BMR: +10 to +100

HYPERTHYROIDISM: GRAVE'S DISEASE

- EXOPHTHALMIC GOITRE:
  - **Exophthalmos**: Protruding eyeballs
  - Is an **autoimmune** disorder
  - Can be also **Hashimoto's Thyroiditis**





TREATMENT OF HYPERTHYROIDISM

- **Antithyroid drugs:**
  - **Most drugs interfere with Iodide trapping.**
  - **Others block iodisation of Tyrosine.**
  - **Examples:**
    - **Perchlorates**
    - **Thiocyanates**
- Decrease **Goitrogen consumption**:

GOITROGENS

- Goitrogens: Goitrin & Progoitrin seen in:
  - Cabbage
  - Rutabagas & Turnips



Central Nervous System



- *The principal cells of the CNS*

: neurons

: glia

: cells that compose the meninges & blood vessels

Neurons

- Structural & functional unit of the CNS.
- Are highly specialized post-mitotic cells which can't be replaced after cell death.

Glia

- derived from neuroectoderm & bone marrow.
- normal functions & reactions to injury.
- Include : astrocyte, oligodendrocyte, microglia & ependymal cells

Cellular pathology of the central nervous system

- *The tissues of the CNS undergo fairly stereotyped changes in response to diverse types of injury*

Reactions of neurons to injury

- Several morphologic forms of rxn

- Neuronal degeneration

- Cell death = apoptosis or necrosis

- Associated with repair after injury

- *Acute neuronal injury (Red neuron)*

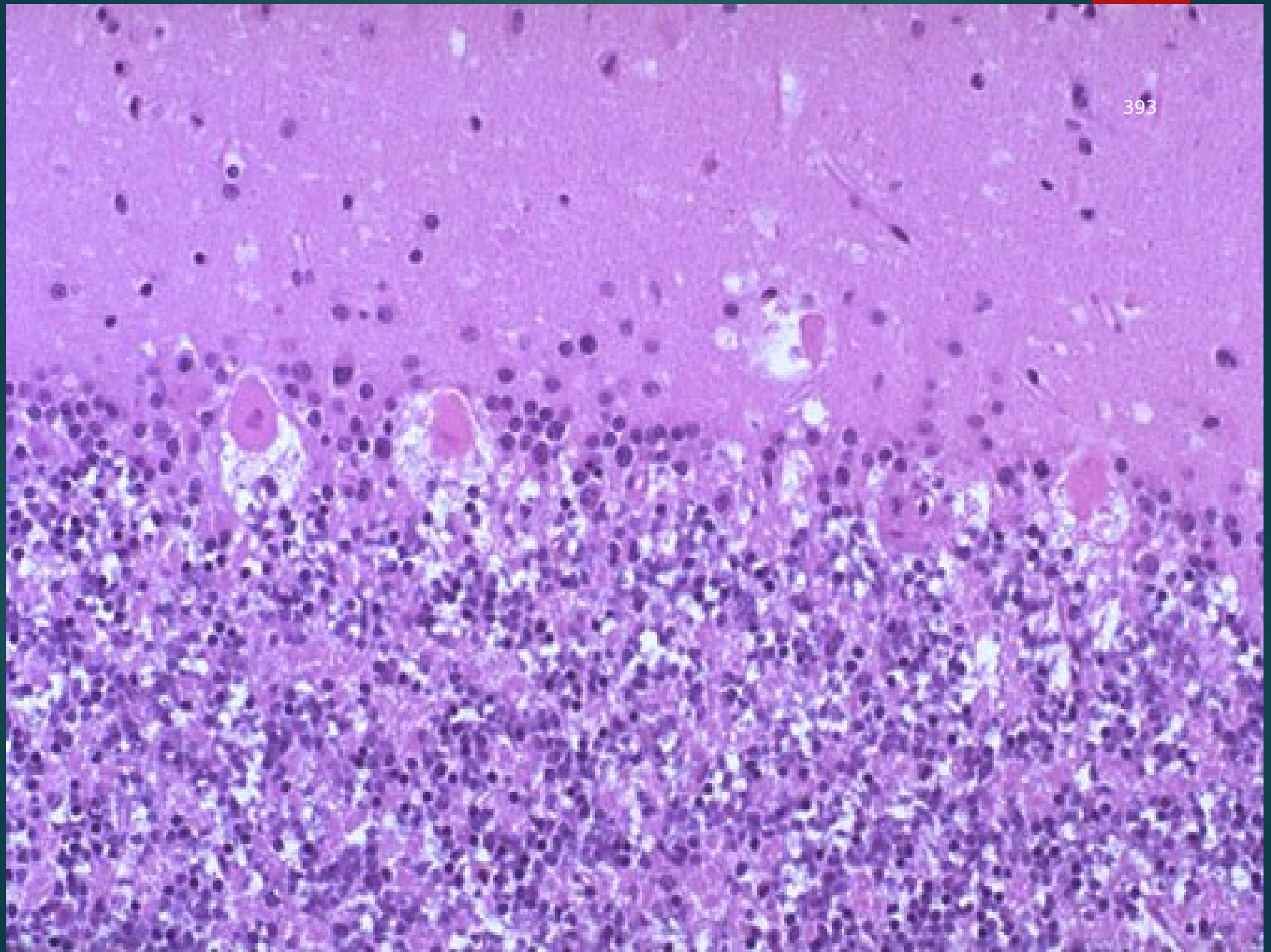
  - acute CNS hypoxia /ischemia or

  - other acute insults = death of the cell

- *Morphologic features of red neurons - shrinkage of the cell body*

  - pyknosis of the nucleus

  - intense eosinophilia of the cytoplasm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Subacute & chronic neuronal injury (degeneration)

- neuronal death occurring as a result of a progressive disease process of some duration .

- histologic picture

= cell loss (often selectively involving functionally related system of neurons) = reactive gliosis

Axonal reaction (central chromatolysis)

- refers to the reaction within a cell body that attends regeneration of the axon

- in motor neurons ff nerve injury

- increased RNA & protein synthesis = axonal sprouting.

Reactions of astrocytes to injury

- Gliosis

  - the most important histopathologic indicator of CNS injury

  - Astrocytic hyperplasia & hypertrophy

- Cellular swelling - occurs regularly in acute insults such as hypoxia, hypoglycemia, toxic injuries

Cerebral edema= brain parenchymal edema

There are two mechanisms

- *Vasogenic edema –*

- integrity of the normal BBB is disrupted

- increased vascular permeability = Fluid escape in to intercellular space

- little lymphatics & close positioning of cell processes of neurons & glia = impair resorption

- localized = vessels near inflammatory focus or neoplasm

- generalized

- *Cytotoxic edema*

  — increase in intracellular fluid

  - neuronal, glial or endothelial cell membrane injury

  - hypoxia/ischemia , intoxications

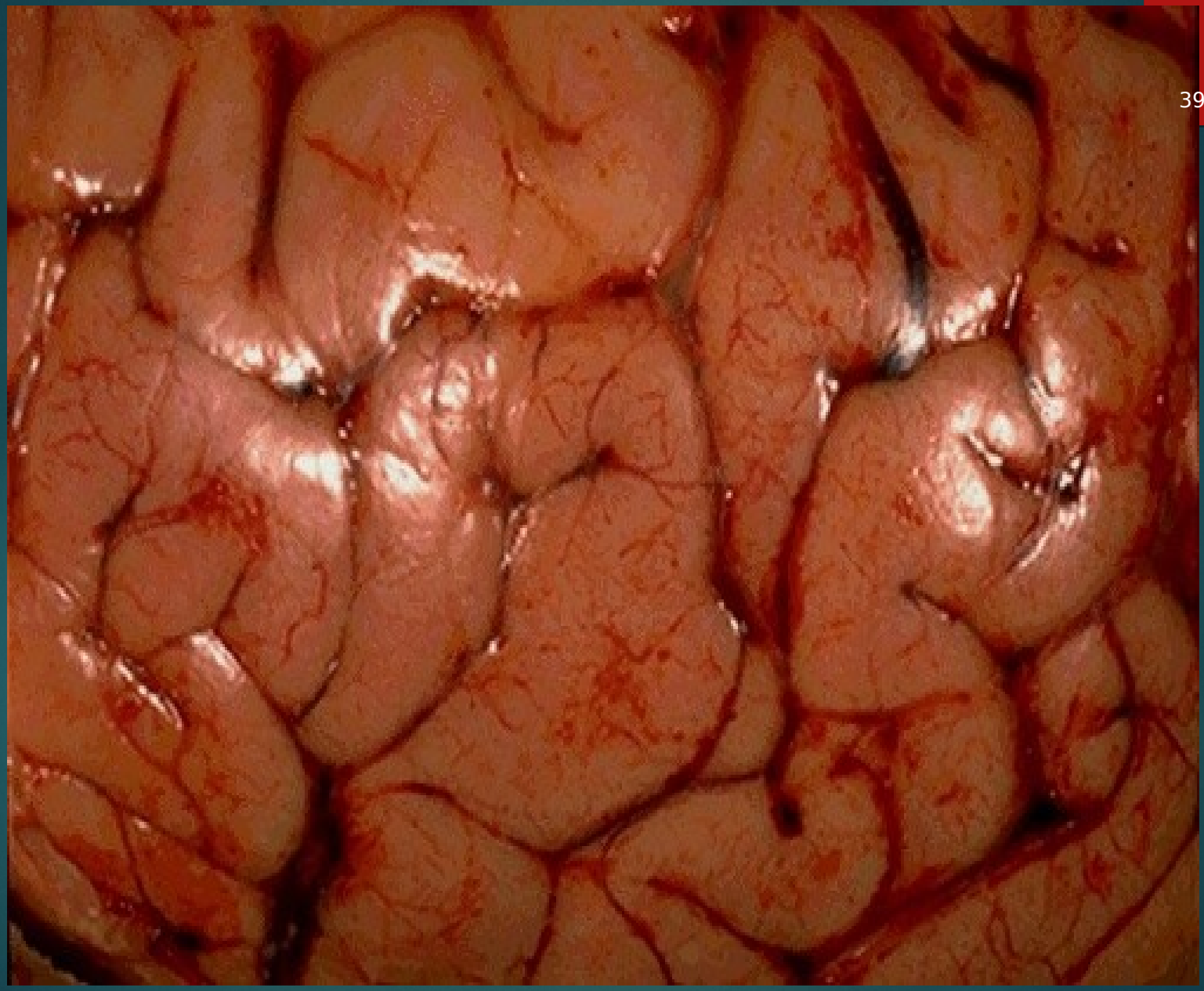
- *Morphology*

  - softer , over fill cranial vault

  - generalized edema = gyri flattened

  = sulci narrowed

  =ventricular cavities compressed



Raised intracranial pressure & herniation

-

- Raised IC pressure = increase in mean CSF pressure above 200mm water with the patient recumbent.

- compression of veins & displacement of CSF

Causes

- most cases associated with a Mass effect
  - . diffuse as in generalized brain edema
  - . focal as with tumors, abscesses or hemorrhages

clinical signs & symptoms

Papilloedema : axonal flow is impeded by pressure on the optic nerve

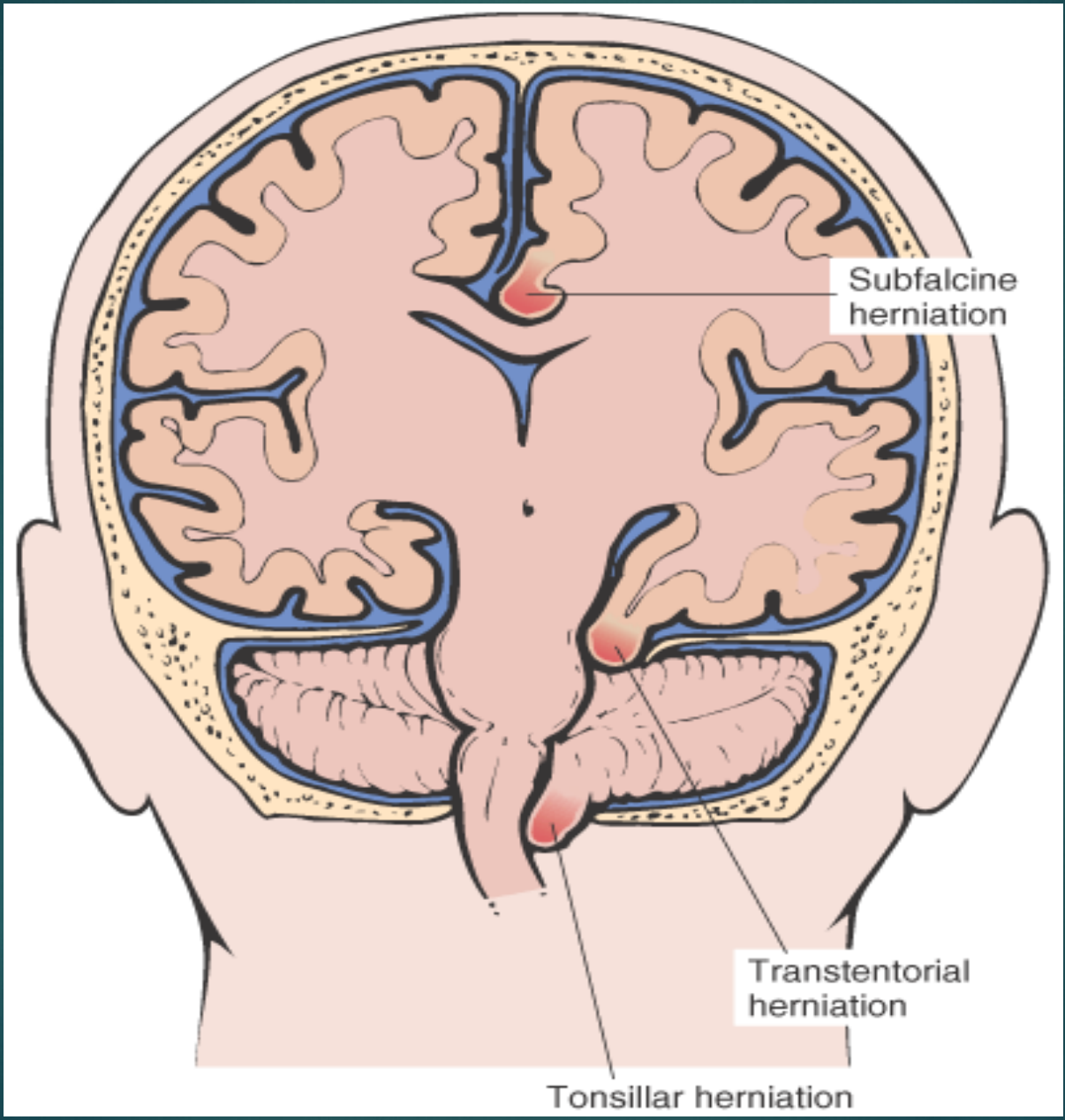
Nausea & vomiting : pressure on vomiting centers in the pons & medulla

Headache : compression & distortion of pain & stretch receptors around intracranial blood vessels & within the dura matter

Impairment of consciousness : ranging from drowsiness to deep coma

- *Cranial vault subdivided by rigid dural folds (falx & tentorium)*

- *Focal expansion of brain (due to ↑ ICP) causes displacement in relation to this partitions . If the expansion is sufficiently severe, a herniation of the brain will occur.*


Subfalcine herniation
Transtentorial herniation
Tonsillar herniation

- *Subfalcine (cingulate) herniation*

- occurs when unilateral or asymmetric expansion of a cerebral hemisphere displaces cingulate gyrus under the falx cerebri .

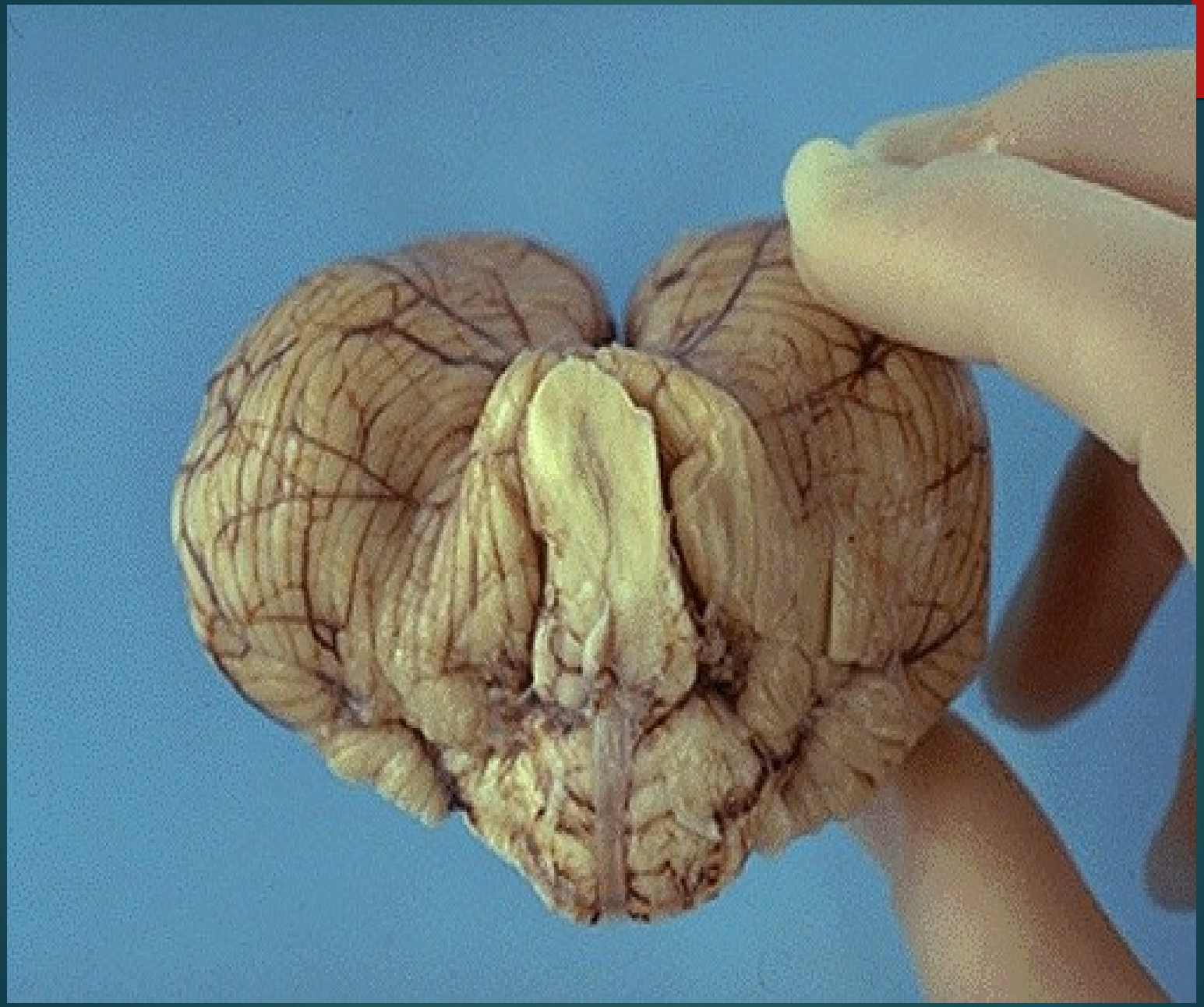
- may be associated with compression of branches of the anterior cerebral artery.

- *Transtentorial (uncinate) herniation — medial aspect of temporal lobe is compressed against the free margin of tentorium cerebelli.*

- third cranial nerve is compromised, resulting in pupillary dilation & impairment of ocular movements on the side of the lesion.

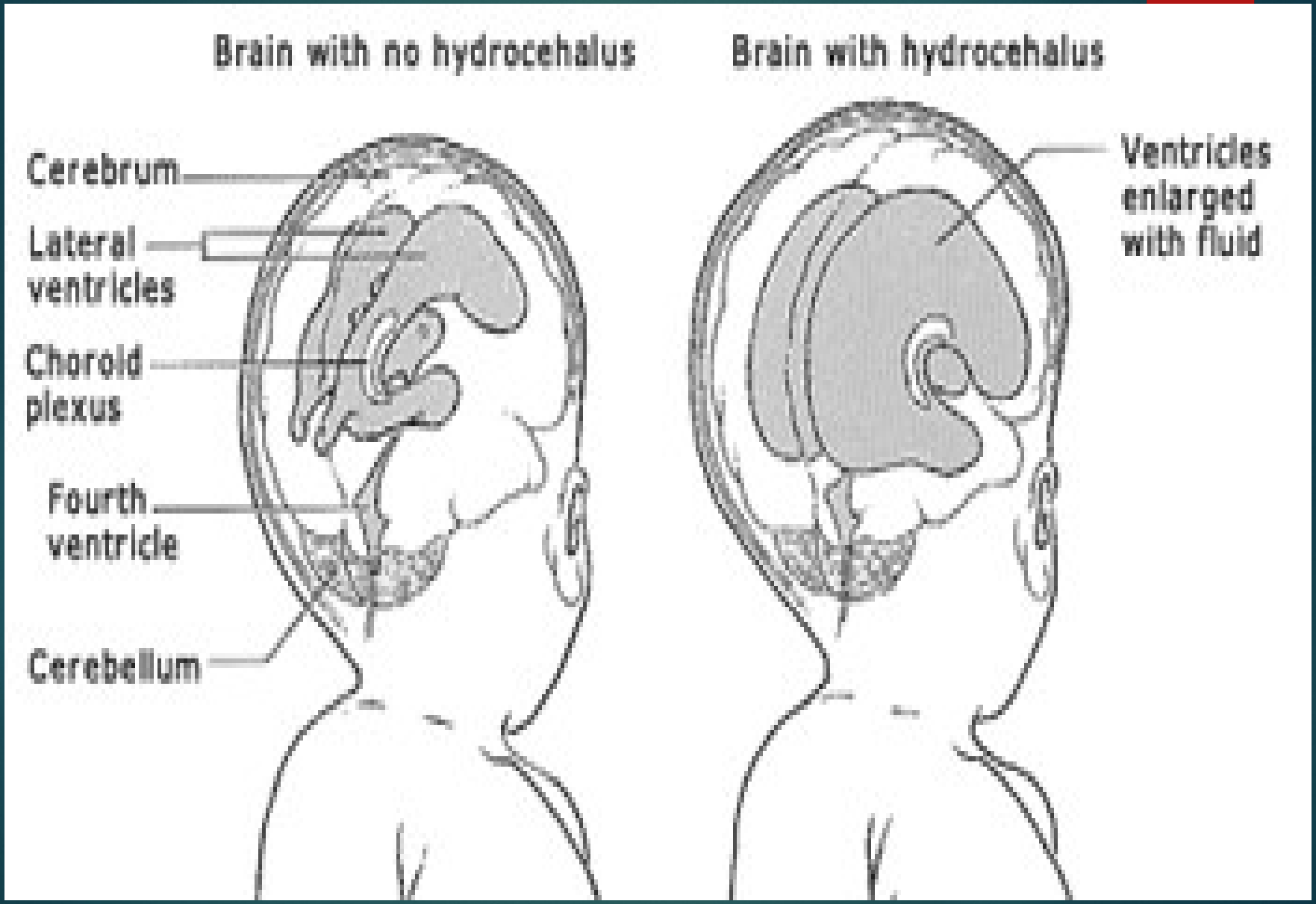
- posterior cerebral artery may be compressed.

- *Tonsillar herniation – displacement of cerebellar tonsils through foramen magnum which lead to compression of medulla oblongata & result in respiratory distress*



Hydrocephalus

- Accumulation of excessive CSF within ventricular system
- Most cases = impairments of flow & resorption of CSF.
- In rare cases= over production of CSF (choroid plexus tumors)
- increased volume of CSF within the ventricles expands them= can cause an elevation in intracranial pressure


Brain with no hydrocehalus
Brain with hydrocehalus
Cerebrum
Lateral ventricles
Chorold plexus
Fourth ventricle
Cerebellum
Ventricles enlarged with fluid

- *If hydrocephalus occurs before closure of the sutures, there is enlargement of the head, manifested by an increase in head circumference .*

- *Hydrocephalus developing after fusion of the sutures is associated with expansion of the ventricles & increased intracranial pressure, without a change in head circumference*



- *Communicating hydrocephalus – there is enlargement of the entire ventricular system*

- *Non communicating – if portion of the ventricular system is enlarged (eg tumor in the third ventricle)*



Malformation and Developmental Diseases

- Malformations of the CNS = 1/3 of congenital malformations

- important cause of infant mortality and long-term disability.

- causes

  chromosomal and/or genetic

  environmental factors.

  majority of cases = unknown.

Neural tube defects

- Failure of a portion of the neural tube to close or reopening of a region of the tube after closure
- Heterogeneous group of diseases
- All are characterized by abnormalities involving some combination of neural tissue , meninges & overlying bone & soft tissue
- Neural tube defect account for most CNS malformation
- The etiology is unknown . Folate deficiency during initial weeks of gestation has been implicated
- Elevation of maternal blood α-fetoprotein occurs

Anencephaly

- malformation of the anterior end of the neural tube
- absent brain & calvarium.
- 1 to 5 per 1000 live births
- develop at ~ 28 wks of gestation
- forebrain development is disrupted
- posterior fossa structures may be spared.

Clinical Features

- Anencephaly is incompatible with life (most die within minutes to hours after birth.)
- The diagnosis of anencephaly can be made prenatally.
- US = can detect the presence of anencephaly in the later stages of the first trimester.



Encephalocele

- Diverticulum of malformed brain tissue through defect in cranium .

- most often occurs in the occipital region or in the posterior fossa

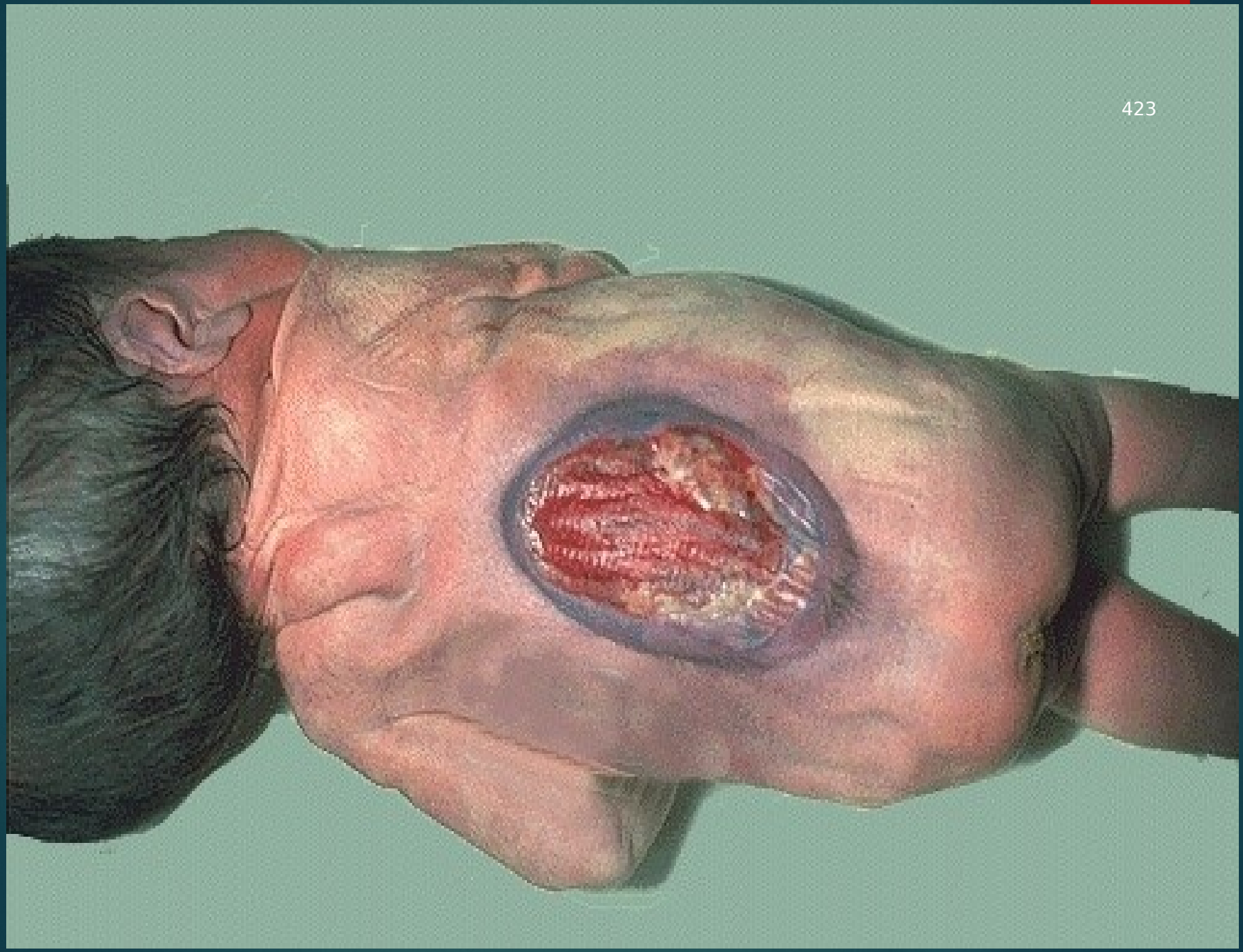
- The most common forms of neural tube defect involve the spinal cord

A. Spina bifida or dysraphism

- asymptomatic bony defect (spina bifida occulta)
- severe malformation with disorganised spinal cord segment associated with an overlying meningeal outpouching.

B. Meningomyelocele:

- extension of CNS tissue through a defect in the vertebral column.
- most commonly in the lumbosacral region
- manifest : deficits of motor & sensory function in lower extremity; disturbance in bladder & bowel control
- Meningocele : applies when there is only meningeal extrusion.



Spina bifida occulta

- *the mildest form of spinal neural tube defect.*
- *defective closure of the posterior vertebral arches*
- *intact meninges and spinal cord.*
- *site of the defect is sometimes marked by a small skin dimple or tuft of hair.*
- *20% of the general population,*
- *asymptomatic.*

Forebrain anomalies

- The volume of the brain can be abnormally large (megalocephaly) or small (microcephaly).
- Microcephaly is more common & is associated with chromosomal abnormalities, fetal alcohol syndrome & HIV infection acquired in utero.

Trauma

- anatomic location of lesion & limited capacity of the brain for functional repair = factors of great significance in CNS trauma

- Head injury

= penetrating or blunt trauma . = an open or a closed injury

- *It can be associated with*
- *Skull fractures*
- *Parenchymal injury*
- *Vascular injury*

Skull fractures

- A fracture in which bones is displaced into cranial cavity by a distance greater than the thickness of the bone is displaced skull fractures
- Site of Fractures of skull is related to pattern of fall
- Awake: occipital impact
- Loss of consciousness: frontal impact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- *Basal skull fracture = occiput or sides of the head.*
- *Orbital or mastoid hematoma raise clinical suspicion of basal skull fracture.*
- *CSF discharge from the nose (rhinorrhea) or ear*
- *infection (meningitis) may follow.*



Parenchymal injuries

Concussion

- alteration of consciousness secondary to head injury typically brought about by a change in the momentum of head (movement of the head arrested by a rigid surface)
- loss of consciousness , temporary respiratory arrest & loss of reflexes.
- neurological recovery is complete , amnesia for the event persists
- Post concussive neuropsychiatric syndromes may occur

Direct parenchymal injury

Contusion

- Direct parenchymal injury brought about by transmission of kinetic energy to brain . It is analogous to bruising

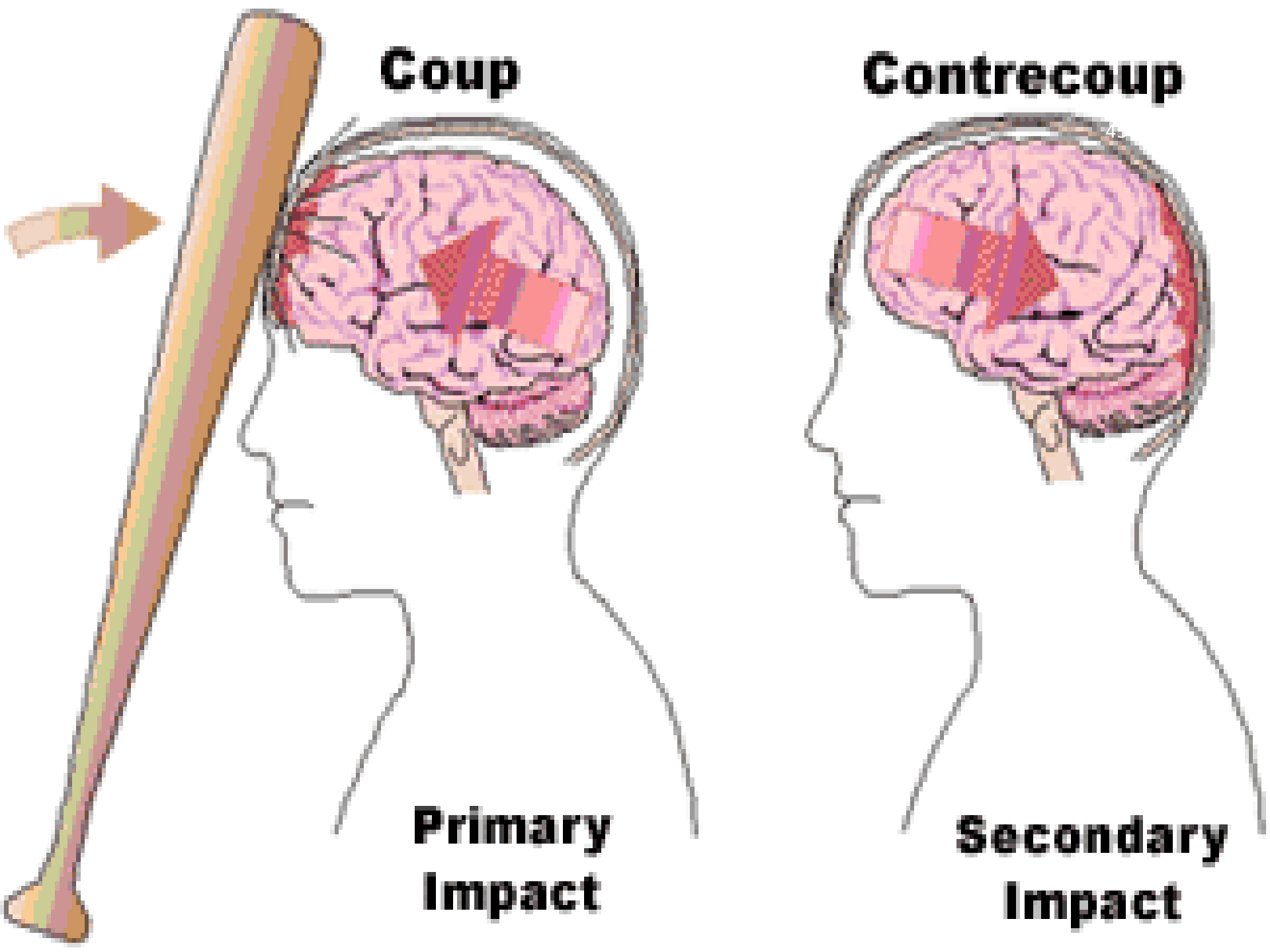
Laceration

- Caused by penetration of an object & tearing of tissue

Cerebral injury following a blow may develop at two points

- *Point of contact (coup injury)*
- *Brain surface opposite to it (counter coup)*

- Both are contusions. If the head is immobile at the time of trauma, only a coup injury is found. When the head is mobile, there may be coup lesion beneath the impact & countercoup lesions. The coup lesion is caused by the force of direct impact between the brain & skull at the site of impact , the countercoup contusion develop when the brain strikes the opposite inner surface of the skull after sudden deceleration


Coup
Contrecoup
Primary
Impact
Secondary
Impact

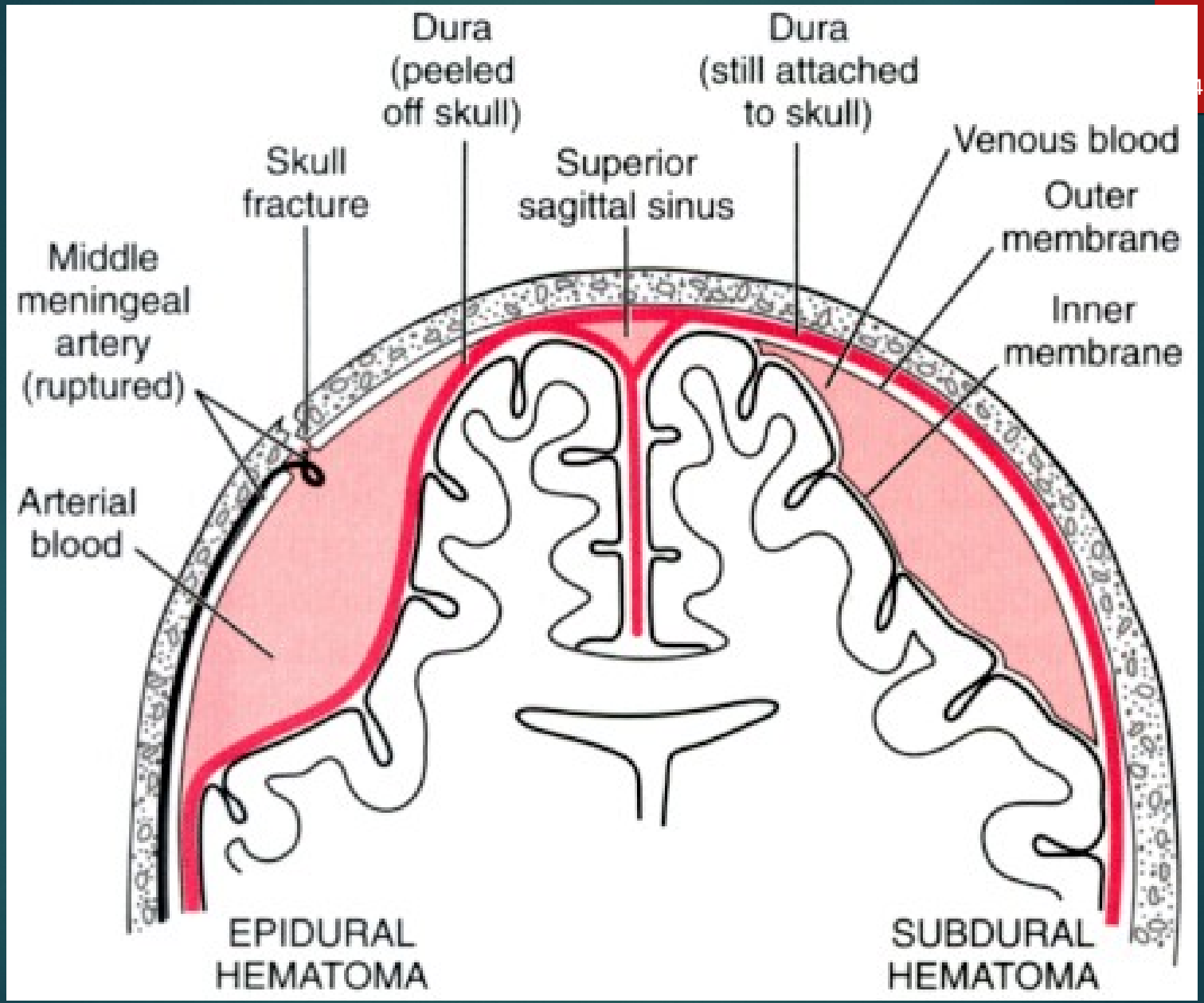
Traumatic vascular injury

-frequent component of CNS trauma

-results from direct trauma & disruption of the vessel wall leading to hemorrhage.

Epidural hematoma

- Epidural space : potential space between dura & skull
- Trauma to temporal bone = tearing of middle meningeal artery = accumulation of blood in epidural space
- patients can be lucid for several hours b/n the moment of trauma & the development of neurological signs
- An epidural hematoma may expand rapidly & is neurosurgical emergency requiring prompt drainage


Dura
(peeled
off skull)
Dura
(still attached
to skull)
Venous blood
Skull
fracture
Superior
sagittal sinus
Outer
membrane
Middle
meningeal
artery
(ruptured)
Inner
membrane
Arterial
blood
EPIDURAL
HEMATOMA
SUBDURAL
HEMATOMA

Subdural hematoma

- Subdural space:potential space beneath inner surface of the dura & outer arachinoid layer

- Bridging veins : prone to tearing along their course through the subdural space; they are the source of bleeding in most cases of subdural hematoma.

Chronic subdural hematomas

- less frequently associated with history of trauma
- often associated with brain atrophy.
- often bilateral.
- liquefied blood or yellow-tinged fluid
- Clinical symptoms : altered mental status, sometimes accompanied by focal neurologic deficits, slowly evolving , confused

Sequel of brain trauma

- *Post traumatic hydrocephalus*
- *Posttraumatic dementia*
- *Posttraumatic epilepsy*
- *Posttraumatic infections*
- *Psychiatric disorders*

Spinal cord trauma

- Usually associated with vertebral column displacement.
- The level of cord injury determines the neurolgical manifestations

Thoracic or lower vertebrae – paraplegia

Cervical lesions – quadriplegia

Those above C4 - respiratory distress

Cerebro vascular diseases

- Any abnormality of brain caused by a pathologic process of blood vessels (non traumatic)

- 'Stroke' – clinical term that apply when symptoms begin acutely

- Cerebrovascular diseases include: thrombosis, emolism & hemorrhage

- *There are two processes*

- Hypoxia, ischemia & infarction resulting from impairment of blood supply & oxygenation of CNS tissue

- Hemorrhage resulting from rupture of CNS vessels

- Hypoxia , ischemia & infarction resulting from impairment of blood supply & oxygenation of CNS tissue.

➢ Global cerebral ischemia (ischemic / hypoxic encephalopathy)

- generalized reduction of cerebral perfusion, such as cardiac arrest or shock

➢ Focal cerebral ischemia

- reduction or cessation of blood flow to a localized area of the brain

. large-vessel disease (such as embolic or thrombotic in setting of atherosclerosis) or

. small-vessel disease (such as vasculitis)

Global cerebral ischemia (Hypotension, Hypoperfusion & Low flow state)

- *Below a systolic pressure of approximately 50 mm Hg,*
- *autoregulatory mechanisms are inadequate to compensate for the reduction in blood flow,*
- *parenchymal injury may occur.*

- *Within the CNS, certain regions and cell populations are more susceptible than others to hypoxic-ischemic injury.*
- *neurons more vulnerable than glial cells.*
- *Among the neurons*
  - *pyramidal cells in the hippocampus,*
  - *Purkinje cells of the cerebellum are sensitive*
- *Areas of the brain located at the junctions of arterial territories (arterial border zones) are also susceptible*

Clinical Features

- degree of parenchymal injury
- age
- duration of the circulatory disturbance
- temperature (hypothermia / hyperthermia)

- deficits = range from transient neurologic disturbances to "brain death," with a global cessation of electrical activity

Focal cerebral ischemia (ischemic stroke)

- Reduction or cessation of blood flow to a localized area of the brain due to a large / small vessel disease (emboli, thrombosis or vasculitis)

- *The majority of thrombotic occlusions = atherosclerosis.*
- *The most common sites are*
  - *carotid bifurcation,*
  - *the origin of the middle cerebral artery*
  - *either end of basilar artery*

- *Embolism to the brain occurs from wide range origins.*
- *Cardiac mural thrombi the most common sources.*

(Myocardial infarct, valvular disease & atrial fibrillation predisposing factors).

- *emboli from atheromatous plaques within the carotid arteries.*

Emboli tend to lodge

- *blood vessels branch*
- *areas of preexisting luminal stenosis*

  * *middle cerebral artery (the direct extension of the internal carotid artery) is most frequently affected by embolic infarction*

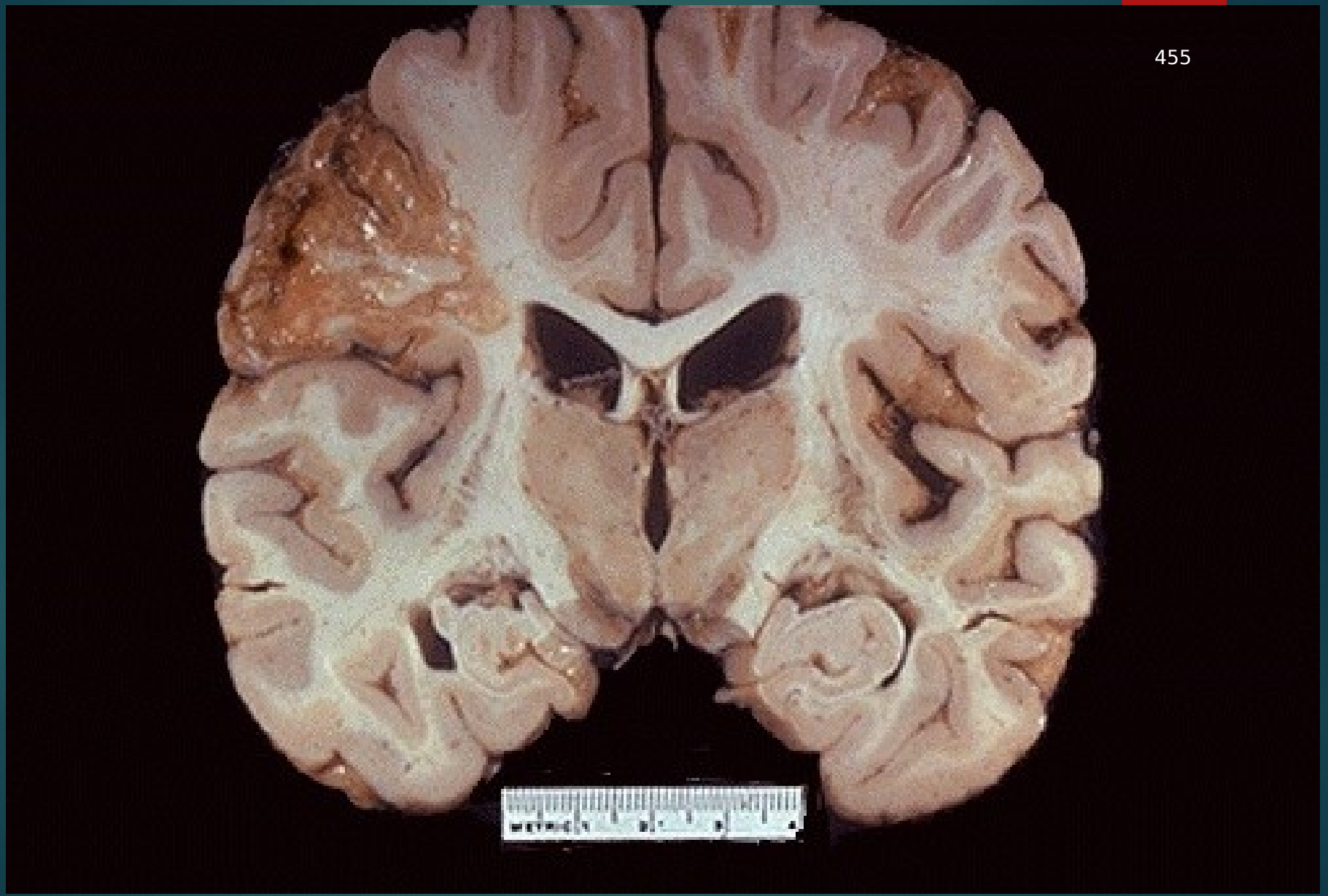
- *Infarcts are subdivided into two broad groups based on macroscopic appearance*
  - *Hemorrhagic (red) infarction*
- *multiple petechial hemorrhages*
- *embolic events*
- *hemorrhage is secondary to reperfusion of damaged vessels & tissue either through collaterals or after lysis of the occlusive material.*

- *Nonhemorrhagic (pale, anemic)*
- *usually associated with thrombosis.*

Morphology

- The macroscopic appearance of nonhemorrhagic infarct changes with time.

- 48 hrs the brain = pale, soft & swollen
- 2 to 10 days = gelatinous & friable
- 10 days to 3 weeks = the tissue liquifies , eventually leaving fluid filled cavity



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microscopic examination

- *first 12 hrs = ischemic neuronal change (red neurons) & edema predominates.*
- *48hrs = neutrophils migration increases*
- *after 48hrs = phagocytic cells dominate in the next 2 to 3 wks*

- *hemorrhagic infarction parallels ischemic infarction with addition of blood extravasation & resorption.*

Clinical features

- *area of brain affected determines*
- *asymptomatic*
- *Develops : hemiplegia , sensory deficit, aphasia or other deficit.*

Hemorrhage resulting from rupture of CNS vessels

- Hemorrhages may occur at any site within the CNS.
- Hemorrhages within the brain parenchyma & subarachinoid space : underlying cerebro vascular disease
- hemorrhages within epidural & subdural space : trauma

Intracerebral (intraparenchymal) hemorrhage

- *Spontaneous (non traumatic) intraparenchymal hemorhages occur most commonly in middle to late adult life with peak = 60yrs.*

- *Most are caused by rupture of a small intraparenchymal vessel.*

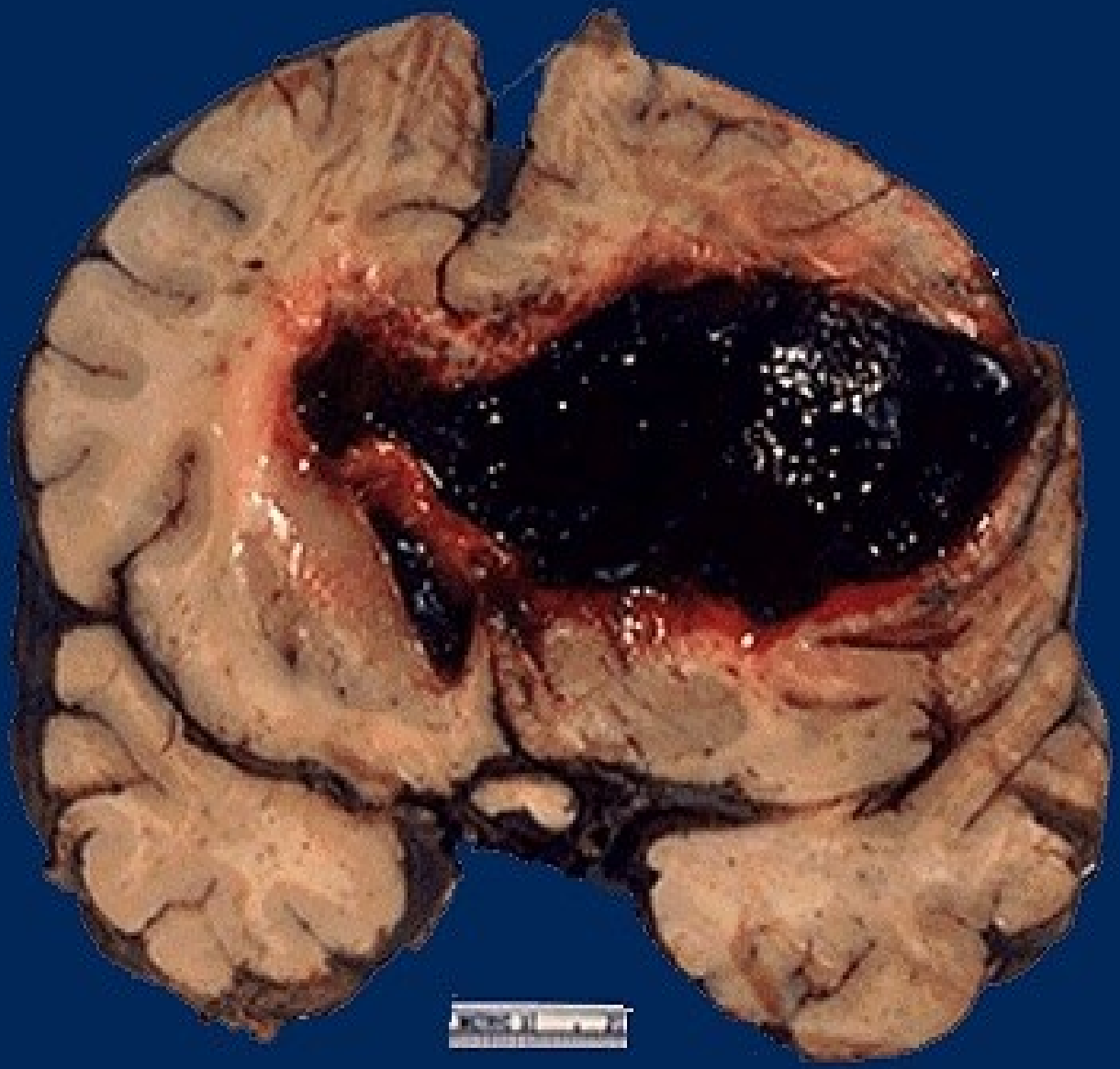
HTN :

- most common underlying cause of primary brain parenchymal hemorrhage (50%).
- accelerated atherosclerosis in large arteries,
- hyaline arteriolosclerosis in small vessels .
- Arteries with this changes are weaker = more vulnerable to rupture

Morphology

- putamen (50-60%) , thalamus, pons, cerebellar hemisphers.

- extravasation of blood with compression of the adjacent parenchyma.

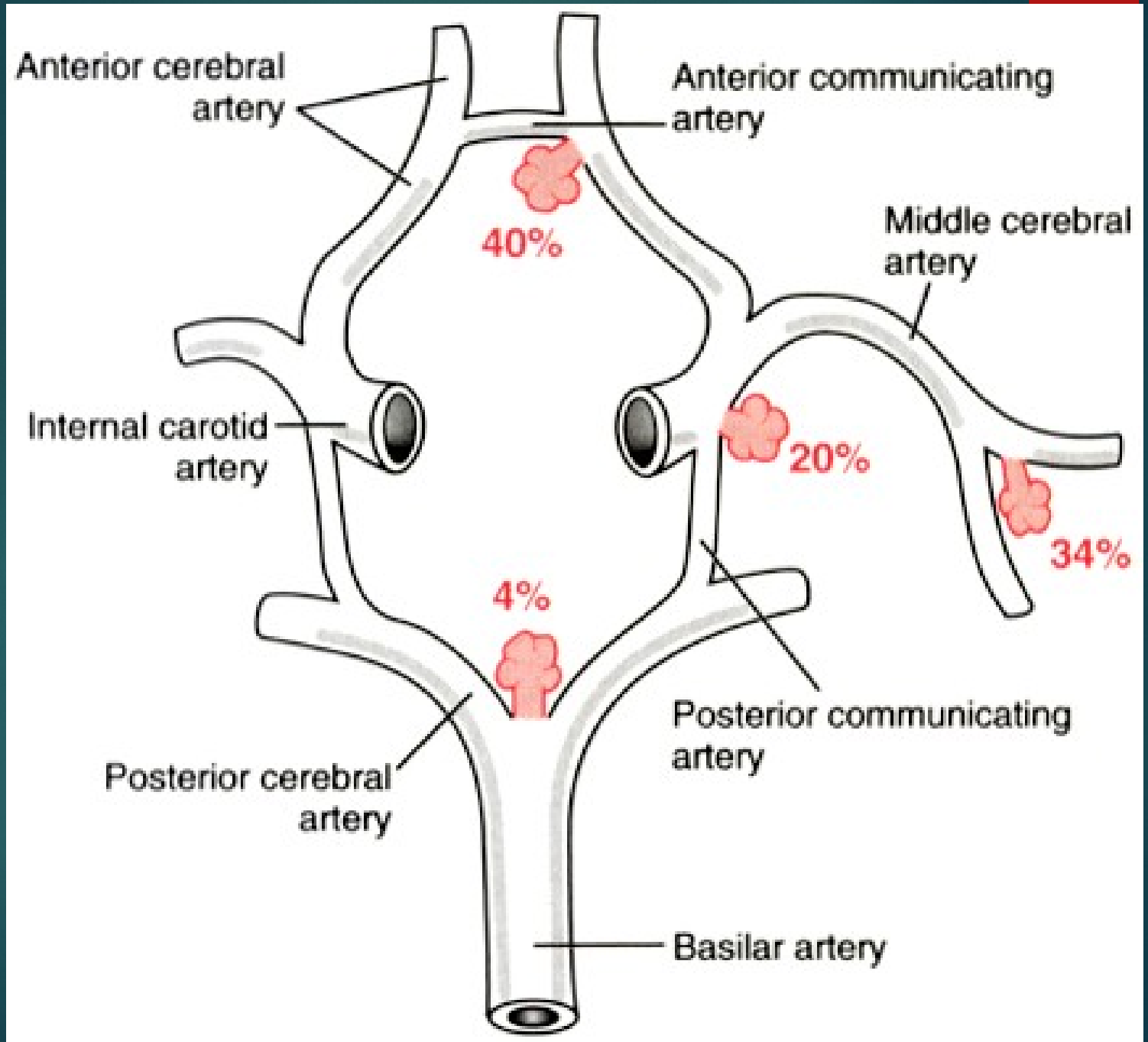


Clinical features

- location of the bleed will determine the clinical manifestation.
- clinically devastating when it affects large portions of the brain & extends into the ventricular system
- small regions = clinically silent .
- Over weeks or months , there is gradual resolution of the hematoma with clinical improvement.

Subarachinoid hemorrhage

- *The most frequent cause is a rupture of a saccular (berry) aneurysm*
- *Berry aneurysm (saccular or congenital aneurysm)*
- *It is the most common type intracranial aneurysm*
- *Most occur in anterior circulation of circle of willis*


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

Pathogenesis

- *majority occur sporadically , genetic factors play a role.*
- *Cigarette smoking & hypertension are predisposing factors.*

- The aneuryms are not present at birth but develop over time owing to underlying defect in the media of the vessel.

Morphology

- Un ruptured berry aneurysm is a thin walled out pouching at arterial branch point along the circle of willis.

Clinical features

- Rupture of an aneurysm = fifth decade
- probability of rupture increases with the size of the lesion
- In most cases, rupture is associated with acute increases in intracranial pressure such as straining at stool
- CSF – xanthochromasia

Infections

- Hematogenous spread – the most common
- Direct implantation – usually traumatic
- Local extension from infection in air sinuses , infected tooth
- Peripheral nervous system eg rabies, herpes zoster

- *Injury to brain occurs*

  - Direct effect of the agent

  - Toxic effect of elaborated toxin, Inflammatory response, or immune mediated mechanisms

Meningitis

- leptomeninges & CSF in subarachnoid space
- Meningoencephalitis : meninges & brain parenchyma
- Meningitis
  - usually caused by infections
  - chemical irritant
  - cancer infiltration

- *Infectious meningitids*
  - *Acute pyogenic meningitis (usually bacterial meningitis)*
  - *Aseptic meningitis (usually acute viral meningitis)*
  - *Chronic meningitis (TB, neurosyphilis)*

Acute pyogenic bacterial meningitis

- Causes

- Streptococci pneumoniae
- Neisseria meningitidis
- Haemophilis influenzae

- *The microrganisms that cause meningitis vary with the age of patients*
  - *Neonates – Escherichia coli, group B streptococci*
  - *Elderly – S. pneumoniae & Listeria monocytogens*
  - *Adolescents & young adults – Neisseria meningitidis*

C/F

- Systemic sign of infections with evidence of meningeal irritation including headache, photophobia, clouding of consciousness , neck stiffness
- A spinal tap yields cloudy or frankly purulent CSF under increased pressure with as many as ~ 90,000/mm3 neutrophils , increased protein & reduced glucose content
- Organisms can be seen on smear or can be cultured

Waterhouse-Frederichsen syndrome

- Results from meningitis associated with septicemia (meningococcemia) with hemorrhagic infarction of adrenal glands & petechial rash on the skin.

Morphology

- An exudate is seen on surface within the leptomeninges over the surface of the brain
- Hydrocephalus can be a long-term complication of infection..

Acute aseptic (viral) meningitis

- It is of viral rarely bacterial origin
- Clinical course is less fulminant than pyogenic meningitis & self limiting
- CSF finding – lymphocytic pleocytosis, protein elevation is moderate , glucose level normal
- Echovirus, coxasackie virus & non paralytic poliomyelitis = 80%

Acute focal suppurative infections

Brain abscess

- direct implantation of organisms,
- local extension from adjacent foci (mastoditis)
- hematogenous spread (usually primary site in the heart ,lung)
- Predisposing conditions : infective endocarditis, cyanotic heart disease.
- Streptococci & staphylococci are the most common offending organisms

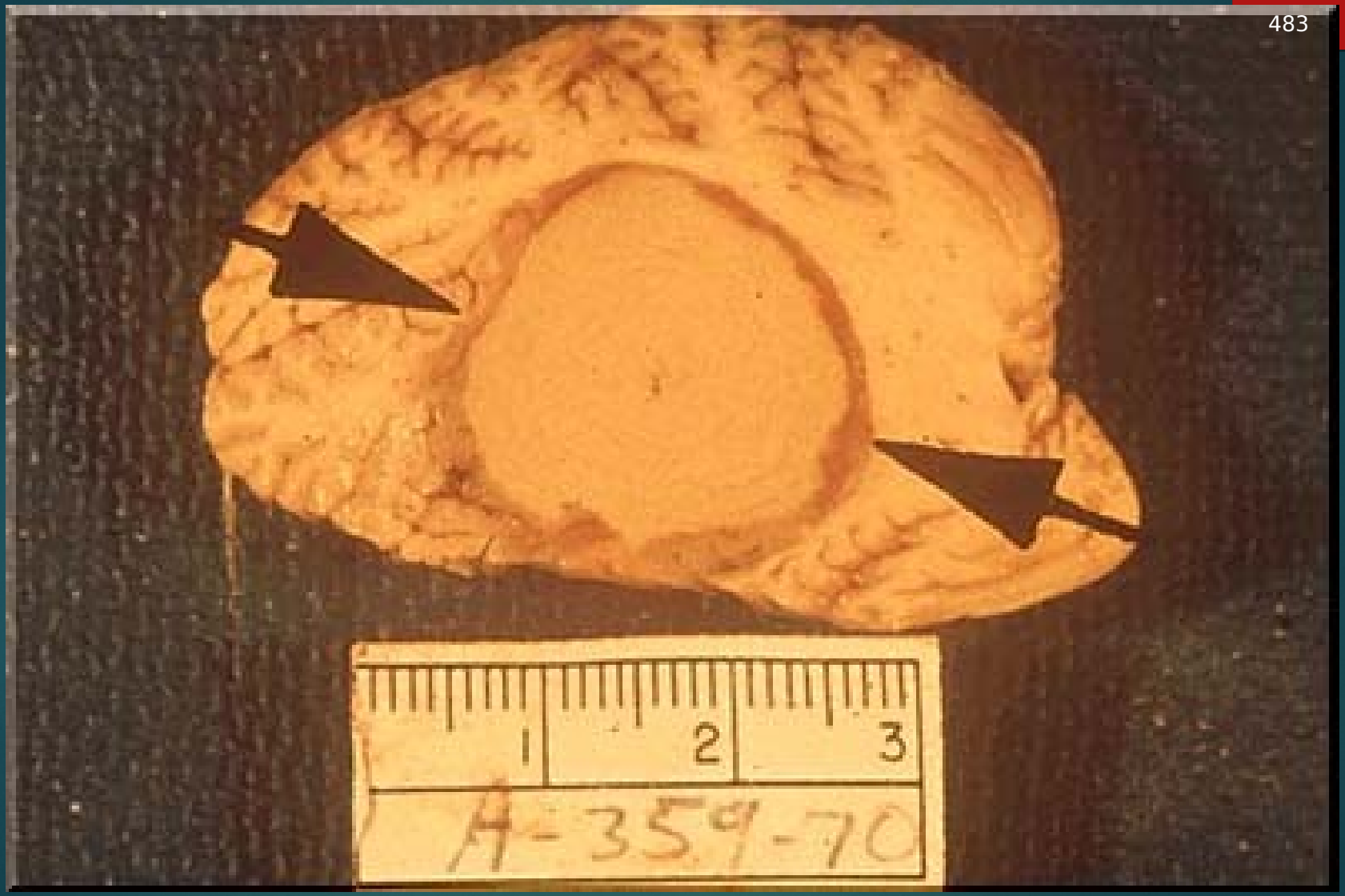
Chronic bacterial meningitis

Tuberculous meningitis

- headache, malaise, mental confusion & vomiting
- moderate CSF pleocytosis (mononuclear cells or mixture of polymorphonuclear & mononuclear cells),
- protein level is elevated,
- glucose content is moderately reduced or normal

Morphology

- The most common pattern of involvement is a diffuse meningoencephalitis
- Tuberculoma :
  - Another manifestation of the disease
  - a single (or often multiple) well circumscribed intra parenchymal mass associated with meningitis .
  - may be up to several cms in diameter causing mass effect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Complication

- *arachinoid fibrosis= which may produce hydrocephalus*
- *obliterative endarteritis = which may produce infarction of underlying brain*

Neurosyphilis

Tertiary syphilis

- *It occurs in 10% of untreated patients*

Viral encephalitis

- *Parenchymal infection of the brain almost invariably associated with meningeal infection (meningoencephalitis)*

Varicella Zoster virus

- Primary varicella infection: chickenpox in children, no neurological involvement
- reactivation in adults (shingles) : painful skin eruptions in single or limited dermatomal distribution.
- Herpes zoster reactivation

  - usually self limited process

  - persistent post herpetic neuralgia syndrome in 10% of patients


A.D.A.M.

Cytomegalovirus

- *Infection of the nervous system occurs in fetuses & immunosuppressed individuals.*

- *most common opportunistic viral pathogen in patients with AIDS affecting the CNS in 15% to 20% of cases.*

Poliomyelitis

- non immunized individuals
  - mild gastroenteritis &
  - in small fraction of those , it invades the nervous system.
- CNS infection
  - meningeal irritation
  - in some progresses & affects the spinal cord with
    * loss of anterior horn motor neuron
    * flaccid paralysis with muscle wasting
    * hyporeflexia

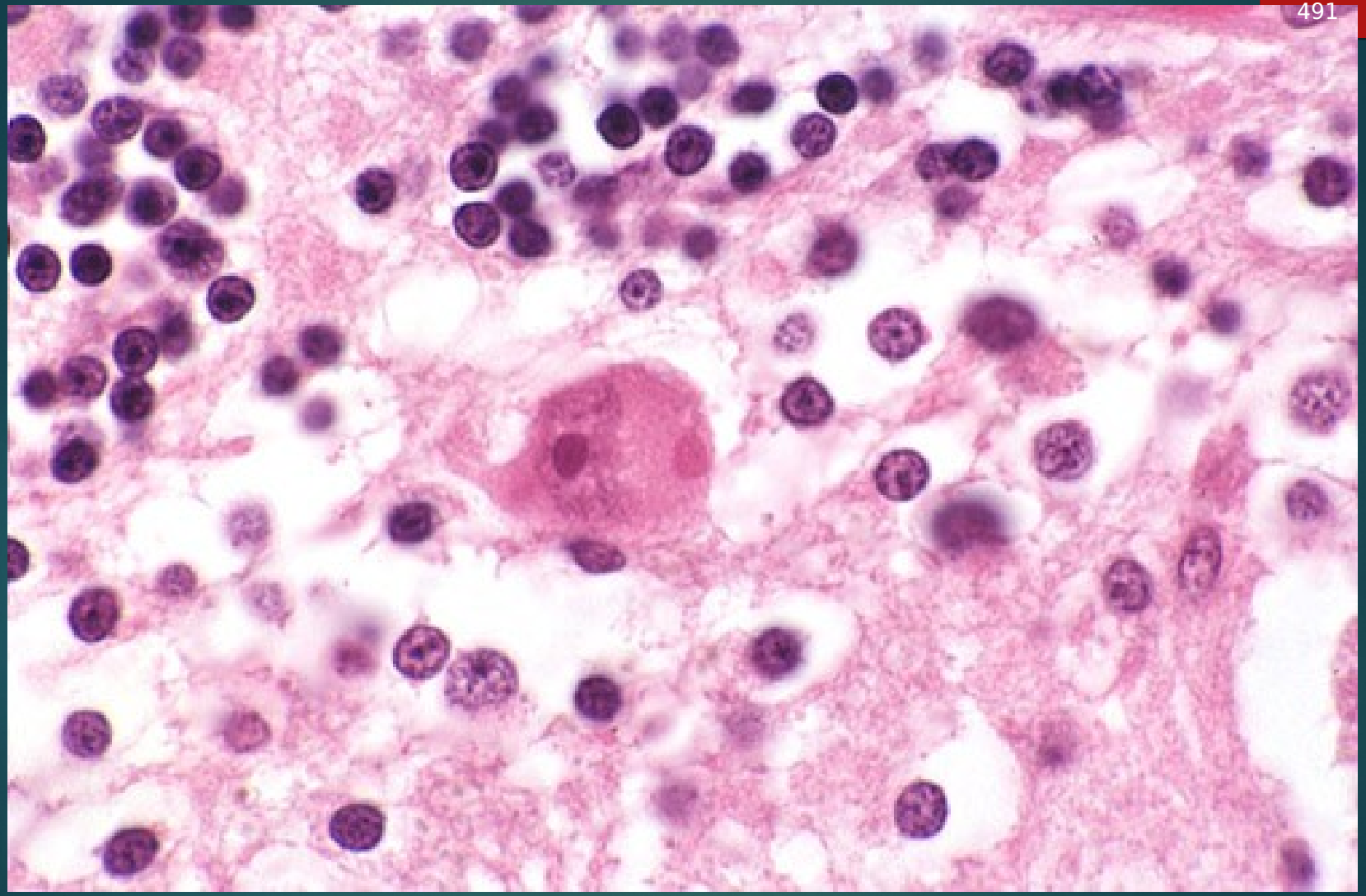
permanent sequel of poliomyelitis

Rabies

- Severe encephalitis
- transmitted to humans by bite of rabid animal (dogs, bats)
- The virus enters CNS by ascending along the peripheral nerves from wound site

Morphology

- Negri bodies: the pathognomonic microscopic finding ; cytoplasmic , round to oval , eosinophilic inclusions that can be found in pyramidal neurons of the hippocampus & Purkinje cells of the cerebellum



Human Immunodeficiency virus

- *60% of patients with AIDS develop neurologic dysfunction during the course of their illness*

- *These include direct & indirect effects of HIV , opportunistic infection & primary CNS lymphoma*

- ***HIV aseptic meningitis :***
- *1 to 2 wks of sero conversion in about 10% of patients*

- ✓ *HIV meningoencephalitis (subacute encephalitis)*
- *Patients with this disorder can manifest clinically with dementia referred to as AIDS dementia complex*
- *The dementia begins insidiously with mental slowing , memory loss, & mood disturbances such as apathy & depression .Motor abnormalities, ataxia, bladder & bowel incontinence & seizure can also be present*

- *It is likely that neurons & oligodendrocytes are not directly infected by HIV & damage to these occurs indirectly through the release of cytoxines & alterations of the blood brain barrier*

- ✓ *AIDS in children*
- *microcephaly with mental retardation*
- *motor developmental delay with spasticity of limbs*

- ✓ *Other changes*
- *AIDS associated myopathy & peripheral neuropathy*
- *Vacuolar myelopathy*

Progressive multifocal leukoencephalopathy

- *viral encephalitis caused by the JC virus*
- *preferentially infects oligodendrocytes .*
- *Demylination is the principal pathologic effect*
- *in immunocompromised individuals such as AIDS*

Fungal meningoencephalitis

Cryptococcal meningitis

Protozoal

Cerebral toxoplasmosis

Tumors

- ½ - ¾ of CNS tumors are primary
- Account for 20% of all cancers in childhood
- 70% childhood CNS tumors arise in the posterior fossa
- 70% of tumors in adults arise with in the cerebral hemispheres above the tentorium (supra tentorial)

- *They differ from other neoplasms in body*
- *Distinction between benign & malignant neoplasm is less evident in the CNS than in other organs*
- *The ability to surgically resect infiltrating glial neoplasms without compromising neurological function is limited*
- *The anatomic site of the neoplasm can have lethal consequences irrespective of histologic classification.*
- *CNS tumors rarely metastasize outside the CNS ; subarachinoid space provide pathway to spread*

The major classes of primary brain tumors

- *Glioma*
- *Neuronal tumors(ganglion cell tumors)*
- *Poorly differentiated tumors (medulloblastoma)*
- *Meningiomas*

Gliomas

- *Glioma are derived from glial cells include astrocytoma, oligodendroglioma & ependymoma*

Astrocytoma

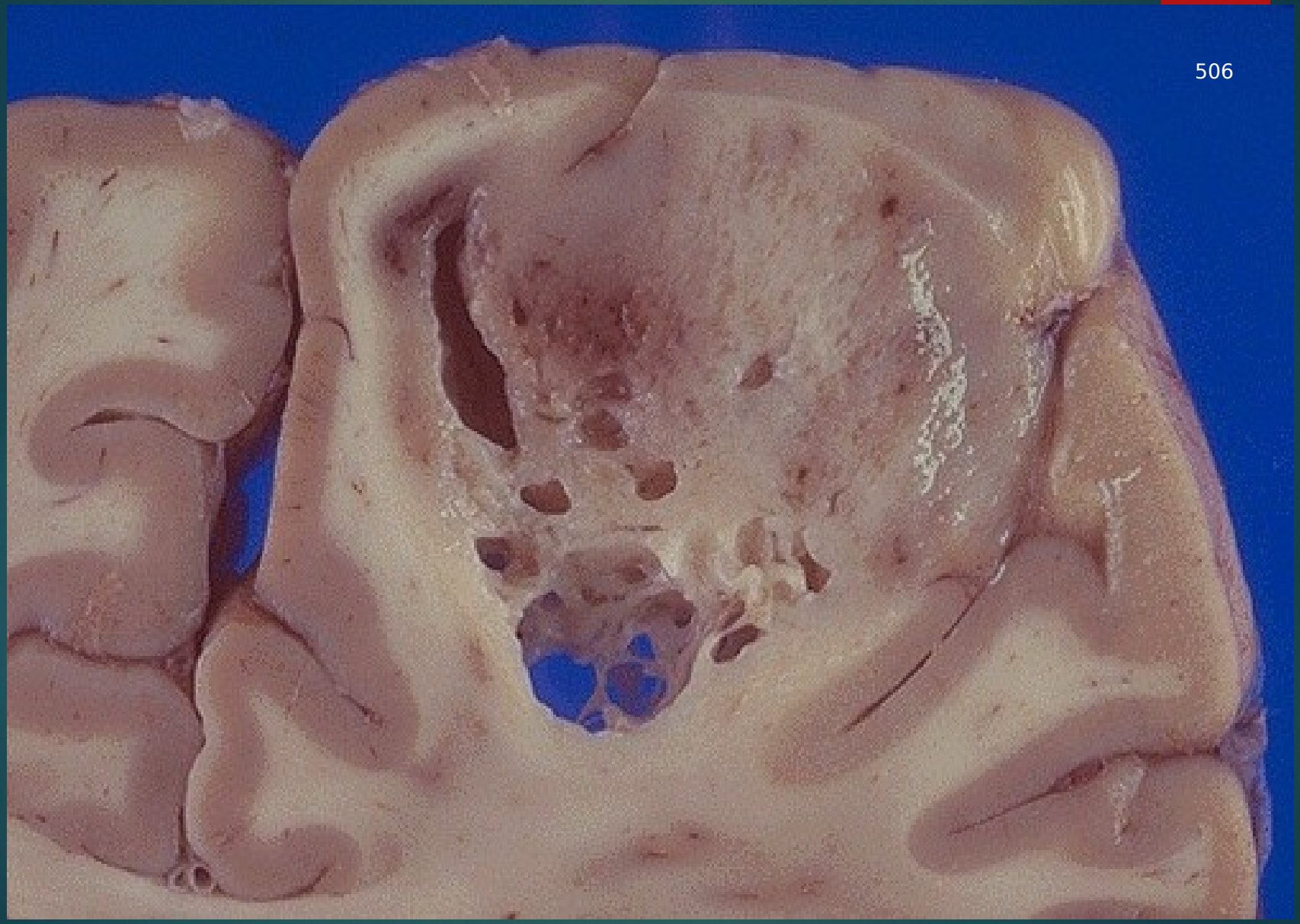
- Several group of tumors derived from astrocytes are recognized (fibrillary astrocytoma, glioblastoma, pilocytic astrocytoma)
- They have characteristic
  - histologic feature
  - distribution within the brain
  - age groups typically affected
  - clinical course.

Fibrillary (diffuse) astrocytoma

- Account for 80% of adult primary tumors
- Usually found in the cerebral hemispheres
- Occur most often in the fourth through sixth decades.
- Tumors can be

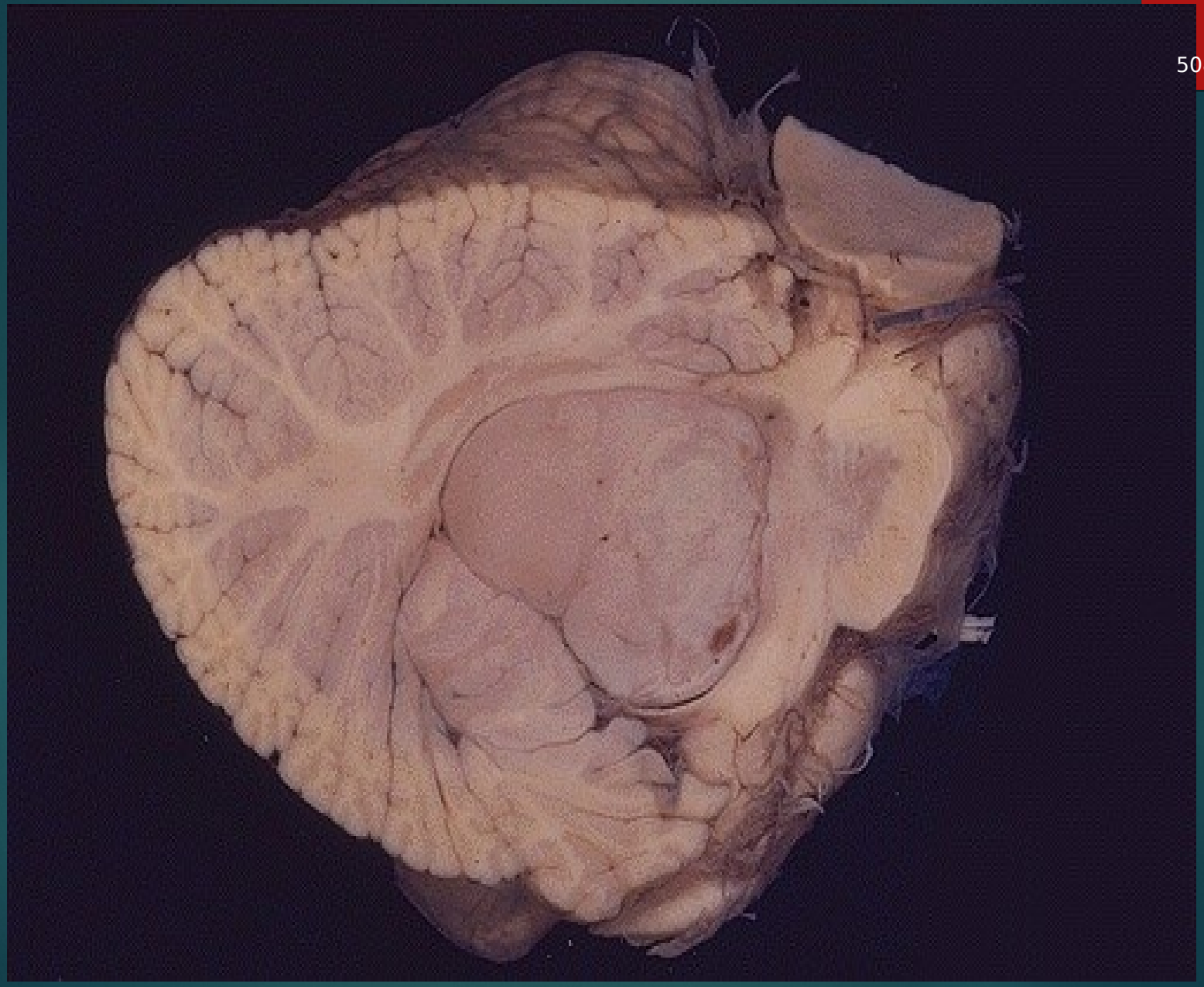
  - well differentiated (astrocytoma)

  - less differentiated(anaplastic astrocytoma to glioblastoma.)
- Macroscopically, the tumor is poorly defined , infiltrative & distorts the invaded brain.



Pilocytic astrocytoma

- Have relatively benign behavior
- Typically occur in children & young adults
- usually in the cerebellum but may appear in the floor of walls of the third ventricle & optic nerves.



Neuronal tumors

Ganglion cell tumors

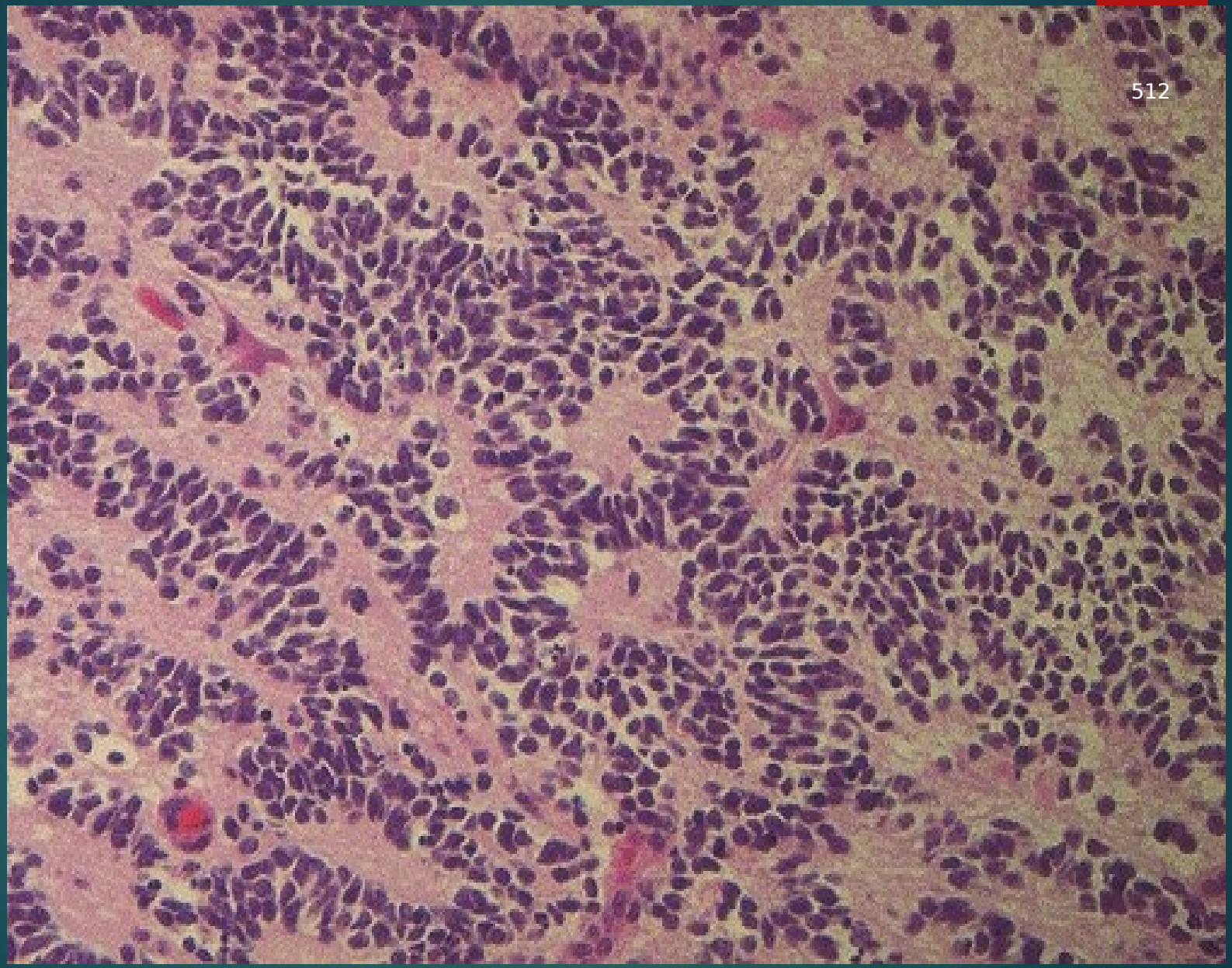
- These contain mature appearing neuron (ganglion cells),
- these may constituent the entire population of the lesion (gangliocytoma)
- Or admixture with glial neoplasm (ganglioglioma)
- Most are slowly growing , occasionaly glial component becomes anaplastic = progress rapidly
- Often seizure disorder
- Surgical excision effectively control seizure

Poorly differentiated neoplasms

Medulloblastoma

- 20% of brain tumors in children
- occurs exclusively in cerebellum (midline, lateral in adults)
- composed of primitive undifferentiated cells
- Rapid growth : occlude CSF flow = hydrocephalus
- Rossette formation
- Highly malignant tumor , radiosensitive
- Rx = surgical resection + radiotherapy
- 5 yr survival rate about 75%

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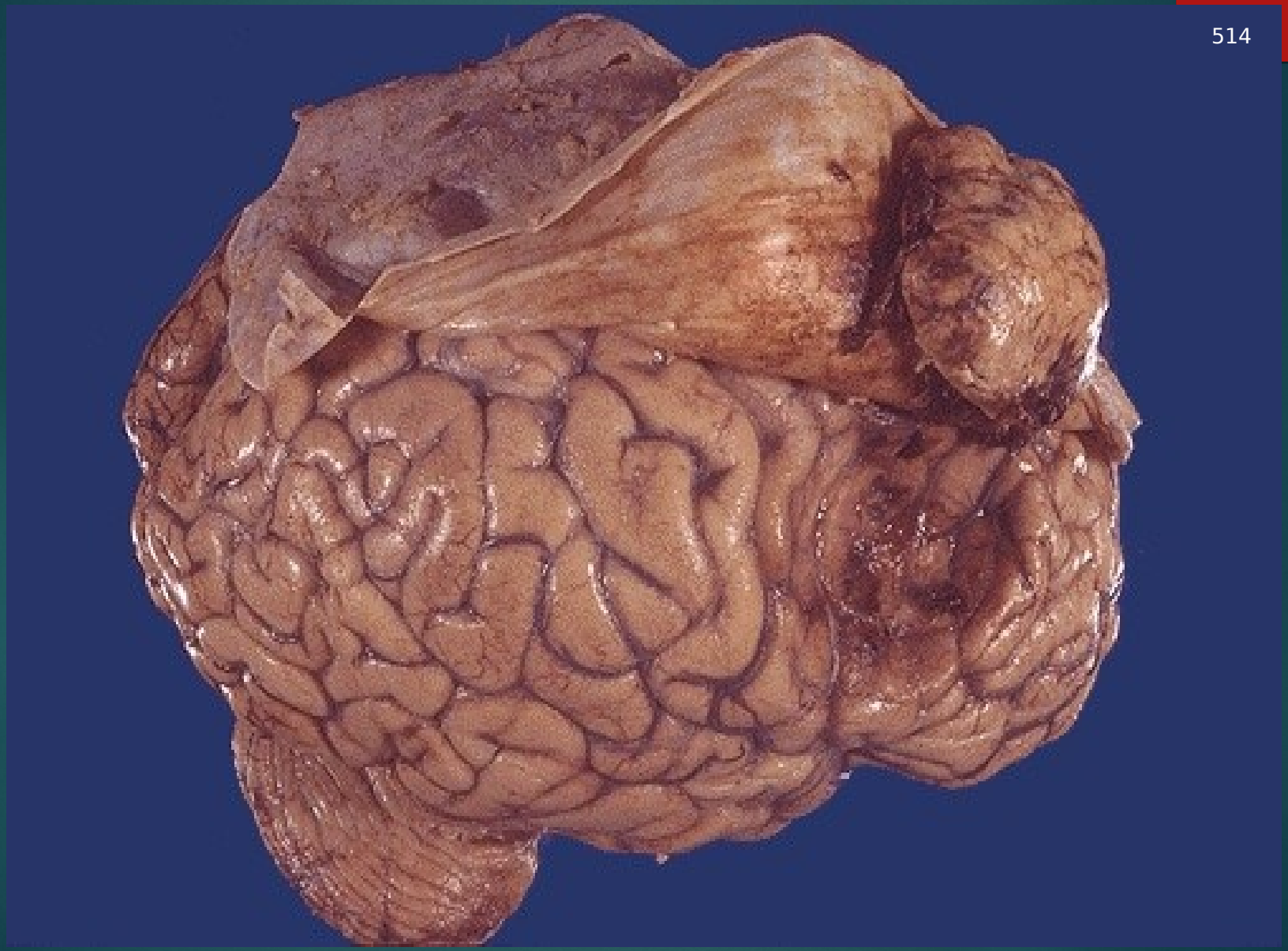
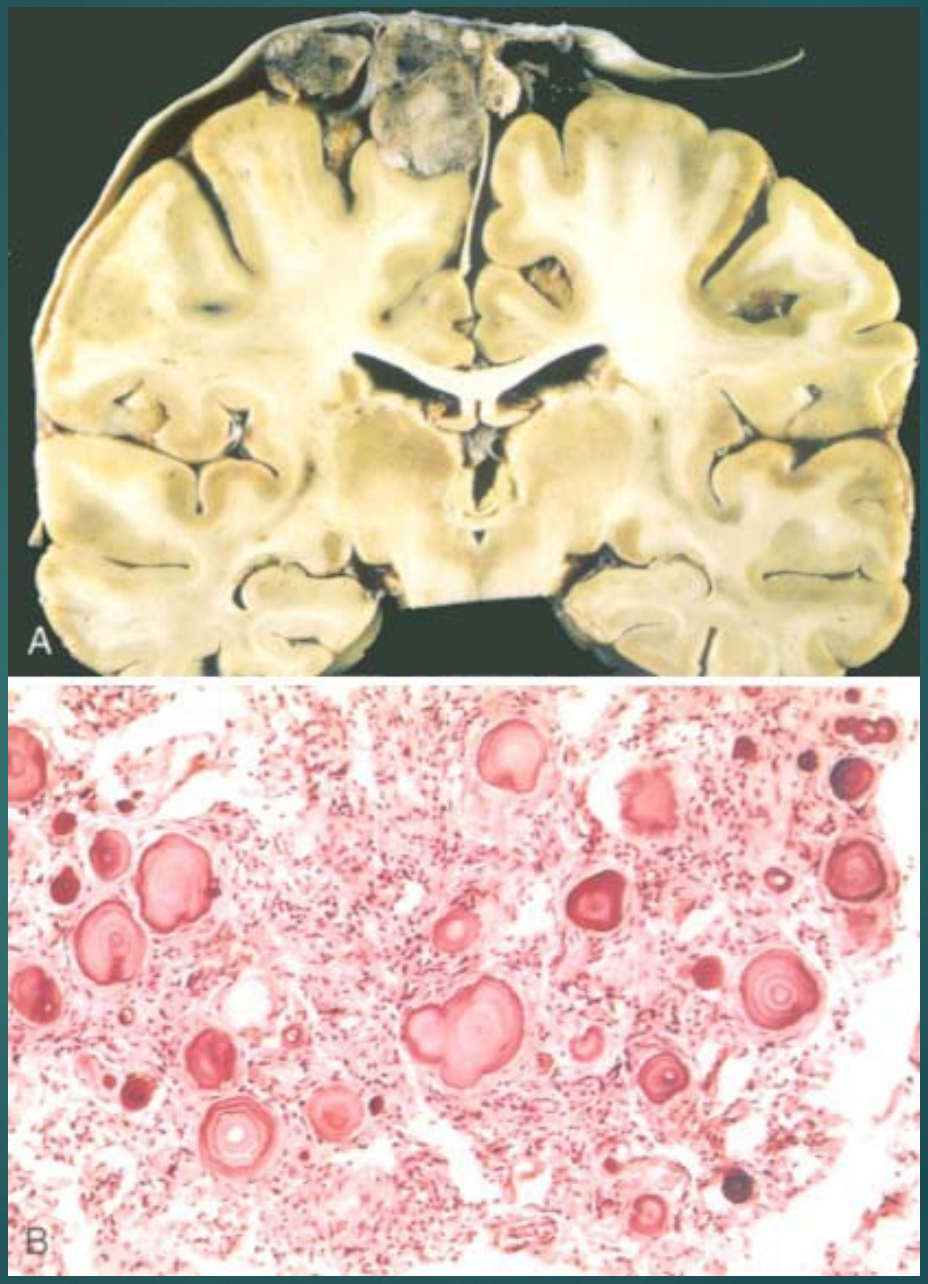
Meningiomas

- Predominantly benign tumors of adults
- usually attached to the dura
- arise from the meningothelial cells of the arachnoid
- Slowly growing
- Vague non localizing symptoms / localizing
- Uncommon in children
- WHO grade - prognosis

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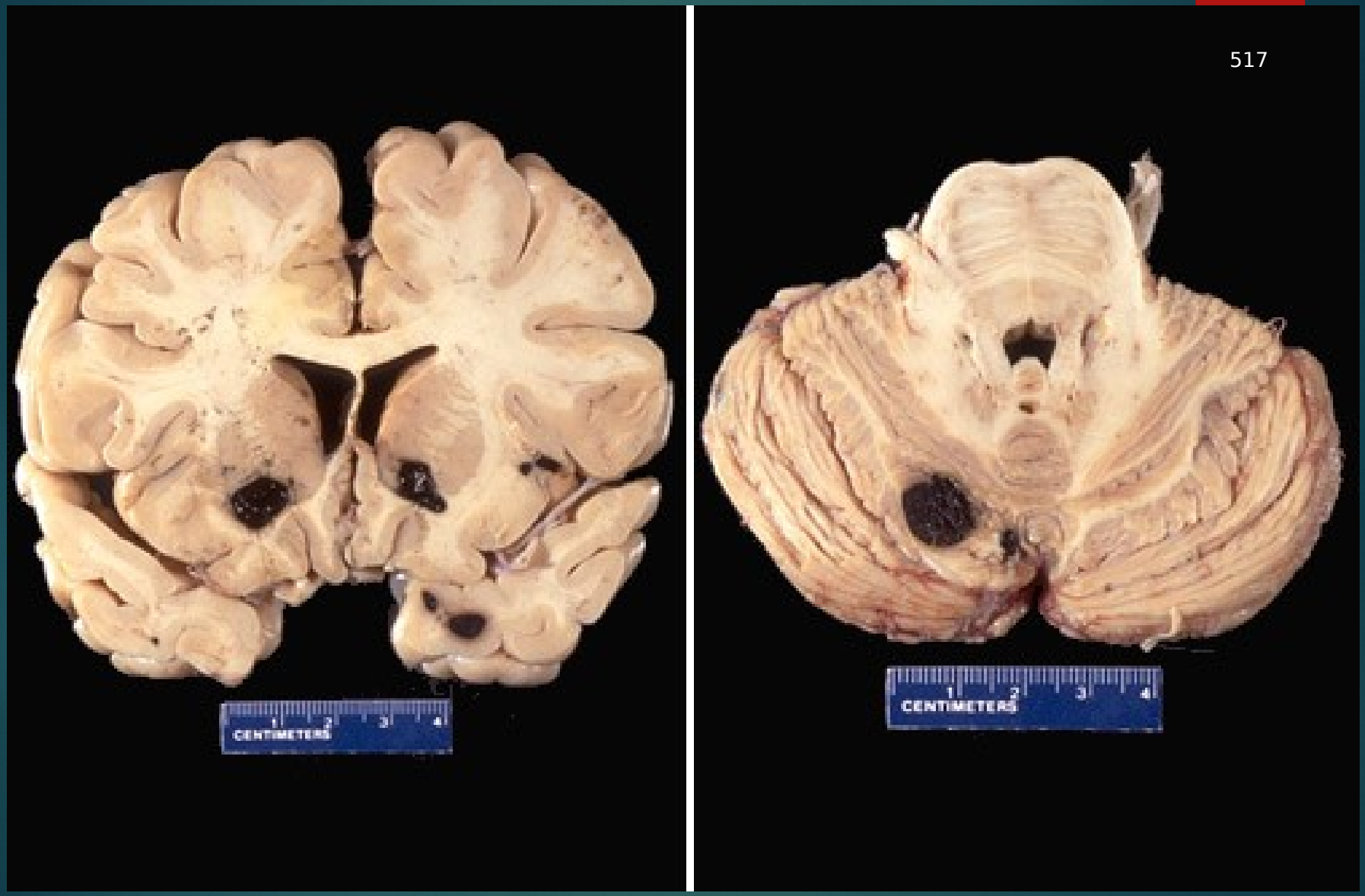
Metastatic tumors

- ¼ - ½ of intracranial tumors
- The five most common primary sites are lung, breast, skin, kidney & GI tract (80% of cases)
- Choriocarcinoma : high likelyhood , prostatic adenocarcinoma : almost never
- Mass lesions , sometimes primary manifestation of the cancer
- Common location : gray matter – white matter junction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CENTIMETERS
CENTIMETERS

8. CNS TUMORS

INTRODUCTION

- Tumors may arise from neural stem cells, precursors of neurons and glial cells.
- Peaks in childhood, then declines to age 25 years, then increases with age
- Childhood tumors: 33% supratentorial, 67% in posterior fossa
- Adults: metastases are more common than 1^0 but are usually not biopsied; of biopsied tumors, 67% supratentorial, 33% in posterior fossa
- Most common spinal cord tumors are schwannoma, meningioma and ependymoma

Unique characteristics about 1º CNS tumors

- *Distinction between benign & malignant lesions is less evident*
- *Benign appearing tumors may still be infiltrative and difficult to resect without compromising neurologic function*
- *The anatomic site of the neoplasm can have lethal consequences irrespective of histologic classification*
- *Subarachnoid space provides a pathway for spread & rarely metastasize outside the CNS (surgery related implantation tumor cells into vessels)*

CLINICAL FEATURES

- *Local effects: neurologic deficits, epilepsy*
- *General effects: ↑ ICP (due to mass effect, hydrocephalus, cerebral edema) => herniation*

CLASSIFICATION 1^0 CNS NEOPLASMS

WHO CLASSIFICATION

- *NEUROECTODERM: glial cells, neurons, mixed, primitive cells*
- *MESENCHYME: meninges, nerve sheath cells, blood vessels, embryonic structures*
- *OTHERS: Choroid plexus tumors, Pineal tumors, Primary CNS lymphoma*

GLIOMAS

- *Arise from neuroglial cells*
- *Astrocytes – astrocytoma*
- *Oligodendrocytes – oligodendroglioma*
- *Ependymal cells – ependymoma*
- *Undifferentiated – glioblastoma (GBM)*
- *Mixture - mixed "glioma"*

WHO GRADING OF ASTROCYTOMAS

Four histological criteria

- *Anaplasia*
- *Increased mitoses*
- *Vascular proliferation*
- *Tumour necrosis*

WHO GRADING ASTROCYTOMA

GRADE	DESIGNATION	CRITERIA
I	PILOCYTIC	TYPICAL HISTOLOGY
II	FIBRILLARY	+/- ANAPLASIA
III	ANAPLASTIC	ANAPLASIA, MITOSES
IV	GLIOBLASTOMA	ANAPLASIA, MITOSES, ANGIOGENESIS, NECROSIS

Pilocytic astrocytoma- grade I

- *Pilocytic means "hair like", due to long, bipolar processes*
- *Most common childhood tumor; peak age 8-13 years*
- *Better prognosis than diffuse types*
- *Usually involves cerebellum*
- *10 year survival is 100% if supratentorial and gross total resection vs. 74% if subtotal resection*

DIFFUSE ASTROCYTOMA-GRADE II

- 80% of adult primary brain tumors; usually cerebrum, but can be anywhere
- Age 40+ years; May become more anaplastic over time
- Median survival is 6-8 years

ANAPLASTIC ASTROCYTOMA-GRADE III

- **Mean survival is 2 years**

GLIOBLASTOMA MULTIFORME- GRADE IV

- Undifferentiated glioma; Usually supra tentorial
- "Multiforme" due to firm white areas, yellow necrotic areas, hemorrhagic areas and cystic areas.
- Either due to progression from lower grade glioma (often with partial #10 deletion) or de novo with p53 mutation
- Median survival is 1 year; 5 year survival is <5%

OLIGODENDROGLIOMA-GRADE II-IV

- *5-15% of gliomas; Usually in cerebral white matter*
- *Slow growing tumors; mean survival 5 years*

EPENDYMOMAL TUMORS – Grade I-III

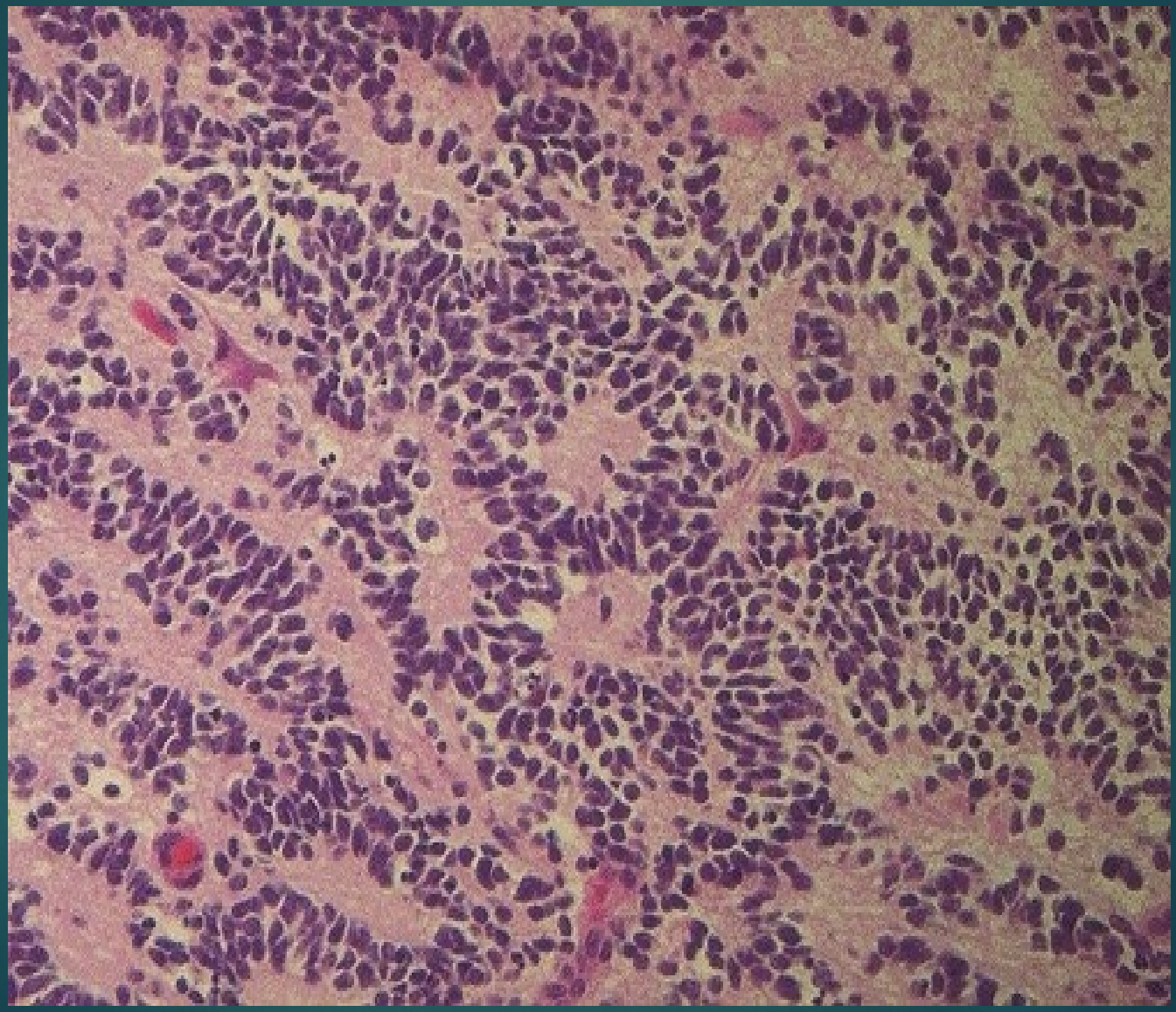
- *Arise in ventricles (lined by ependyma) in cerebrum or brainstem, including spinal cord remnant of central canal*

- *3-9% of primary CNS tumors, more common in children/young adults*

MEDULLOBLASTOMA - Grade IV

- Major subtype of central primitive neuroectodermal tumor/PNET
- Cerebellum; may arise from primitive cells of external granular layer of cerebellum; Children (5-10 years) and adults in 20's
- 20% of brain tumors in children (#2 after pilocytic astrocytoma of cerebellum)
- 5 year survival is 75% with surgery/radiation

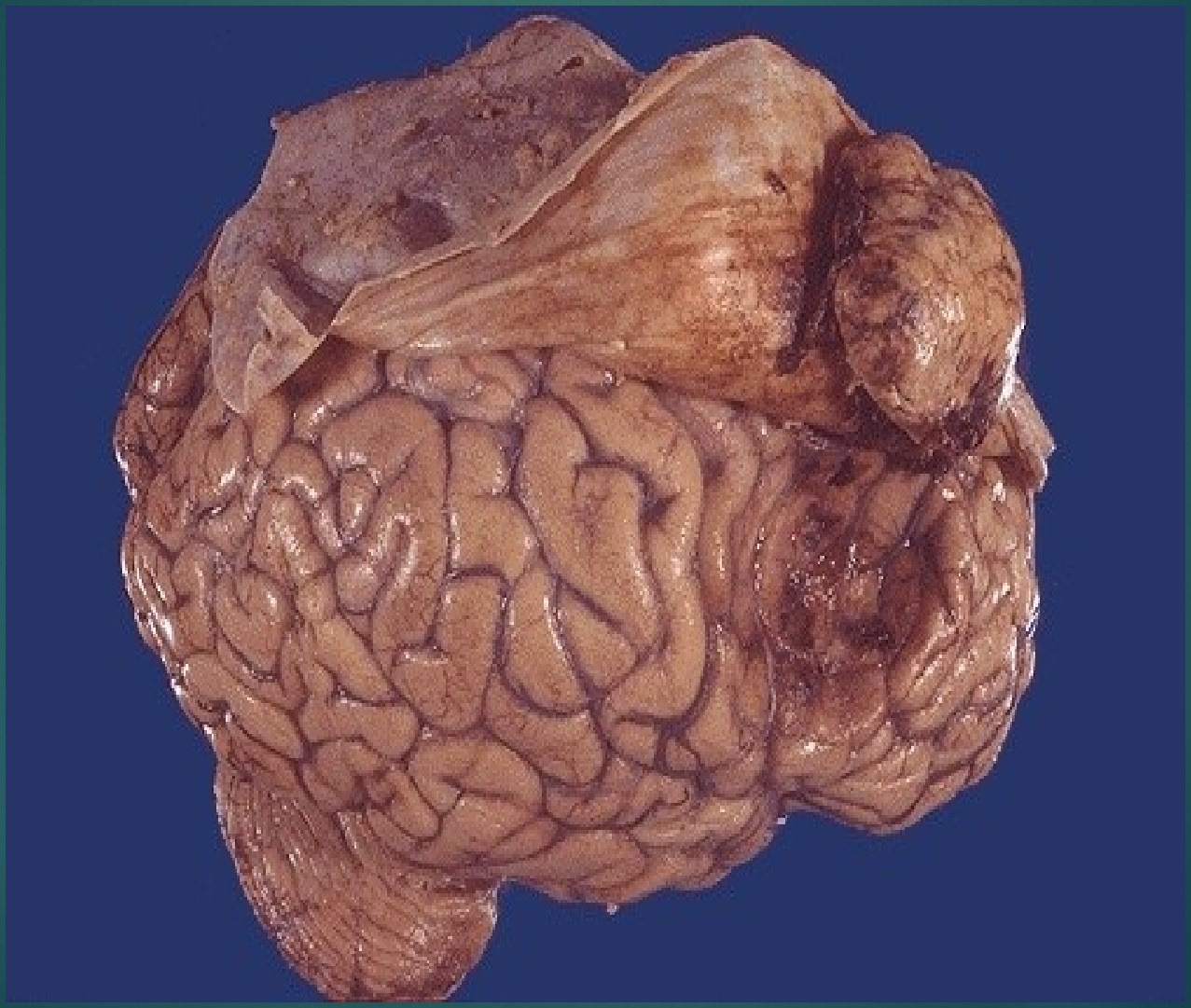
MEDULLOBLASTOMA



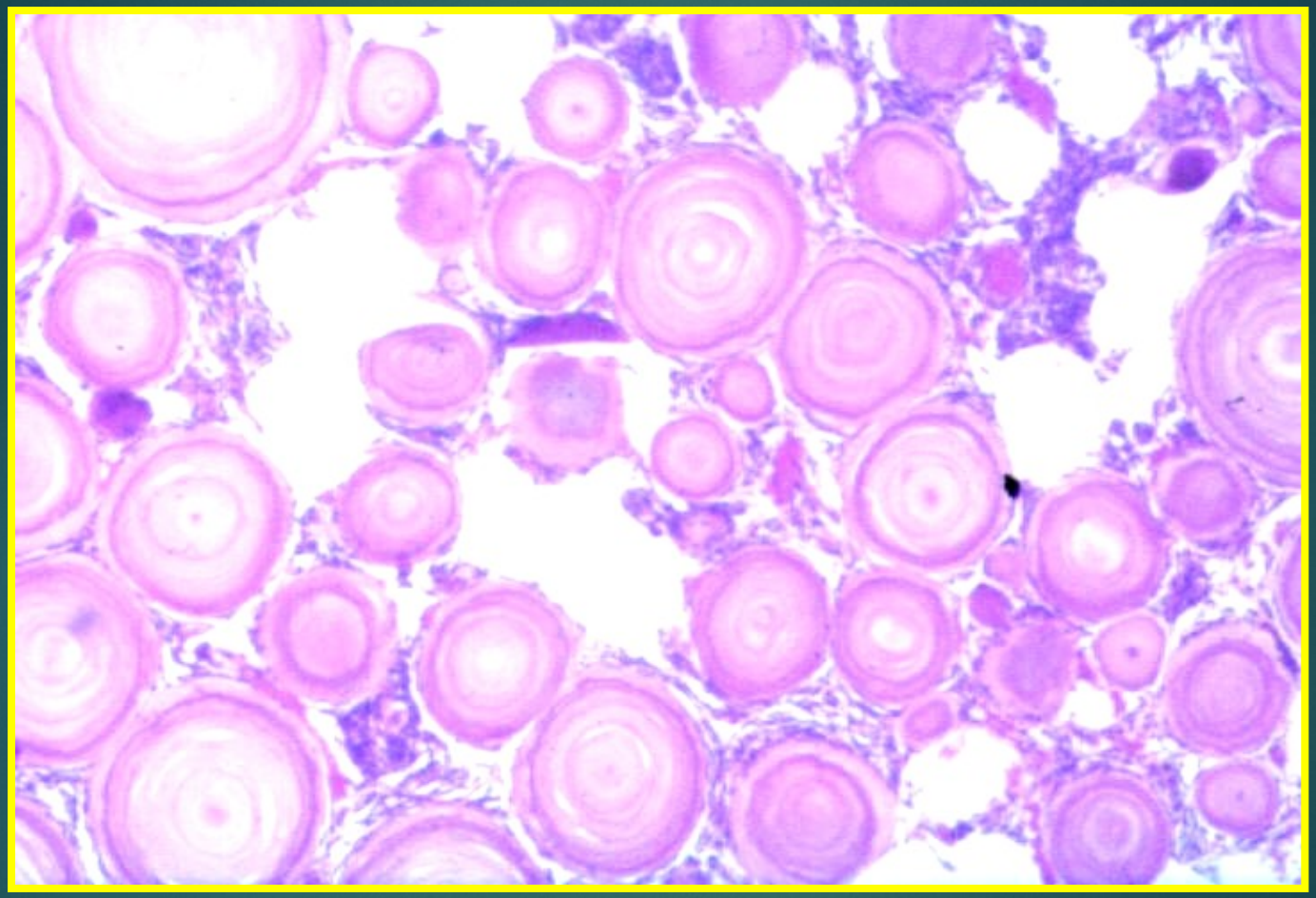
MENINGEAL TUMORS - MENINGIOMA

- 20% of brain tumors; Derive from arachnoid cap cells (associated with dura)
- Grow along external surface of brain or within ventricular system
- Slow growing: symptoms vague or related to brain compression
- Usually adults
- Usually solitary; Usually benign; not considered malignant even if invades bone and skeletal muscle
- Difficult to predict recurrence - incomplete resection and grade of tumor are most predictive

MENINGIOMA



MENINGIOMA



METASTATIC TUMORS TO CNS

- *Primary is usually known - melanoma or carcinoma, occasionally germ cell tumor*
- *80% from lung, breast, skin (melanoma), kidney, GI*
- *Common presentation is adult with seizures or ataxia*
- *Sharply demarcated lesion at gray-white matter junction, surrounded by edema*
- *Multiple lesions are suggestive of metastasis vs. primary CNS tumor*
- *Usually to cerebrum, but no distinct patterns*


THANKS FOR LISTENING