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Leicester Warwick Medical School

Mechanisms of Disease

ACUTE INFLAMMATION

The response of living tissue to injury.

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Department of Pathology

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Features of acute inflammation

- Main clinical signs:
  - RUBOR
  - TUMOR
  - CALOR
  - DOLOR

    & Functio laesa

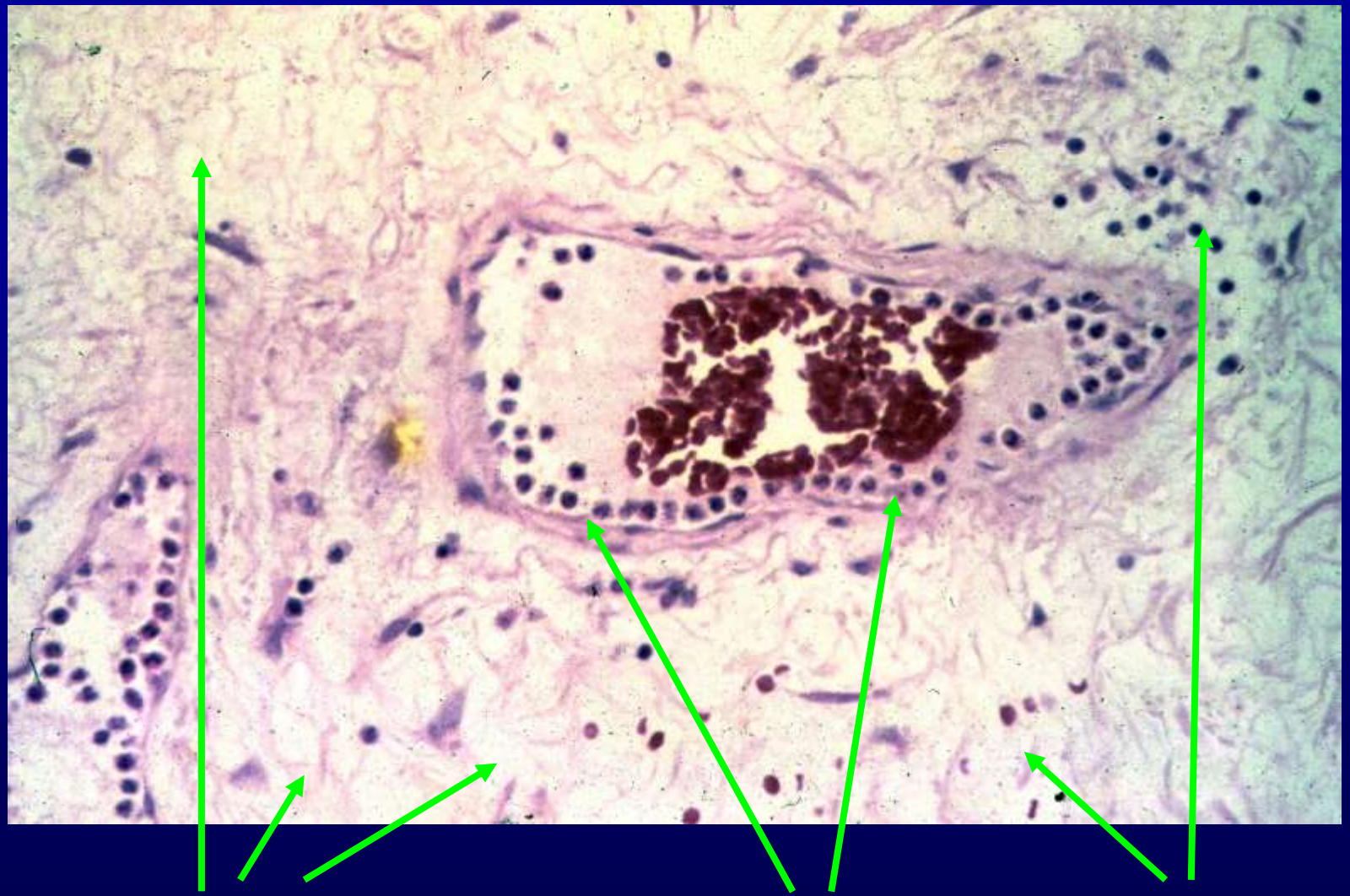
- Also described in terms of the ‘triple response’: brief blanching, followed by REDDENING, FLARE and WHEAL.

Microscopic changes

Original observations made with frog foot-web and rat mesentery.

- Dilatation of vessels
- Sludging of rbcs
- Fluid leaks into interstitium
- Implies increased permeability of vessels: (**not** to water but to **protein)**.

- Cells move into interstitium



Tissue oedema

Neutrophil margination …. And emigration

PART 1: THE FLUID
Definitons

- A **TRANSUDATE** has a **low protein content**, usually caused by alterations in hydrostatic or oncotic pressure.
  Implies a hydrostatic (pressure) problem.

- An **EXUDATE** has a **high protein content,** caused by increased vascular permeability.
  Implies an inflammatory process.

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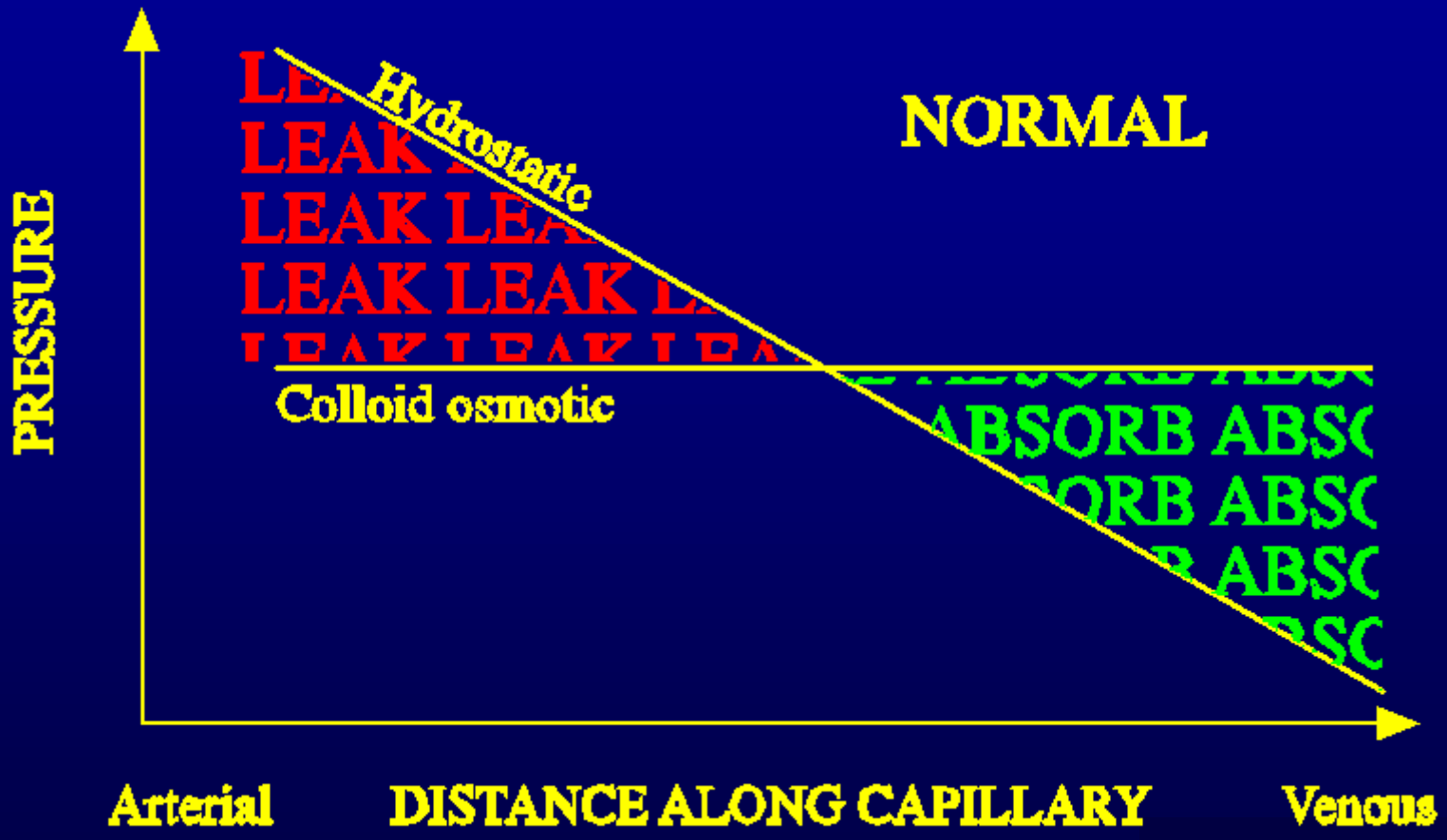
‘Starling’s law’

relating to fluid flux between vessels and interstitium



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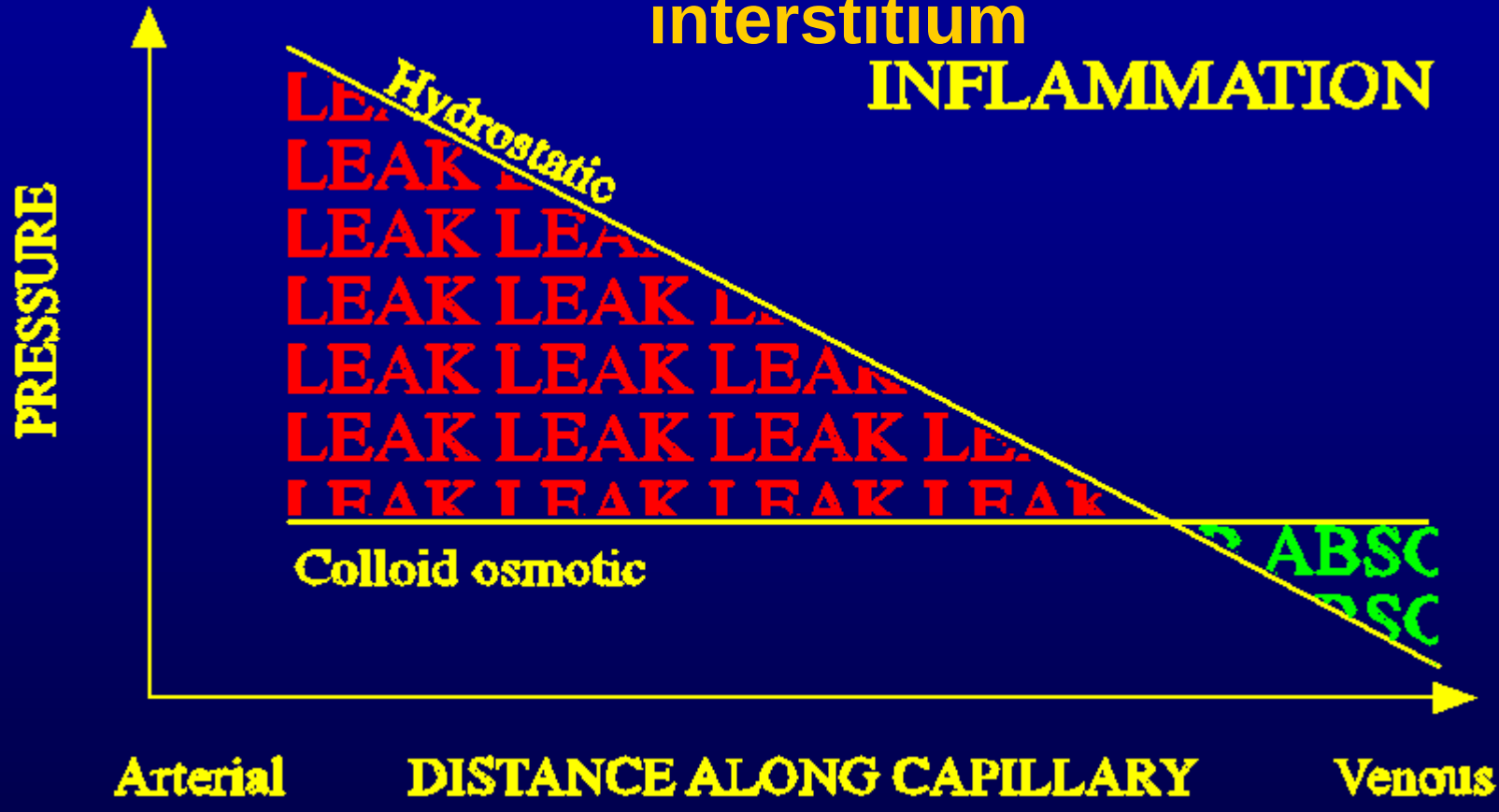

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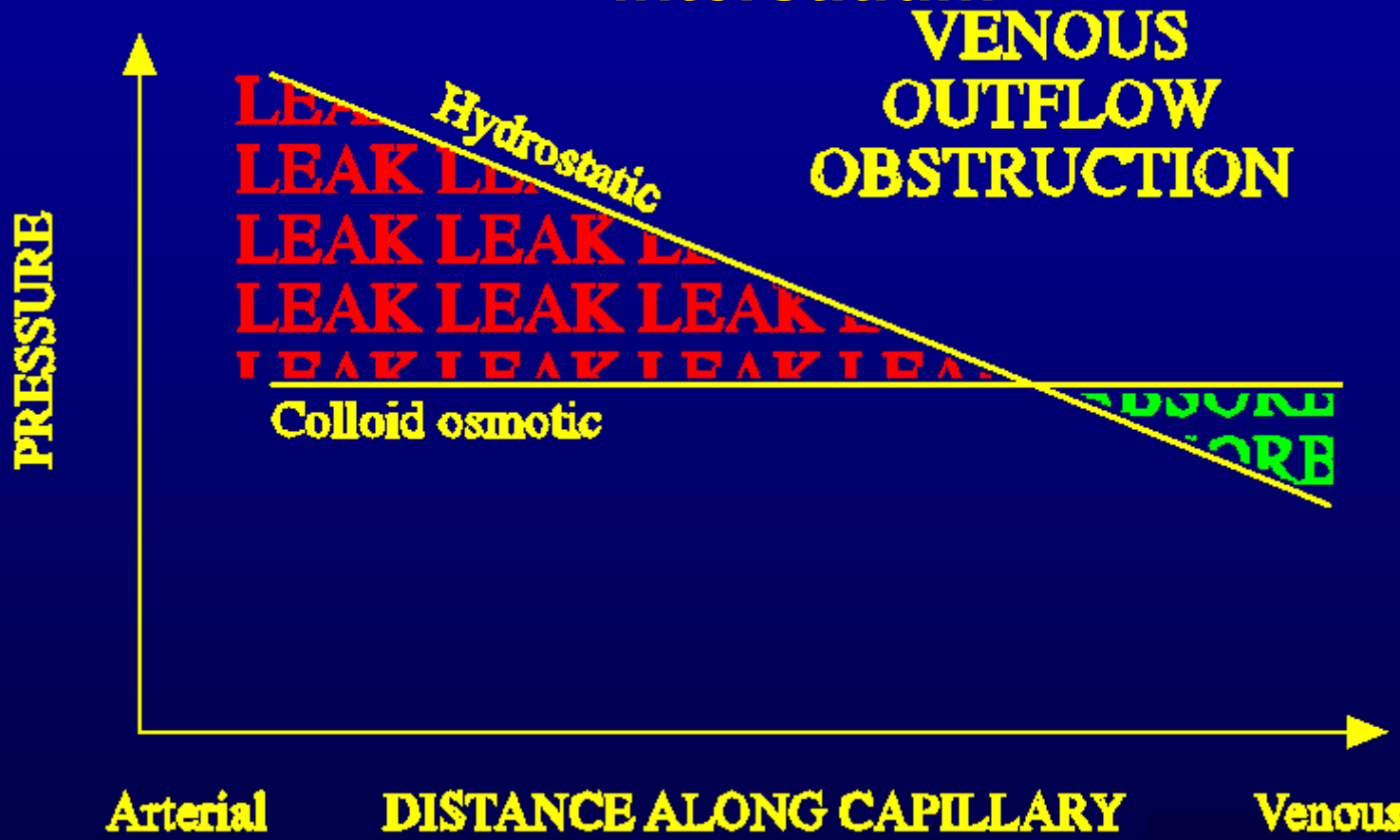

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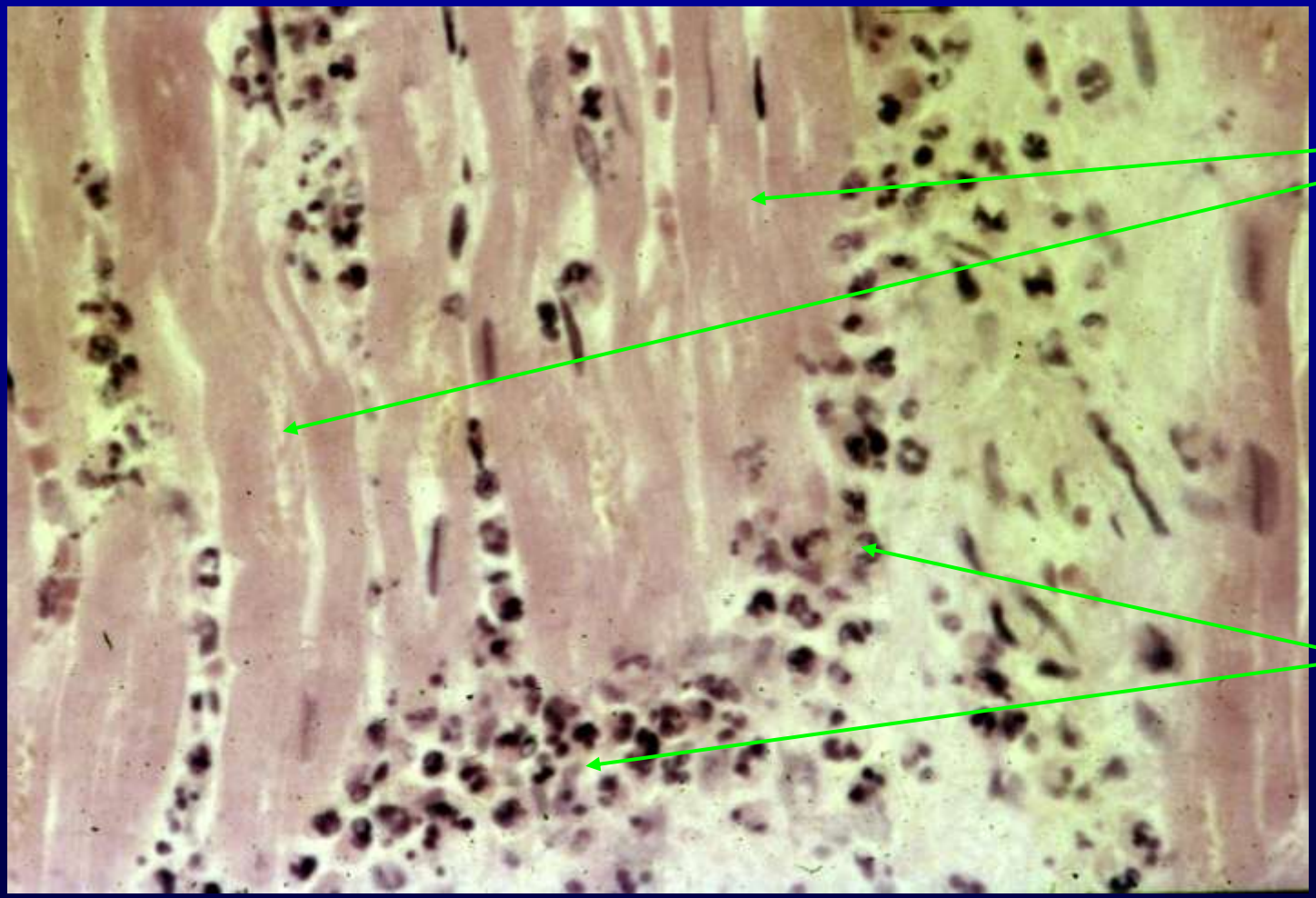
PART 2: THE CELLS

- White blood cells MARGINATION and EMIGRATION.
- Implies binding to endothelium then directional movement through vessel wall towards injured area.

Myocardial infarct - neutrophil infiltration



How do these changes combat injury?

- Vasodilatation:
  - Increases delivery, increases temperature, removes toxins.
- Exudate:
  - Delivers immunoglobulins etc., dilutes toxins, delivers fibrinogen, increases lymphatic drainage.
- Increased lymphatic drainage:
  - Delivers bugs to phagocytes and antigens to immune system.
- Cells:
  - Removes pathogenic organisms, necrotic debris etc.
- Pain and loss of function:
  - Enforces rest, reduces chance of further traumatic damage.
- How is all this brought about?

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What are the mechanisms? CHEMICAL MEDIATORS.

Three phases:

1) Immediate early response ($^1/_2$ hr):

- HISTAMINE
  - Released from mast cells, basophils and platelets, in response to many stimuli: physical damage, immunologic reactions, C3a, C5a, IL1, factors from neutrophils and platelets
  - **Effects:** Largely vascular. Pain. Not chemotactic.

2) Immediate sustained response:

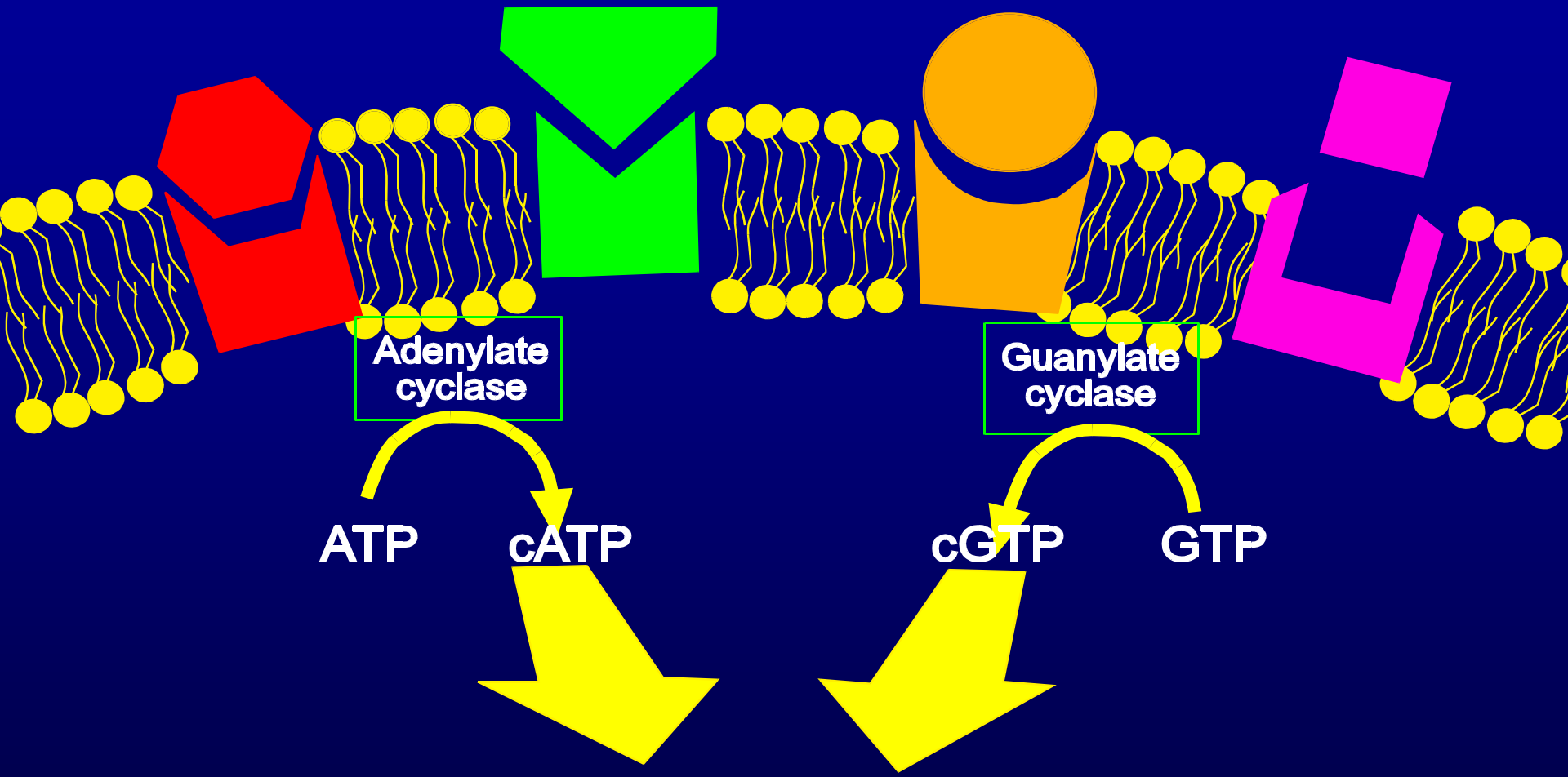
(Not always seen. Due to direct damage to endothelial cells.)

3) Delayed response: (Peaks about 3hrs):

- Many and varied chemical mediators, interlinked and of varying importance
- Incompletely understood.

- IMPORTANT because of possibility of therapeutic intervention

Mechanism of effect of chemical mediators - see ‘Membranes and receptors’ module



Chemical mediators of acute inflammation

- **Proteases**
  - Kinins (Bradykinin and Kallekrein)
  - Complement system
  - Coagulation / fibrinolytic system
- Prostaglandins / Leukotrienes
  - Numerous metabolites of arachidonic acid
  - Synthesis blocked by NSAIDs, e.g. aspirin
- Cytokines / chemokines
  - Many and varied! Interleukins, PAF, TNF alpha, PDGF, TGF beta, MCP, ...

Other inflammatory mediators:

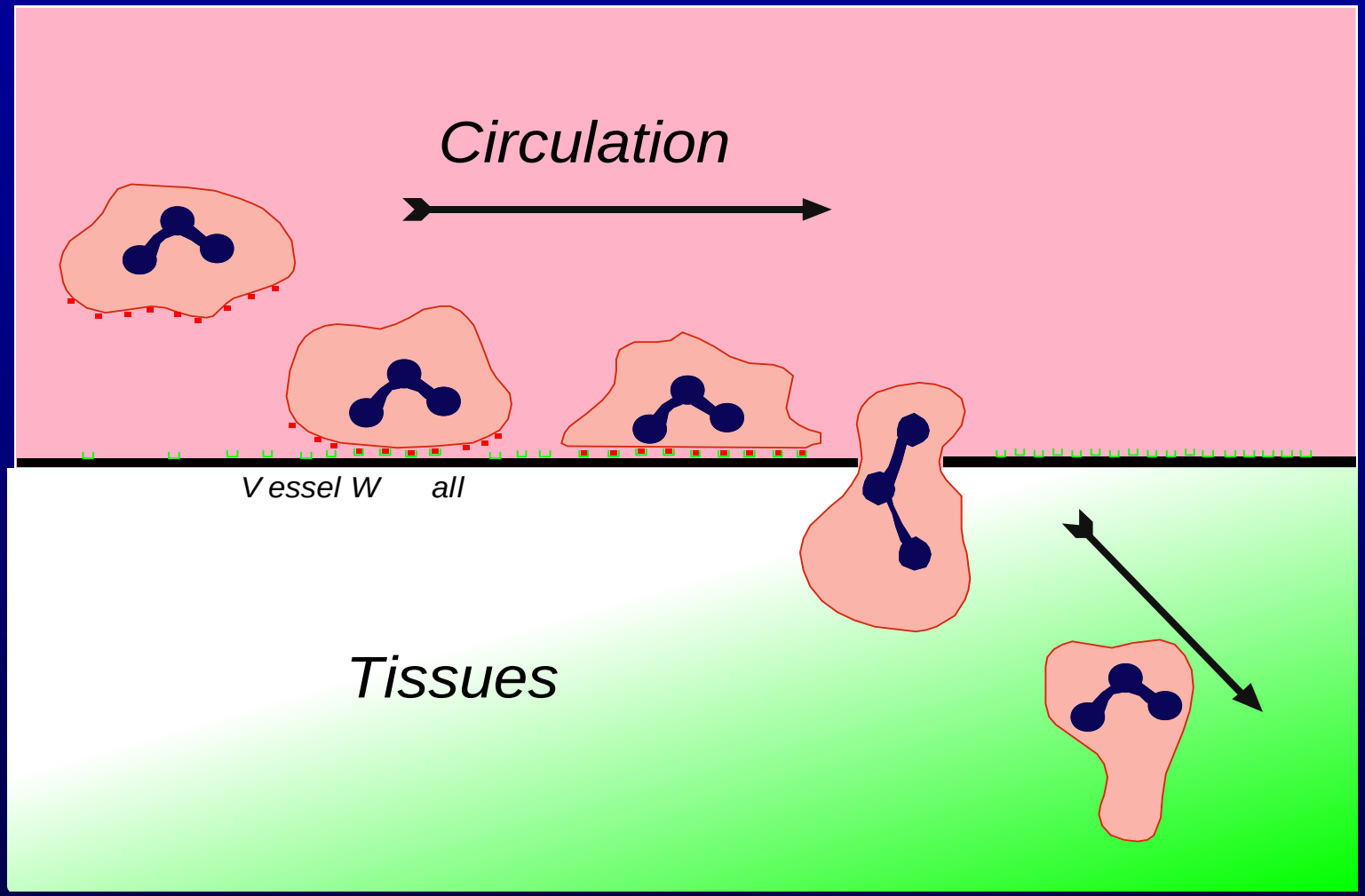
- PRODUCTS FROM PLATELETS
  - 5-hydroxy tryptamine, histamine, ADP...
  - Platelet-derived growth factor, coagulation proteins...
- PRODUCTS FROM NEUTROPHILS
  - Lysosomal constituents
  - Products released on neutrophil death
- PRODUCTS FROM ENDOTHELIUM
  - PGI_2 (prostacyclin)
  - Nitric oxide (EDRF: = NO)
  - Endothelin
- Plasminogen activators / inhibitors
- OXYGEN DERIVED FREE RADICALS
  - Endothelial damage, inactivation of antiproteases, injury to other cells.
- **One could continue.....**

THE PHAGOCYTES

- Margination
  - Endothelium-phagocyte interactions; adhesion molecules.

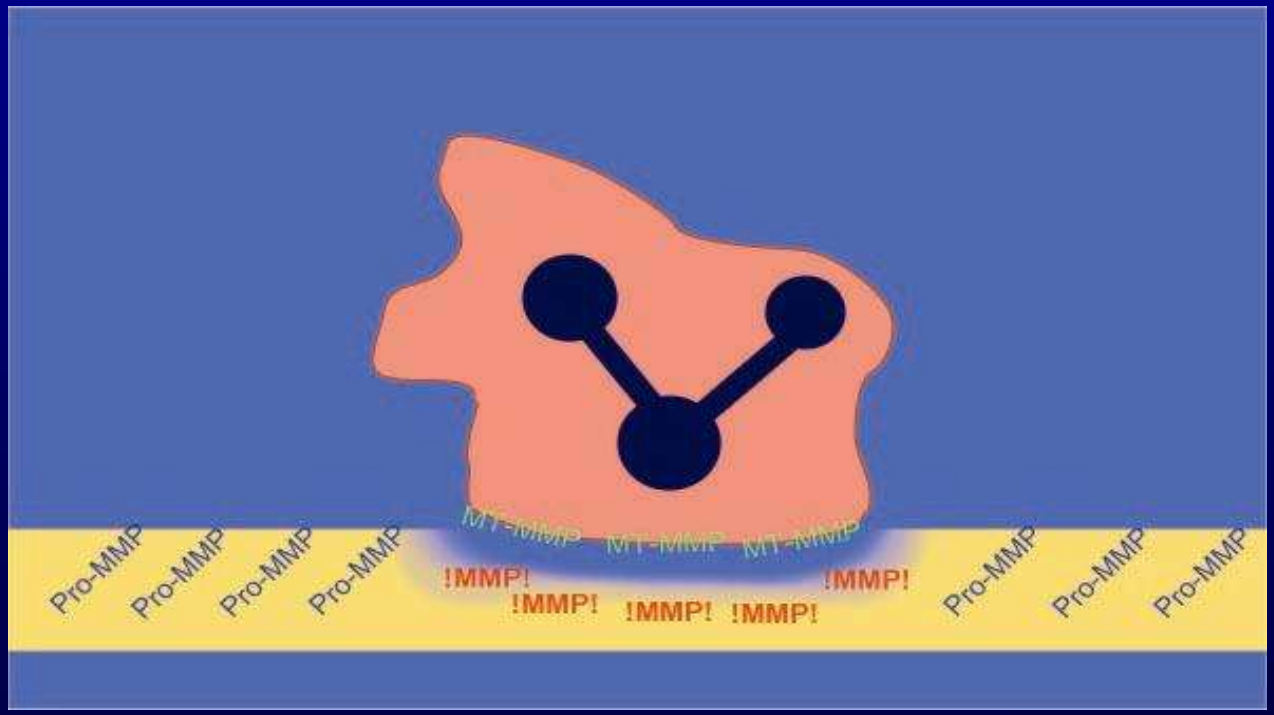
    - Histamine & thrombin activate P-selectin on endothelium (minutes)
    - IL-1, TNF activate E selectin on endothelium (hours)
    - ICAM-1 and VCAM-1 also upregulated on endothelium
    - LFA-1, VLA-4 activation on neutrophils

Margination, emigration, chemotaxis



How do neutrophils escape from vessels?

- Relaxation of inter-endothelial cell junctions
- Digestion of vascular basement membrane
- Movement



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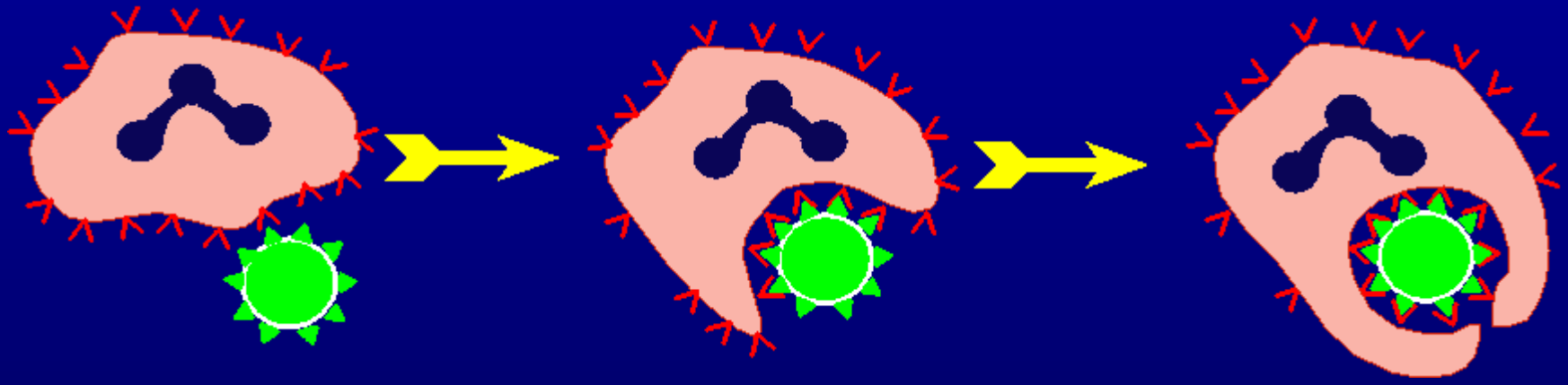
How do neutrophils move? Diapedesis and Emigration; Chemotaxis.

- Chemotaxis implies detection of concentration gradients
- Receptor-ligand binding
- Phospholipase C activation
- Local release of free intracellular Ca+
- Rearrangement of cytoskeleton
- Production of pseudopod

What do neutrophils do? Phagocytosis



- Contact, Recognition, Internalisation.
- Opsonins: e.g. Fc and C3b receptors
- Cytoskeletal changes (as with chemotaxis); ‘zipper’ effect.

What do neutrophils do? Microbial killing

- Phagosomes fuse with lysosomes to produce secondary lysosomes.

  Mechanisms:

- **O_2 dependent**
  - NADPH oxidase activated; produces superoxide ion. This converts to hydrogen peroxide.
  - H_2O_2-Myeloperoxidase-halide system: produces $HOCl^{\cdot}$ (i.e. bleach!)

  - **Myeloperoxidase independent:**
  - Uses superoxide and hydroxyl radicals. Less efficient.

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O_2 independent killing mechanisms

- Lysozyme & hydrolases
- Lactoferrin
- Bactericidal Permeability Increasing Protein (BPI)
- Cationic proteins (‘Defensins’)
- Major Basic Protein (MBP; Eosinophils)

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

- **Fever**
  - 'Endogenous pyrogens' produced: IL1 and TNFα
  - IL1 - prostaglandins in hypothalamus
    hence aspirin etc. reduce fever
- **Leukocytosis**
  - IL1 and TNFα produce an accelerated release from marrow
  - Macrophages, T lymphocytes produce colony-stimulating factors
  - Bacterial infections - neutrophils, viral - lymphocytes
  - Clinically useful

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

- **Acute phase response**
  - Decreased appetite, altered sleep patterns and changes in plasma concentrations of:
- **Acute phase proteins**:
  - C-reactive protein (CRP) (Clinically useful)
  - α_1 antitrypsin
  - Haptoglobin
  - Fibrinogen
  - Serum amyloid A protein

PROBLEMS CAUSED BY ACUTE INFLAMMATION

- Local
  - Swelling: Blockage of tubes, e.g. bile duct, intestine
  - Exudate: Compression e.g. cardiac tamponade Loss of fluid e.g. burns
  - Pain & loss of function - especially if prolonged
  - ‘Bystander effect’ exacerbates damage, may initiate autoimmunity

PROBLEMS CAUSED BY ACUTE INFLAMMATION

- Systemic
  - Acute phase response
  - Spread of micro-organisms and toxins

–SHOCK

ACUTE INFLAMMATION: RESOLUTION.

- **What may happen after the development of acute inflammation?**

1) Complete resolution.
2) Continued acute inflammation with chronic inflammation; chronic suppuration.
3) Chronic inflammation and fibrous repair, probably with tissue regeneration.
4) Death.

RESOLUTION OF ACUTE INFLAMMATION

- Morphology

  Changes gradually reverse.

  Vascular changes stop:

  – neutrophils no longer marginate

  – vessel permeability returns to normal

  – vessel calibre returns to normal.

RESOLUTION OF ACUTE INFLAMMATION

- Therefore:
  - Exudate drains to lymphatics
  - Fibrin is degraded by plasmin and other proteases
  - Neutrophils die, break up and are carried away or are phagocytosed
  - Damaged tissue *might* be able to regenerate.

  - **Note that if tissue architecture has been destroyed, complete resolution is not possible.**

MECHANISMS OF RESOLUTION

- All mediators of acute inflammation have short half-lives.
- May be inactivated by degradation, e.g. heparinase
- Inhibitors may bind, e.g. various anti-proteases
- May be unstable e.g. some arachidonic acid derivatives
- May be diluted in the exudate, e.g. fibrin degradation products.
- Specific inhibitors of acute inflammatory changes
  - e.g. lipoxins, endothelin...

CLINICAL EXAMPLES

- **LOBAR PNEUMONIA**
  - Causative organism?
    - Streptococcus pneumoniae ('Pneumococcus')
  - Population at risk?
    - Young adults in confined conditions; alcoholics;....
  - Clinical course?
    - Worsening fever, prostration, hypoxaemia over a few days. Dry cough. Fairly sudden improvement ('resolution by crisis') when antibodies appear.

Lobar pneumonia

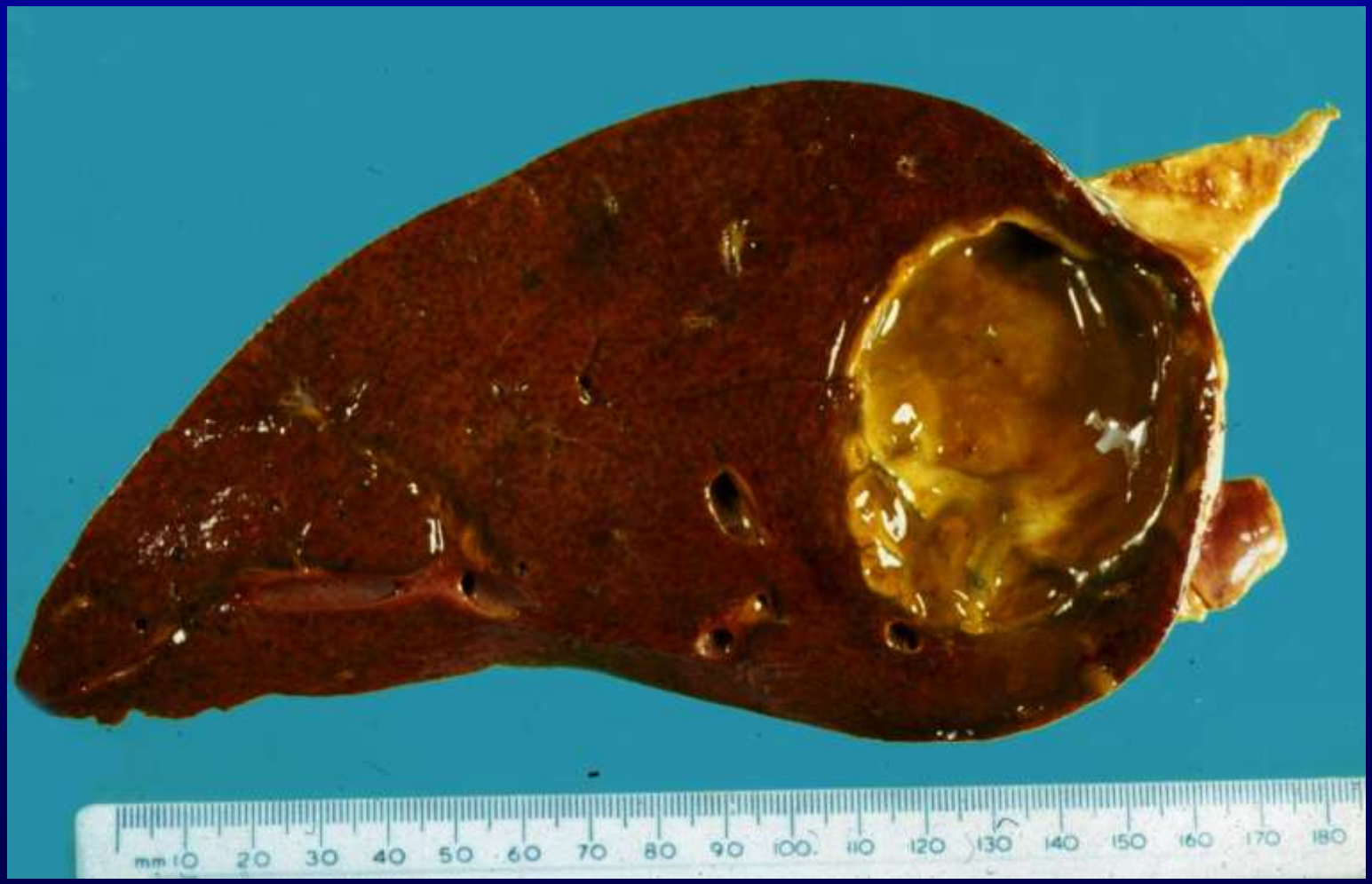
SKIN BLISTER

- Cause irrelevant; heat, sunlight, irritant chemical...
- Predominant features:
- PAIN
- EXUDATE
  - Collection of fluid strips off overlying epithelium
  - more pain, more tissue damage.
  - Inflammatory cells relatively few:
    therefore exudate clear UNLESS bacterial infection develops.

ABSCESS

- Solid tissues
- Inflammatory exudate forces tissue apart
- Liquefactive necrosis in centre
- May cause high pressure therefore PAIN
- May cause tissue damage
- May squash adjacent structures

Hepatic abscess

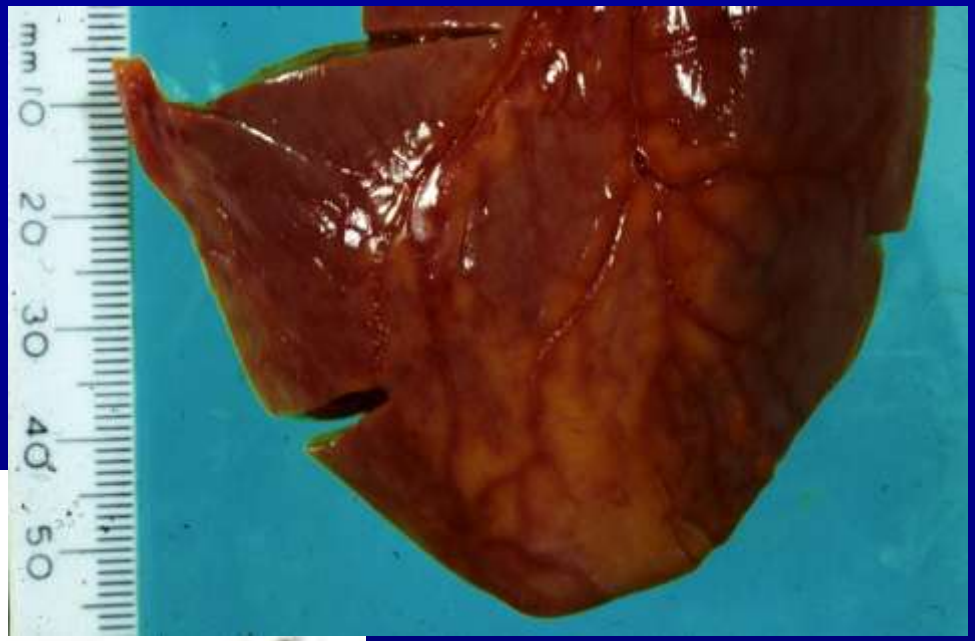


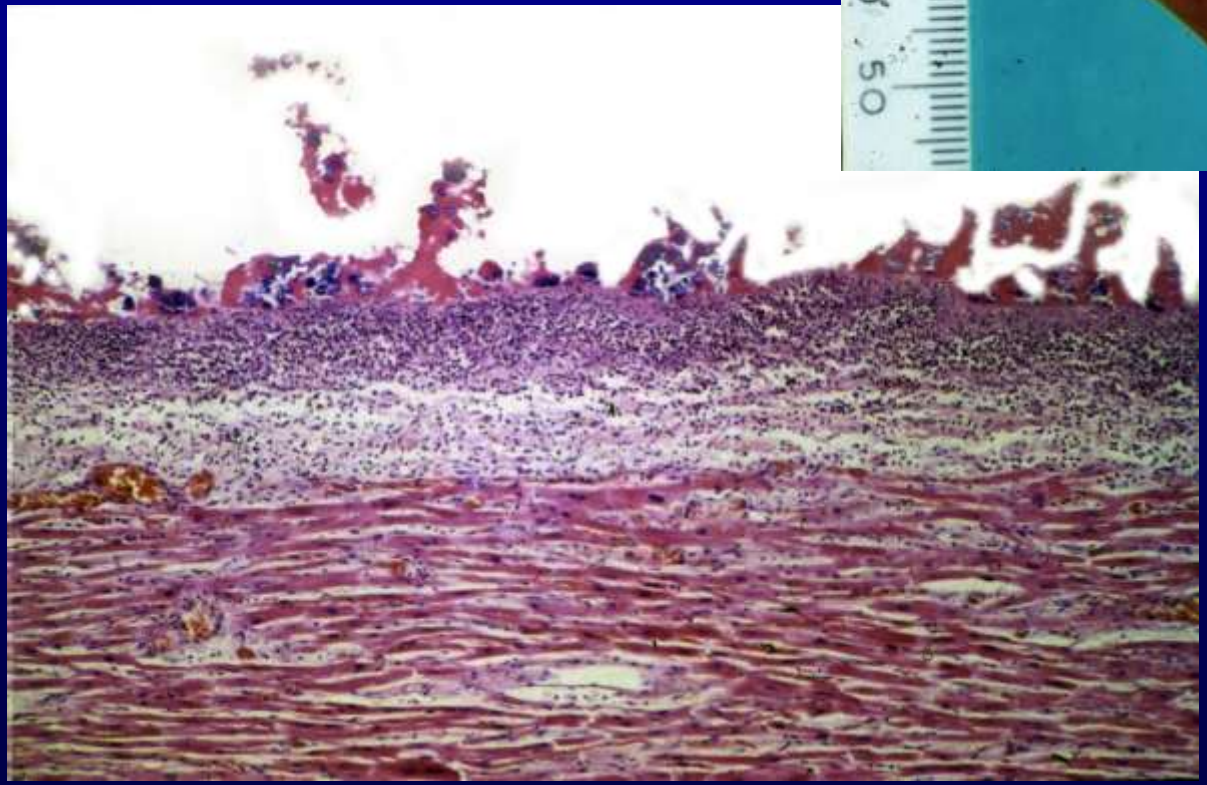
ACUTE INFLAMMATION IN SEROUS CAVITIES

- **Exudate pours into cavity**

- ascites, pleural or pericardial effusion
- respiratory or cardiac impairment
- Localised fibrin deposition
- ‘bread and butter’ pericarditis

Pericarditis





Inflammatory exudate

Myocardium

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DISORDERS OF ACUTE INFLAMMATION

- These are rare diseases (natural selection ensures that!) but illustrate the importance of apparently small parts of this complex web of mechanisms.

A few examples:

- **Hereditary angio-oedema ('angioneurotic oedema')**
- **Alpha-1 antitrypsin deficiency.**
- **Inherited complement deficiencies.**
- **Defects in neutrophil function.**
- **Defects in neutrophil numbers.**

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ANATOMICAL TERMINOLOGY OF INFLAMMATION

By……Dr. AJWADASSUMAIDAEE

bile duct

cholangiitis

bladder

cystitis

blood vessel

vasculitis

bone

osteitis

bone marrow

osteomyelitis

brain

encephalitis

bursa

bursitis

cecum

typhlitis

connective tissue

cellulitis

cornea

keratitis

dura mater

pachymeningitis

ear

otitis

eye

ophthalmitis

eyelid

blepharitis

fascia

fasciitis

fat

steatitis

gall bladder

cholecystitis

gill (branchia)

branchiitis

glans penis

balanitis

heart

carditis

intestine

enteritis

iris

iritis

kidney

nephritis

knee

gonitis

lacrimal gland

dacryoadenitis

ligament

desmitis

lip

cheilitis

liver

hepatitis

lung

pneumonitis (pneumonia)

lymph node

lymphadenitis

lymph vessel

lymphangiitis

meninges

meningitis

mouth

stomatitis

muscle (skeletal)

myositis

myocardium

myocarditis

nerve

neuritis

ovary

oophoritis

oviduct

salpingitis

pancreas

pancreatitis

pericardium

pericarditis

peritoneum

peritonitis

pleura

pleuritis

prepuce

posthitis

renal glomerulus

glomerulitis

renal pelvis

pyelitis

salivary gland

sialadenitis

sinus

sinusitis

skin

dermatitis

spinal nerve root

radiculitis

spleen

splenitis

stomach

gastritis

testicle

orchitis

tongue

glossitis

trachea

tracheitis

tympanum

tympanitis

uterus

metritis

vagina

vaginitis

vas deferens

vasitis

vein

phlebitis

vertebra

spondylitis

vessel

vasculitis

PATHOPHYSIOLOGY

CANCER: PATHOPHYSIOLOGY

Dr. AJWADASSUMAIDAEE

31-12-2014

Free will doesn't mean doing whatever you want. It means having the freedom to do what is right.

What is Cancer?

- **Division – uncontrolled cell division**
- **Growth – formation of a lump (tumour) or large numbers of abnormal white cells in the blood**
- **Mutation – changes to how the cell is viewed by the immune system**
- **Spread – ability to move within the body and survive in another part**

Division – uncontrolled cell division

- Oncogenes
- Tumour suppressor genes – p53
- Suicide genes – apoptosis
- DNA repair genes

Growth

- Tumour
  - Pressure on nerves
  - Blocking organs
  - Stopping normal function
  - Altering nerve signals
  - Fungating

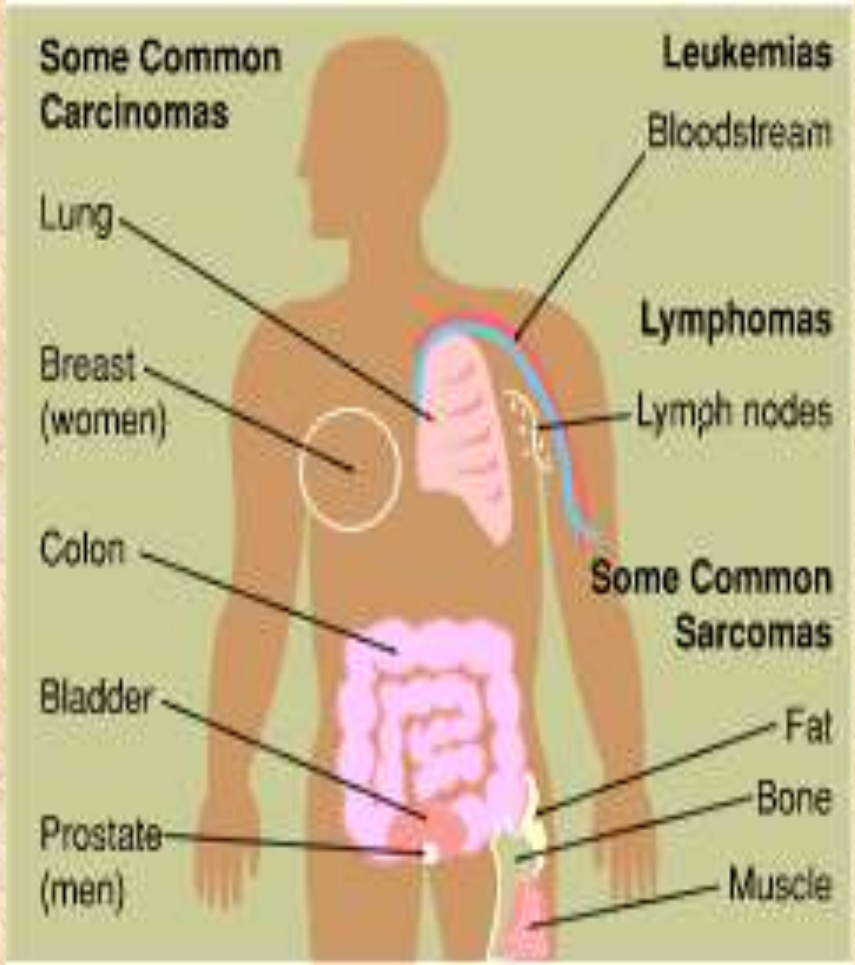
Mutation and Spread

- Invasion
- Angiogenesis

Types of Cancer

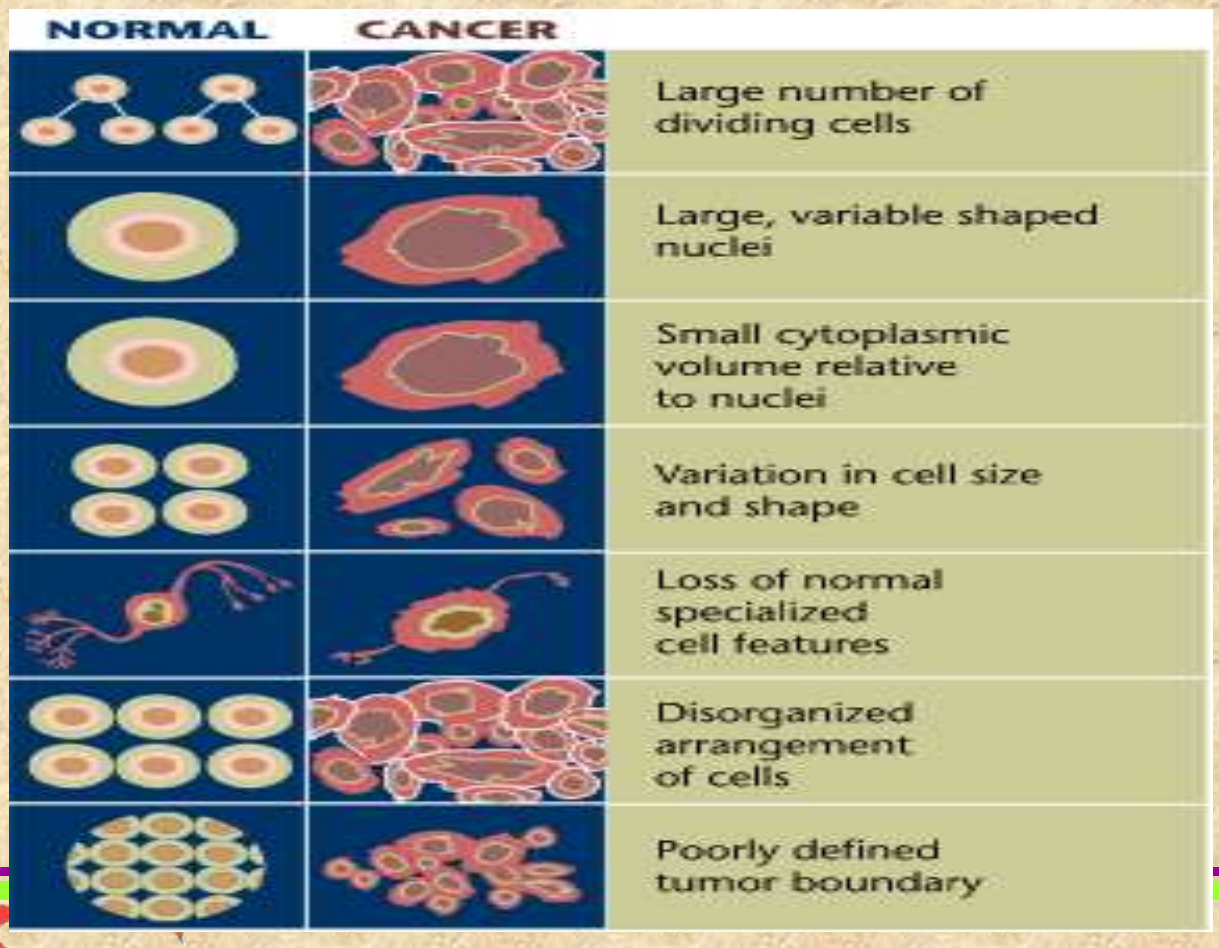
- Carcinomas
- Sarcomas
- Lymphomas
- Leukaemias
- Adenomas

- Often prefixed by the specific cell



Some Prefixes Used in Naming Cancers	
PREFIX	MEANING
adeno-	gland
chrondro-	cartilage
erythro-	red blood cell
hemangio-	blood vessels
hepato-	liver
lipo-	fat
lympho-	lymphocyte
melano-	pigment cell
myelo-	bone marrow
myo-	muscle
osteo-	bone

What are the differences in the features of normal and cancer cells?



Two major types: Benign and Malignant

Benign: grow slowly

low mitotic rate

well differentiated

not invasive; well-defined borders

remain localized; do not metastasize

Malignant – cancer – from Latin for crab

autonomy and anaplasia

Grow rapidly ; high mitotic index, poorly differentiated; do not have a capsule; invade surrounding structures; can metastasize from the primary to a secondary site (metastasis).

Nomenclature – In General :

Tissue of origin + “-oma” indicates a benign tumor

Malignant tumors – use embryonic origin of tissue

Carcinomas come from ectoderm and Endoderm - epithelial and glandular tissue

Sarcomas arise from mesoderm

connective tissue, muscle, nerve and endothelial tissues

Viral causes of cancer:

viruses assoc. with about 15 % of cancers world wide – us. Cervix or liver

hepatitis B or C in chronic form

Human papilloma virus

spread through sexual contact

HPV integrates into DNA and uses viral oncogenes

Epstein-Barr and Kaposi sarcoma

both herpes viruses

Human T cell leukemia-lymphoma virus

blood transfusions, needles, sex and breast feeding

infections may be asymptomatic

may have high incidence, but low #'s of cancer

cofactors increase the risk of cancer

Bacterial causes of Cancer

Helicobacter pylori **infects >1/2 world's population**

assoc. with B cell lymphomas of the stomach

treatment with antibiotics can cause regression of lymphoma

Tumors arise in MALT -MALTomas

Environmental factors

- Tobacco use
- Diet
- Alcohol use
- Sexual and reproductive behavior
- Air pollution
- Occupation hazards – asbestos
- UV radiation and other radiation
- hormones

Gene-Environment Interactions:

Exposure to environmental agents can cause increased risk of cancer

cancer in lab animals – carcinogens

Comparisons of populations

genetics vs. lifestyle

“Genetics loads the gun; the environment pulls the trigger.” director of Nat’l Institute of Environmental Health & Safety

Tumor spread

- Local spread
  - Cellular multiplication
    - Function of generation time
    - Growth if cell reproduction > cell death

Mechanical invasion

along path of least resistance

compresses blood vessels, leading to tissue death and increased space

Lytic enzymes

proteases, collagenases, plasminogen activators, lysosomal enzymes

some involved in producing new blood vessels

Decreased cell adhesion

loss of anchoring molecules allows cancer to slip between normal cells

Increased motility

- **essential for metastasis**
  - **intravasation**
  - **extravasation**
- **may secrete autocrine motility factor**
- **extend psuedopodia**
- **three step hypothesis:**
  - **attachment to the matrix**
  - **dissolution of the matrix**
  - **locomotion through the matrix**

Stages of cancer spread:

Stage 1 – confined to site of origin

Stage 2- cancer is locally invasive

Stage 3 – cancer has spread to regional structures

Stage 4- cancer has spread to distant sites

TNM system:

tumor spread

node involvement

presence of distant metastasis

Staging may influence choice of treatment

Staging TNM system

1. **Size of tumor – T_0, T_1, T_2, T_3**
2. **Degree of local invasion – lymph node involvement**
3. **Extent of spread – metastasis**

Patterns of spread: Metastasis

- Direct or continuous extension
- By lymphatics or blood stream
  - As clumps or as single cells
  - Lymphatics most common

Patterns of spread: Metastasis

- Angiogenesis
  - Due to production of angiogenic factors
  - Due to drop in antiangiogenic factors

A metastasis grows when:

vascular network is developed

host defenses are evaded

a compatible environment is available

Distribution and common sites of distant metastases

- often occurs in the first capillary bed encountered

•Others show "organ tropism"

•Due to:

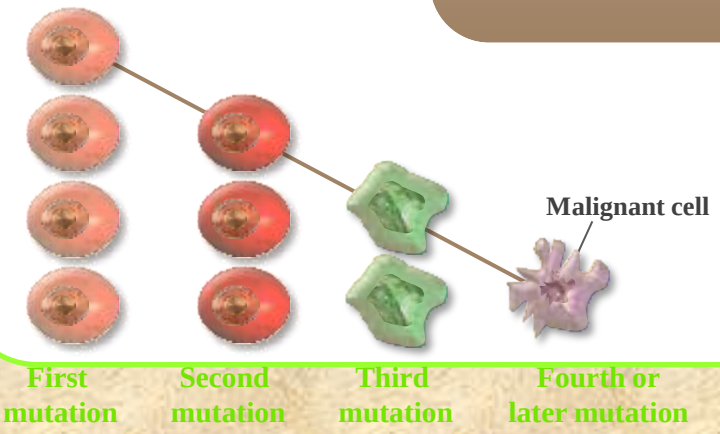
- **•Local growth factors or hormones**
- **•Preferential adherence to the surface**
- **•Presence of chemotactic factors**

Emergence of a cancer cell

Cancers originate from a single cell

Genetic mutations, i.e. changes to the normal base sequence of DNA, contribute to the emergence of a cancer cell

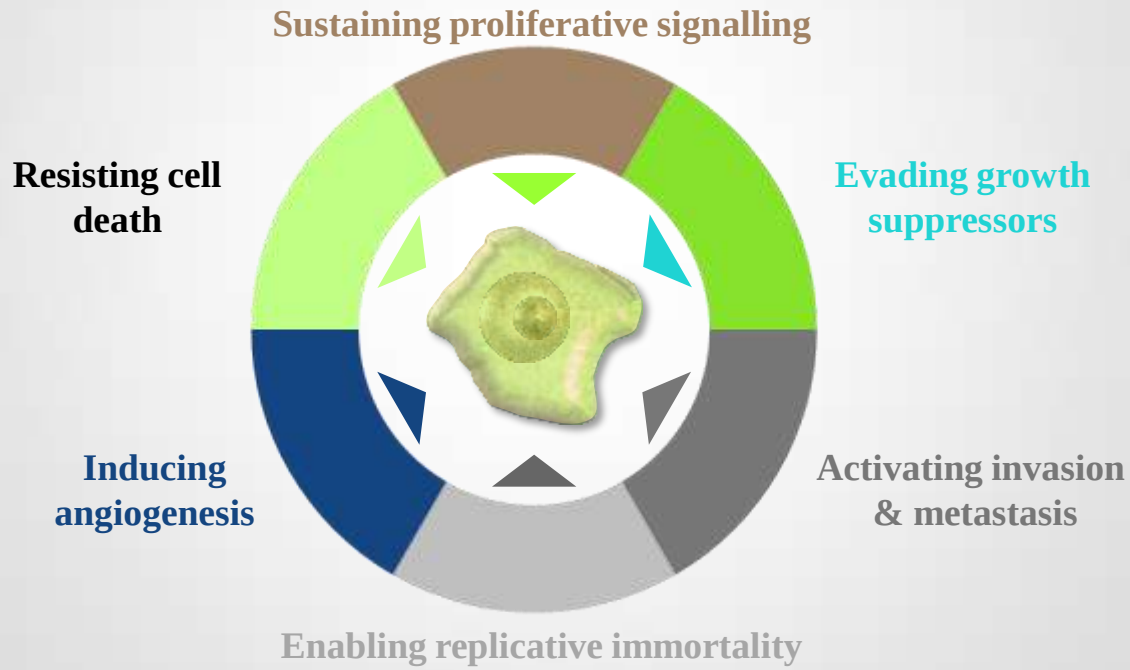
A series of mutations accumulate in successive generations of the cell in a process known as clonal evolution



Eventually, a cell accumulates enough mutations to become cancerous

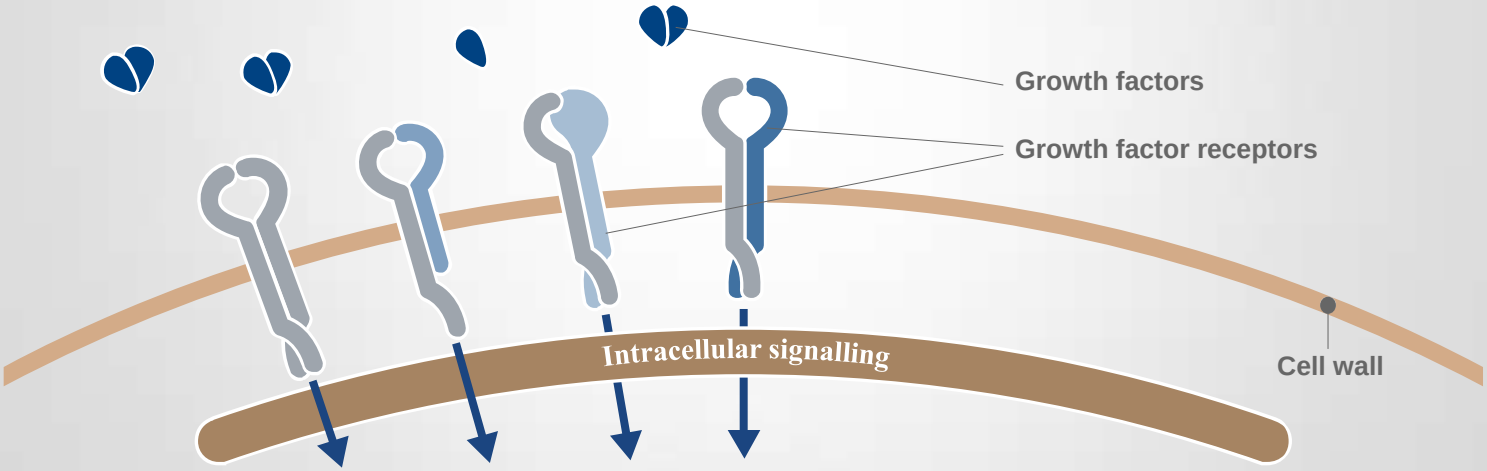
The hallmarks of cancer

In order for cancerous cells to develop and form a tumour, mutations and other alterations that allow the cell to acquire a succession of the following biological capabilities must occur:[1,2]



Sustaining proliferative signalling

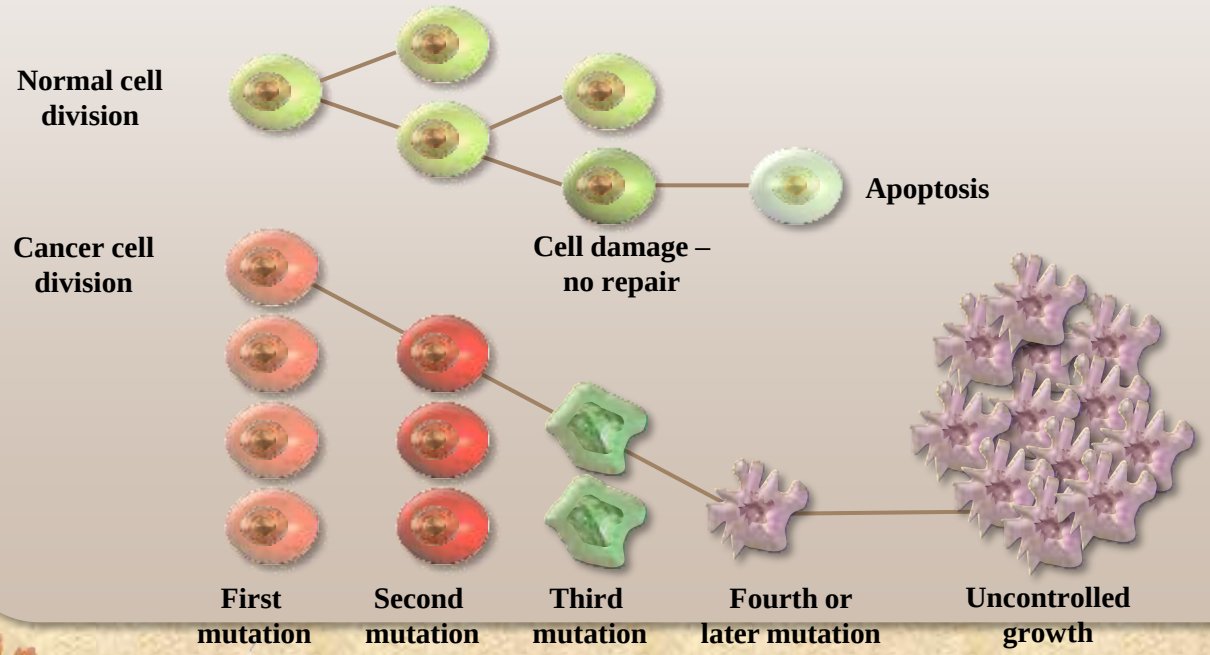
Normal cells rely on positive growth signals from other cells
Cancer cells can reduce their dependence on growth signals by:[1,2]
- Production of their own extracellular growth factors -
- Overexpression of growth factor receptors -
- Alterations to intracellular components of signalling pathways -



Resisting cell death

When normal cells become old/damaged, they go through apoptosis (programmed cell death)

An important hallmark of many cancers is resistance to apoptosis, which contributes to the ability of the cells to divide uncontrollably[1,2]

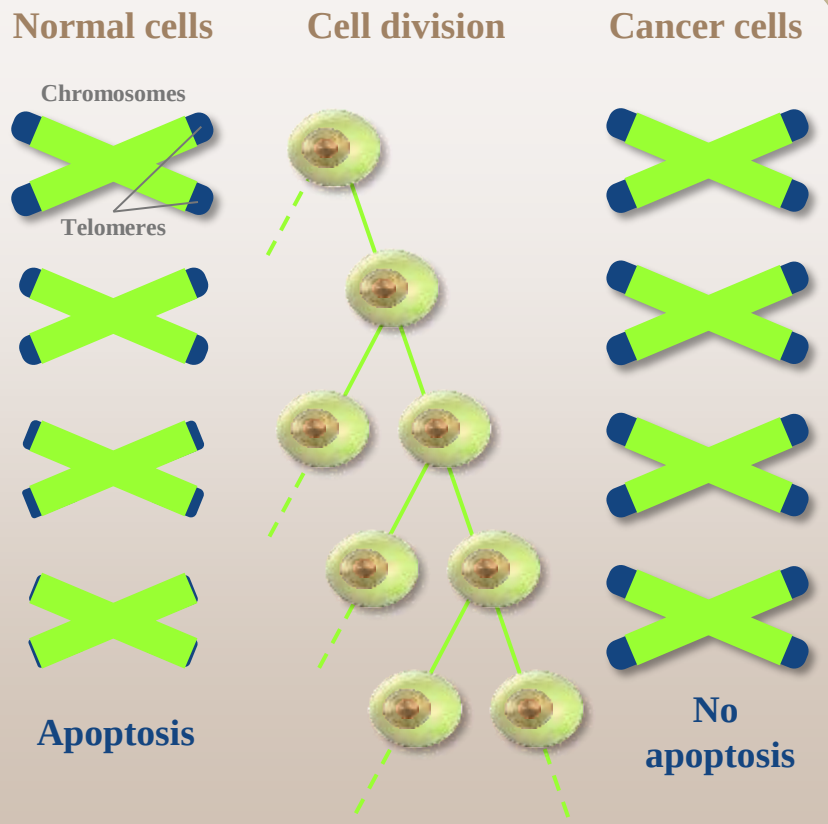


Enabling replicative immortality

Another important hallmark of cancer is the ability of the cell to overcome the boundaries on how many times a cell can divide[1]

These limits are usually set by telomeres (the ends of chromosomes):[1,2]

- In normal cells, telomeres get shorter with each cell division until they become so short that the cell can no longer divide
- In cancer cells, telomeres are maintained, allowing the cell to divide an unlimited number of times



Inducing angiogenesis

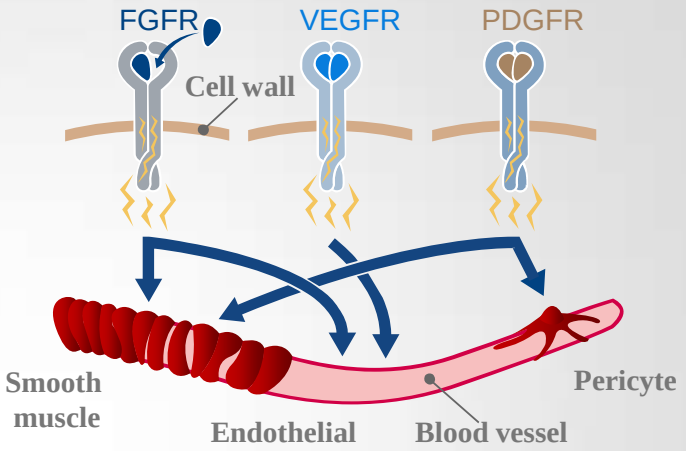
The formation and maintenance of new blood vessels (angiogenesis) plays a critical role in tumour growth

New blood vessels supply the cancer cells with oxygen and nutrients, allowing the tumour to grow.

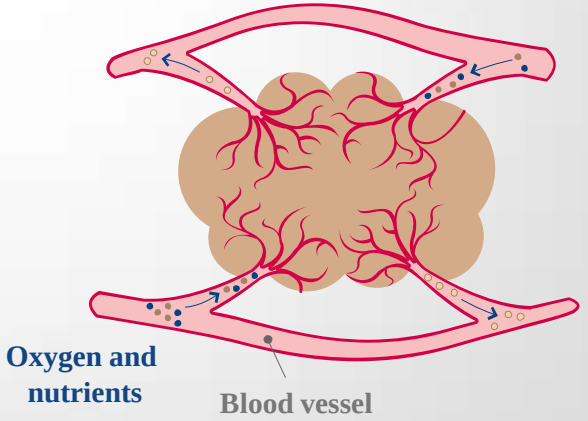
Angiogenesis is mediated principally through vascular endothelial growth factor (VEGF)

Other growth factors also play a role, e.g.:

- Fibroblast growth factor (FGF)
- Platelet-derived growth factor (PDGF)



Nearby blood vessels grow into the tumour.

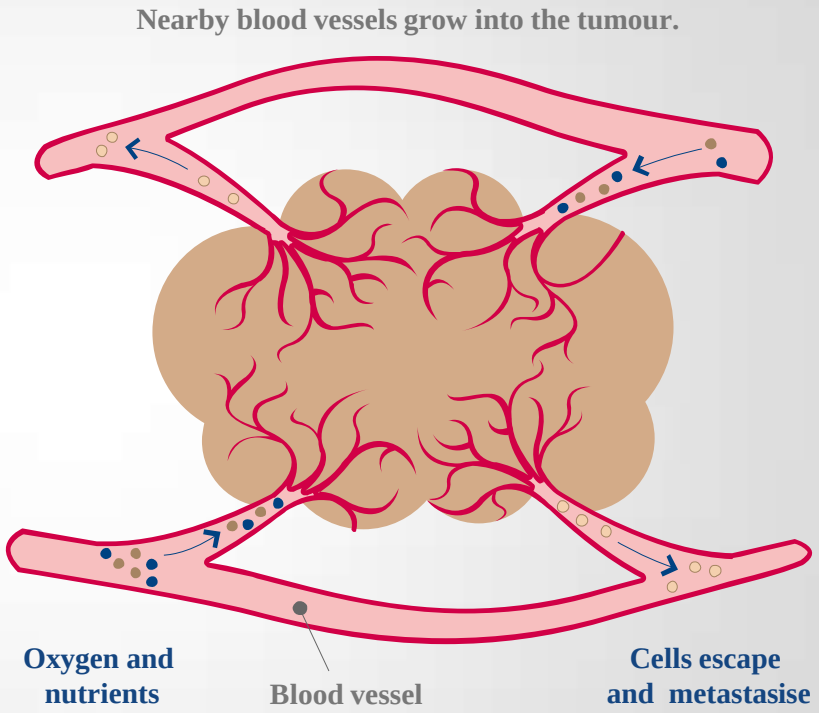


Activating invasion & metastasis

Eventually, tumours may spawn pioneer cells that can invade adjacent tissues and travel to other sites in the body to form new tumours (metastasis)[1]

This capability allows cancerous cells to colonise new areas where oxygen and nutrients are not limiting

Metastasis causes 90% of deaths from solid tumours[2]



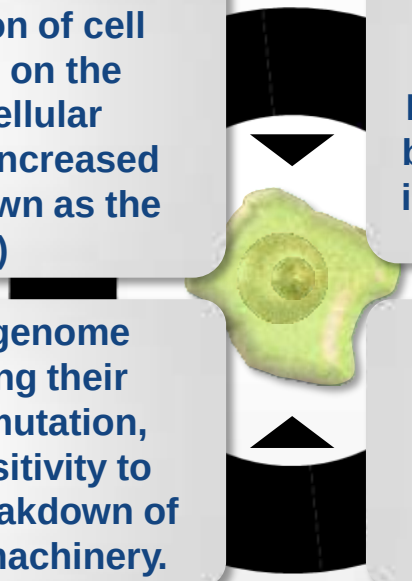
Enabling characteristics and emerging hallmarks

There is evidence that a further two emerging hallmarks are involved in the pathogenesis of cancer[1]

The acquisition of these hallmarks of cancer is made possible by two enabling characteristics[1]

The uncontrolled growth and division of cancer cells relies not only on the deregulation of cell proliferation, but also on the reprogramming of cellular metabolism, including increased aerobic glycolysis (known as the Warburg effect)

The immune system is responsible for recognising and eliminating cancer cells, and therefore preventing tumour formation. Evasion of this immune surveillance by weakly immunogenic cancer cells is an important emerging hallmark of cancer.



Cancer cells achieve genome instability by increasing their mutability, or rates of mutation, through increased sensitivity to mutagenic agents or breakdown of genomic maintenance machinery.

Immune cells infiltrate tumours and produce inflammatory responses, which can paradoxically enhance tumourigenesis, helping tumours acquire the hallmarks of cancer

Enabling characteristics

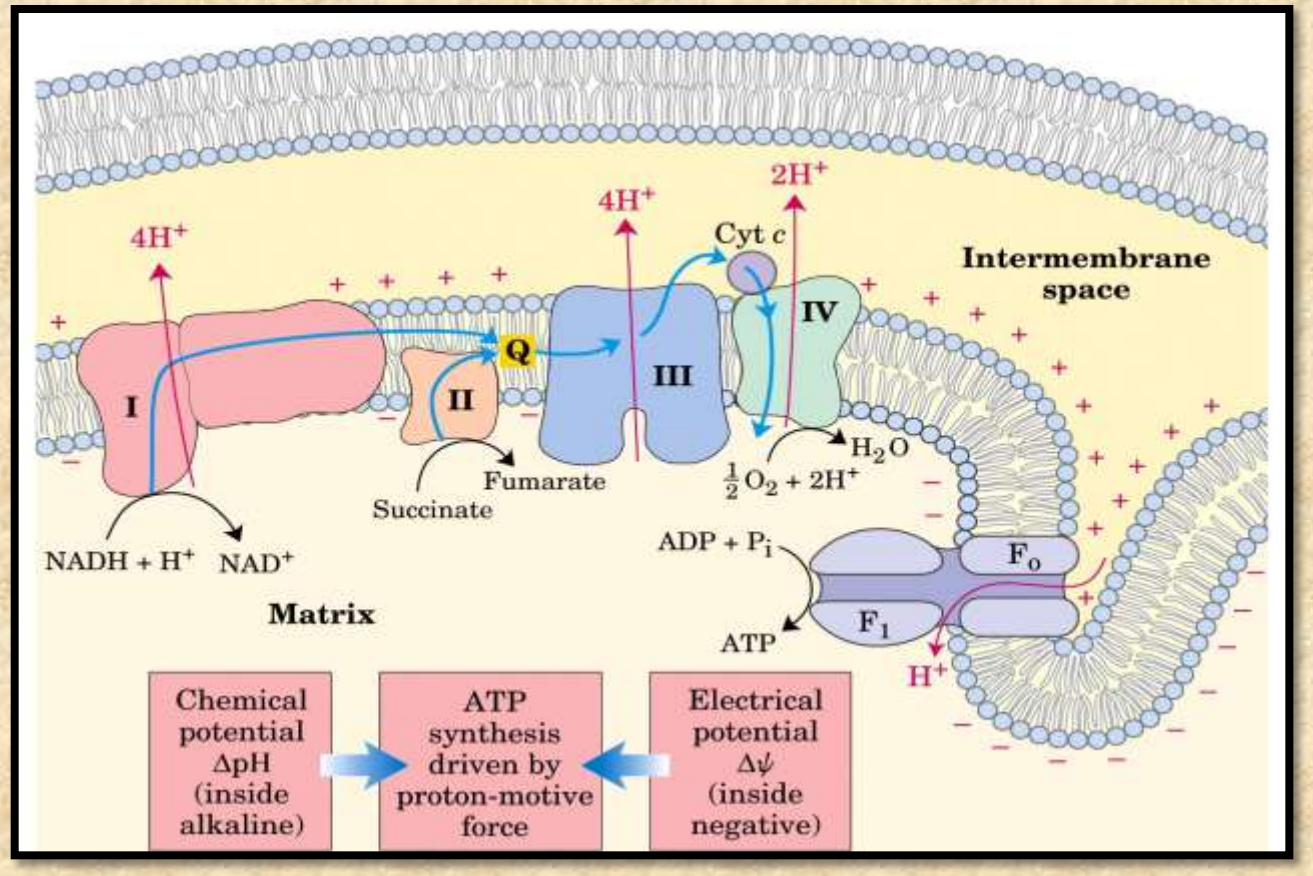
Metabolic Oxidative Stress and Cancer

What is life?

"An electron, given off easily, has a high energy level, while an orbital which tends to take up an electron, has a low energy level. The transmitted electron thus goes from a high to a low level, and releases the energy which corresponds to the difference of the two levels. It is this energy which drives life."
***Albert Szent-Györgyi*, Electronic Biology and Cancer, Marcel Dekker Inc. 1976**

- **In essence, *Szent-Györgyi* was one of the first scientists to recognize that all of the forces necessary for the maintenance of living systems derive from the ability of complex higher order biological structures to extract, store, and move electrons.**

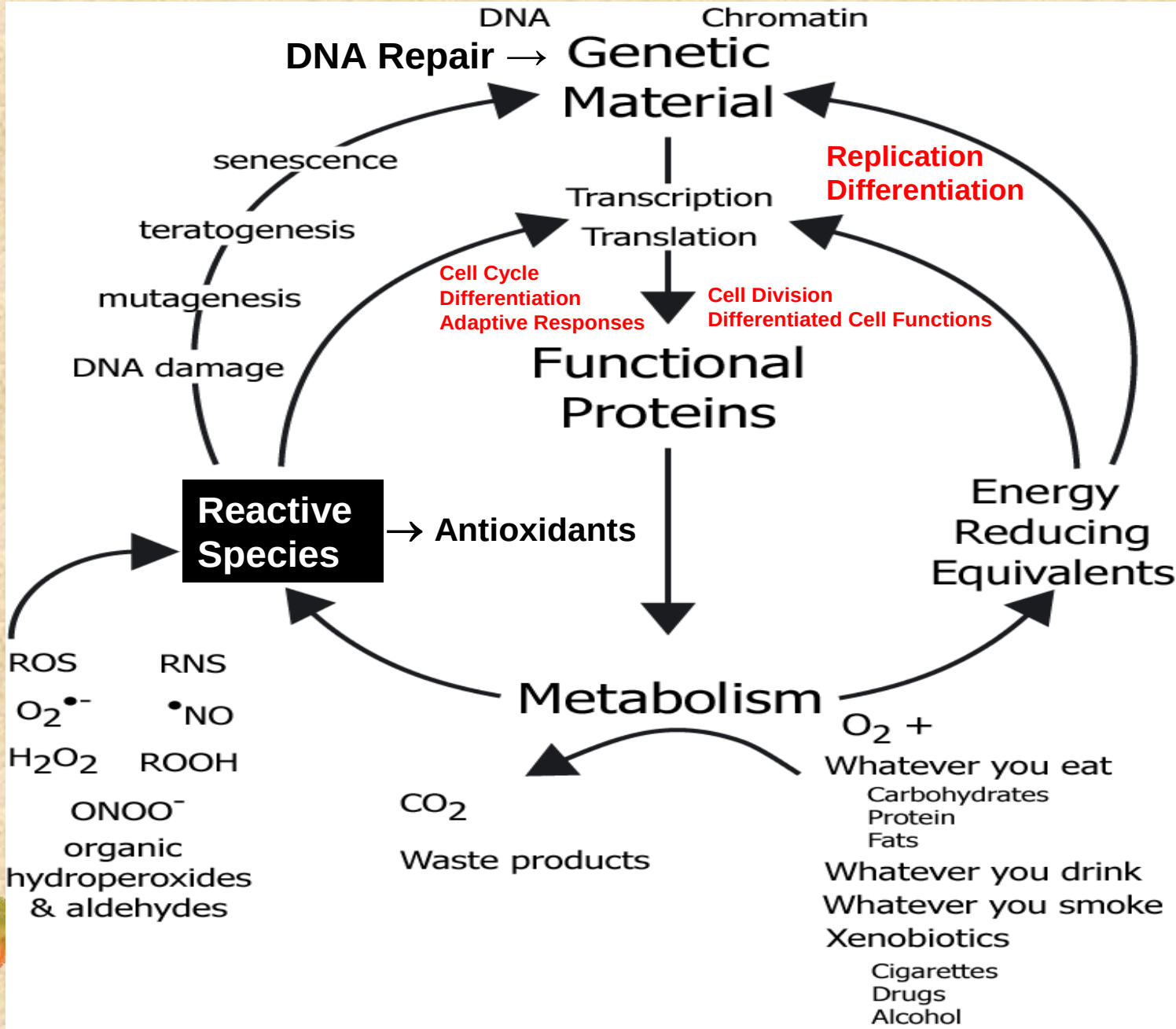
Why do we breath oxygen? ***The Chemiosmotic Hypothesis***
Why is it potentially harmful?



Chemiosmotic model. In this simple representation of the chemiosmotic theory applied to mitochondria, electrons from NADH and other oxidizable substrates pass through a chain of carriers arranged asymmetrically in the inner membrane. Electron flow is accompanied by proton transfer across the membrane, producing both a chemical gradient (ΔpH) and an electrical gradient (Δψ). The inner mitrochondrial membrane is impermeable to protons; protons can reenter the matrix only through proton specific channels (F_0). The proton-motive force that drives protons back into the matrix provides the energy for ATP synthesis, catalyzed by the F1 complex associated with F_0.

The Circle of Life and The Circle of Death

What is the relationship between metabolic and genetic processes necessary for life?



Spitz DR, Azzam EI, Li JJ, and Gius D: Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: a unifying concept in stress response biology. ***Cancer and Metastasis Reviews*** 2004; 23:311–322.

Metabolic Theories of Cancer

Warburg O (1956) *Science* 123:309-314

• Cancer cells exhibit increased rates of glycolysis and slightly decreased rates of respiration.

• It was proposed this was the result of "damage" to the respiratory mechanism and tumor cells increased glycolysis to compensate for this defect.

Weber G (1977) *New Engl. J. Med.* 296:541-551

• Cancer cells exhibit increased rates of pentose phosphate cycle activity characterized by increases in glucose-6-phosphate dehydrogenase activity.

Oberley LW, Oberley TD, and Buettner GR (1980 and 1981) *Med. Hypoth.* 6:49-68; 7:21-42

• Tumor cells have aberrant respiration caused by a decrease in MnSOD activity leading to increased steady state levels of superoxide and hydrogen peroxide that causes DNA damage and activates signaling pathways leading to uncontrolled growth, the inability to differentiate, and the malignant phenotype.

Genetic Theory of Cancer

Bishop (1987) *Science* 235:305-311; Varmus (1987) *Science* 238:1337-1339

- **Cancer is a multi-step genetic disease in which mutations resulting in the aberrant expression of cellular homologues of oncogenes (i.e., Ras, c-Fos, c-Jun, and c-Myc, etc.) associated with growth and development as well as tumor suppressor genes (i.e., p53) gradually accumulate over time, eventually resulting in immortalization, the loss of control of cell proliferation, and progression to the malignant phenotype.**

How can we unify metabolic and genetic theories of cancer?

In the mid-1990's Dr. Yong J. Lee's laboratory showed:

- **Within minutes - glucose deprivation-induced activation of signal transduction in human breast cancer cells.**

- **Within 2-4 hours - glucose deprivation-induced increases in steady state levels of mRNA coding for bFGF and c-Myc in MCF-7/ADR.**

- **Within 4 hours - glucose deprivation-induced clonogenic cell killing in MCF-7/ADR cells.**

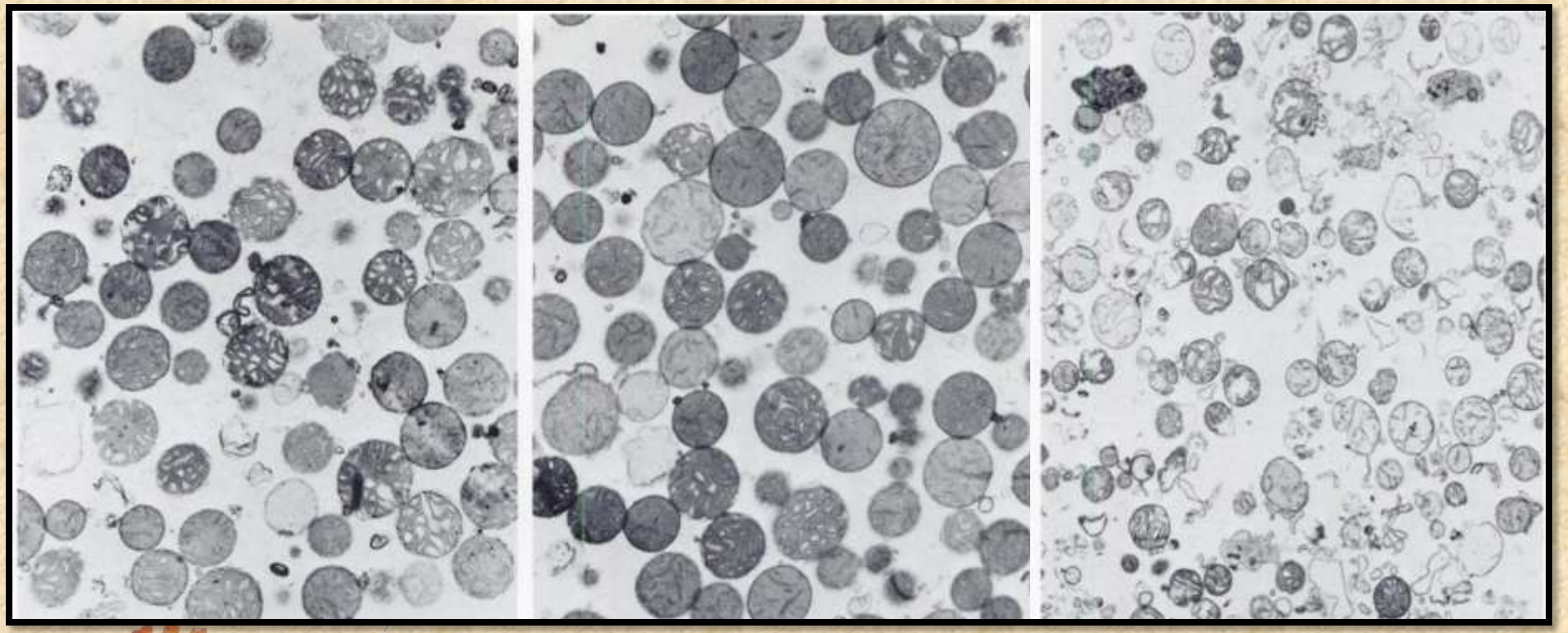
- **This work supported the existence of a mechanistic link between glucose metabolism, signal transduction, and gene expression governing the malignant phenotype that also governed the survival of cancer cells.**

What is this mechanistic link?

- **Dr. Lee and his collaborators then discovered that all the effects of glucose deprivation in MCF-7 ADR could be suppressed by treatment with the thiol antioxidant, N-acetylcysteine, indicating a causal role for oxidative stress in the effects of glucose deprivation in cancer cells.**

- **Rodent tumor cells had reduced levels of Mn-SOD activity that were proportional to increased growth rate and lack of ability to differentiate.**

- **Rodent Tumor cells demonstrated mitochondrial abnormalities that were more pronounced in fast growing undifferentiated cancers.**



normal liver mitochondria	well differentiated hepatoma slow growing	undifferentiated hepatoma fast growing

• Human cancer cells demonstrated mitochondrial abnormalities that are more pronounced in more malignant tissues.

• The cytoplasmic organelles of 16 human cell types derived from normal as well as from primary and metastatic carcinomas were characterized by electron microscopy in a blinded fashion.

• Mitochondrial pleomorphisms was expressed slightly by normal cells and to a much greater extent by all cell types derived from malignant tissues.

• These pleomorphisms were characterized by hypertrophied mitochondria with longitudinal cristal arrangements in almost all the malignant cells lines, but not in any lines derived from nonmalignant tissues of cancerous organs or from normal tissues.

• Increasing mitochondrial superoxide scavenging by increasing expression of MnSOD alters the malignant phenotype of cancer cells

• **These findings were the first demonstration that stable over expression MnSOD suppressed the malignant phenotype in human cancer cells.**

• **These results suggested that increased steady-state levels of superoxide and/or H_2O_2 significantly contributed to the maintenance of the malignant phenotype in human cancer cells.**

- **Human cancer cells were reported to produce large amounts of H_2O_2, relative to normal cells**

Szatrowski TP and Nathan CF: Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Res.* 1991; 51(3):794-8.

- **Seven human tumor cell lines demonstrated constitutively elevated H_2O_2 such that cumulative amounts were comparable to the amount of H_2O_2 produced by phorbol ester-activated neutrophils.**

- **Constitutive generation of large amounts of reactive oxygen intermediates by cancer cells, if it occurs *in vivo*, might contribute to genomic instability, tumor heterogeneity, invasion, and metastasis.**

• Mutations in mtDNA encoded genes (ND6) can lead to increased ROS and increased metastatic potential that is suppressed by ROS scavengers.

• The mtDNA conferring high metastatic potential contained mutations in the gene encoding NADH (reduced form of nicotinamide adenine dinucleotide) dehydrogenase subunit 6 (ND6) that was associated with overproduction of reactive oxygen species (ROS).

• Pretreatment of the highly metastatic tumor cells with ROS scavengers suppressed their metastatic potential in mice.

Conclusions

- **Cancer cells appear to exist in a condition of metabolic oxidative stress characterized by increased steady-state levels of superoxide and hydrogen peroxide.**
- **This increase in reactive oxygen species (ROS) appears to be compensated for by increases in glucose and hydroperoxide metabolism.**
- **The condition of metabolic oxidative stress in cancer cells may be the result of alterations in mitochondrial oxidative metabolism.**
- **Metabolic oxidative stress appears to contribute to selective sensitivity of cancer vs. normal cells to glucose deprivation-induced cytotoxicity and oxidative stress.**

Clinical Implications: Therapy

If glucose metabolism is increased in cancer cells to compensate for excess hydroperoxide production from mitochondrial respiration, then inhibiting glucose and hydroperoxide metabolism while forcing cells to derive energy from respiration should preferentially kill cancer cells, relative to normal cells.

Combinations of agents designed to take advantage of this hypothesis might include:

- **Inhibitors of Glucose Metabolism**
- **Inhibitors of the Pentose Phosphate Cycle**
- **Inhibitors of Hydroperoxide Metabolism**
- **Dietary Manipulation**
- **Agents that Increase the Metabolic Production of Prooxidants and Increase Oxidative DNA Damage (ie., Radiation, quinones, Cisplatin, inflammatory mediators, etc.)**

• **Inhibitors of glucose and hydroperoxide metabolism selectively (relative to normal cells) enhance cancer cell killing as well as selectively sensitizing cancer cells to therapeutic agents.**

Clinical Implications: Imaging

- **If glucose metabolism is increased in cancer cells to compensate for increased production of prooxidants by mitochondrial metabolism, then alterations in glucose metabolism and mitochondrial function should be proportional to susceptibility to therapies based on taking advantage of this metabolic defect to selectively kill cancer cells.**

Conclusions

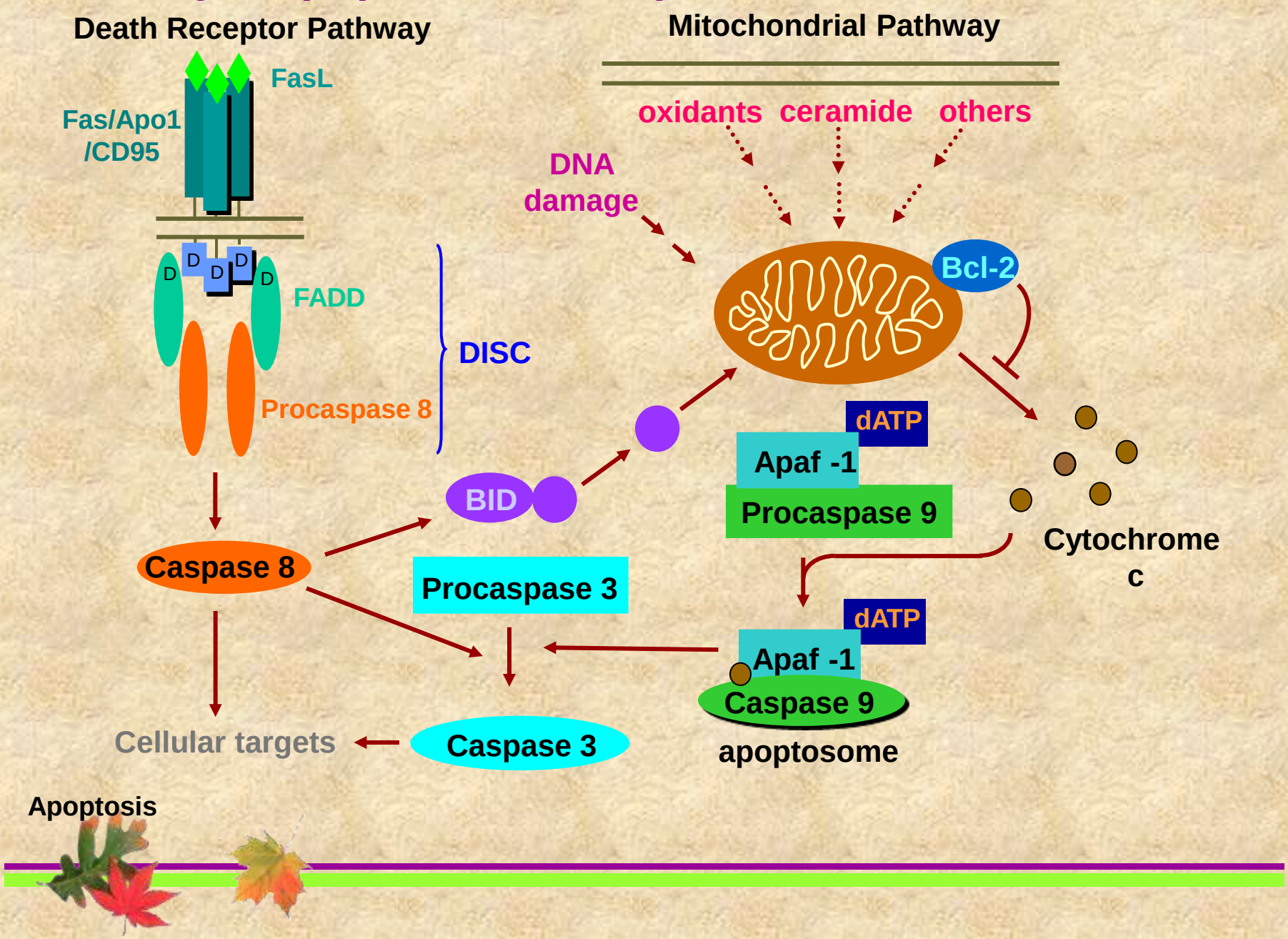
- **Metabolic oxidative stress appears to contribute to the selective sensitization of cancer vs. normal cells to 2DG and inhibitors of glutathione and thioredoxin metabolism in a variety of human cancer cell models.**

- **Inhibition of glucose and hydroperoxide metabolism may provide a biochemical target for selectively enhancing cytotoxicity and oxidative stress in cancer cells treated with conventional therapeutic agents (radiation and/or chemotherapy) that cause oxidative stress in clinical trials.**

Apoptosis - (Gr. "falling") a process seen in multicellular organisms, by which specific cells are killed and removed for the benefit of the organism.

Kerr, J.F.R., Wyllie, A.H. and Currie, A.R. 1972. *Br. J. Cancer* **26**:239.

Major Apoptotic Pathways in Mammalian Cells



Apoptotic Pathways Effectors and Modulators

- There are two major apoptotic pathways in mammalian cells.
  - The death receptor pathway, exemplified by activation of caspase-8.
  - The mitochondrial pathway is activated by most cellular stresses. A resulting signal or intracellular change causes the release of cytochrome c into the cytosol. Cytochrome catalyzes the activation of caspase-9.
- Initiator caspases, such as 8 and 9, activate effector caspases that cleave multiple cellular proteins. Caspases are characterized by an active site cysteine

Apoptosis and Cellular Redox Environment

- **Oxidants such as hydrogen peroxide can trigger apoptosis.**
- **Intracellular ROS generation by chemotherapeutics and ionizing radiation may be critical to induction of apoptosis by these agents.**
- **Depletion of glutathione pools occurs during apoptosis and GSH depletion can increase apoptosis, in some systems.**
- **Antioxidant enzymes and chemical antioxidants can protect against apoptosis.**
- **Oxidative damage to lipids and DNA is seen during apoptosis in some systems.**
- **ROS production can also attenuate apoptosis.**

Apoptosis Signaling and Cellular Redox Environment

Themes emerging from research on signaling pathways include:

- **The activity of multiple apoptosis regulators is modulated by the cellular redox environment. Examples include p53, NF-kappaB and apoptosis signal-regulating (ASK1) kinases.**
- **Downstream targets of these regulators function in the control of the cellular redox environment. Examples include differential regulation of oxidative stress-related genes during p53-induced apoptosis, regulation of the mitochondrial antioxidant protein (MnSOD) by NF-κB and phosphorylation of Bcl-2 downstream of the ASK1signaling pathway.**
- **Whether or not the cellular redox environment is maintained in balance, following an apoptotic signal, influences the decision of cell fate: life vs. death.**

Cytochrome c and Cellular Redox Environment

- **Cytochrome c in solution can act as an antioxidant and an ROS scavenging function for cytochrome c in the intermembrane space has been proposed..**
- **Release of cytochrome c into the cytosol from the mitochondrion interrupts the electron transport chain resulting in increased production of superoxide from the mitochondrion.**
- **Binding of cytochrome c to form the apoptosome and activate caspase-9 does not appear to depend on the ability of cytochrome c to transfer or accept electrons.**
- **However, the reduction state of cytochrome c may still be important because reduction and oxidation cause conformational changes that may be critical for cytochrome c binding to procaspase-9.**

Caspases and Cellular Redox Environment

- **The cysteine in the caspase active site is sensitive to oxidation or to thiol alkylation.**
- **Intracellular superoxide or hydrogen peroxide concentrations have been implicated in regulating caspase activity and modulating apoptosis.**
- **The cysteine sulfhydryl can also be S-nitrosylated, inactivating the caspase and providing a mechanism to reversibly modulate caspase activity.**
- **In some systems, caspases play a role in the life and death decision; therefore, their inactivation may promote functional cell survival.**

Oxidative Stress and Phagocytosis in Apoptosis

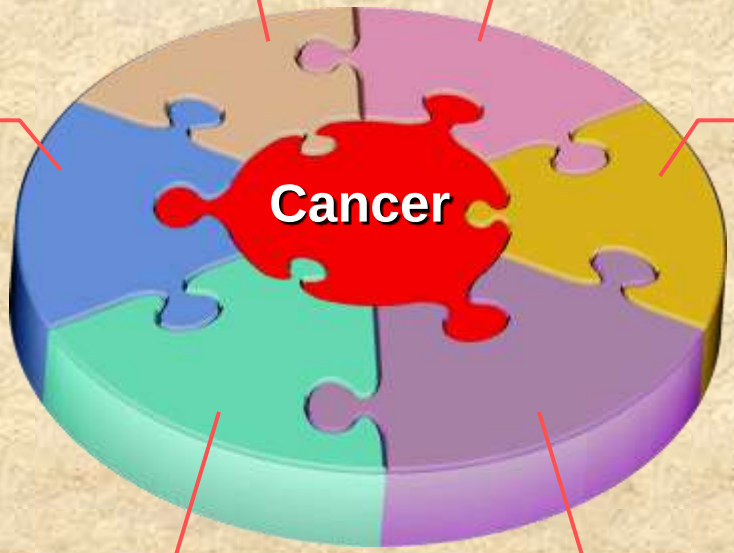
- ROS released by macrophages can induce apoptosis in target cells suggesting a role for phagocytes in cell population control.
- Phosphatidylserine is selectively oxidized in some cells in response to oxidants.
- Work by Kagan and colleagues has suggested that externalization of oxidized phosphatidylserine during apoptosis may increase phagocytosis of these cells.

Duffield, J.S. *et al.* 2000. *J. Immunol.* **164**:2110.
Fabisiak, J.P. *et al.* 1997. *Am. J. Physiol.* **272**:C675.

Apoptosis and Cancer

Self-sufficiency in Growth Signals

Insensitivity to Anti-growth Signals



Evading Apoptosis

Limitless Replicative Potential

Sustained Angiogenesis

Tissue Invasion and Metastasis

Hanahan and Weinberg have proposed that normal cells must acquire six phenotypes to become malignant. One of these traits is resistance to apoptosis. In this model, the chronological order and mechanism by which these phenotypes are acquired may differ in each tumor. Genomic instability provides the driving force for acquiring new phenotypes. Thus, mutations in genomic "caretaker" systems such as p53 may increase the rate at which other alterations occur.

Oxidative Stress and Cancer

Disorders Sharing Oxidative Stress and Cancer Proneness

- Fanconi anaemia
- Xeroderma pigmentosum
- Ataxia telangiectasia
- Bloom syndrome
- Down syndrome
- Cystic fibrosis

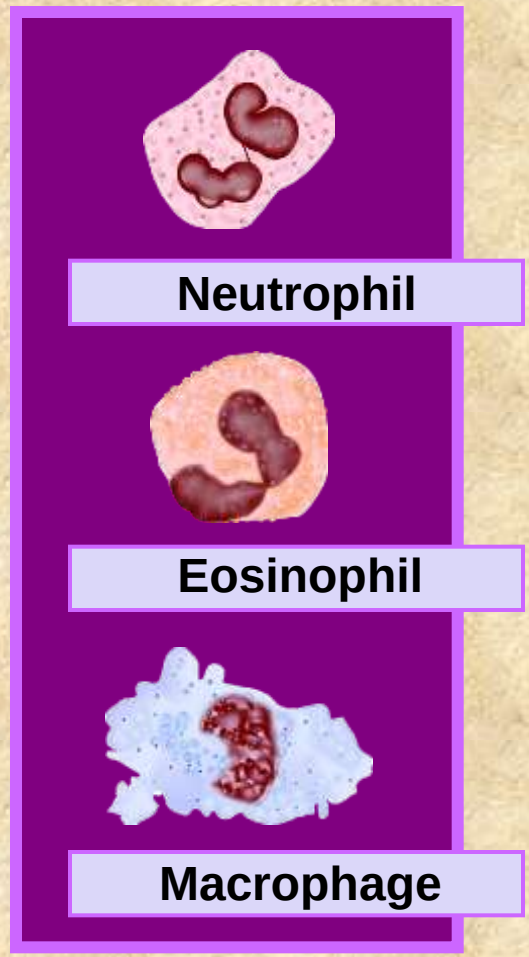
In each of these congenital disorders the cells show evidence of increased oxidative stress. Affected individuals show an increased incidence of cancer. Chromosomal instability is also a common feature of the first four disorders. Taken together these data suggest that the increased oxidative stress may contribute to development of genomic instability (a mutator phenotype) that is a hallmark of cancer cells.

Oxidative Stress and Cancer

Chronic Inflammation is Associated with Malignancy

Cancer	Inflammatory Condition
Lymphoma	HIV, Epstein-Barr and Herpes 8 virus, chronic host *vs.* graft disease
Colon	Ulcerative colitis
Lung	Asthma, chronic bronchitis, emphysema
Ovarian	Ovarian epithelial inflammation
Bladder	Eosinophilic cystitis, schistosomiasis
Pancreatic	Pancreatitis
Esophago-gastric junction carcinoma	Barret's esophagus
Gastric	*Heliobacter pylori* infection
Liver	Sarcoidosis, hepatitis B virus
Cervical	Human papilloma virus
Mesothelioma	Asbestos fiber exposure

Oxidative Stress and Cancer



Oxidants Released by Inflammatory Cells

$O_2^{\bullet -}$

H_2O_2

HOCl

$^{\bullet}NO$

$ONOO^-$

$^{\bullet}NO_2$

$HO^{\bullet}$

$^1O_2$

The continuous production of oxidants at the site of chronic inflammation may cause cancer.

Oxidative Stress and Cancer Therapy

Anti-Cancer Agents

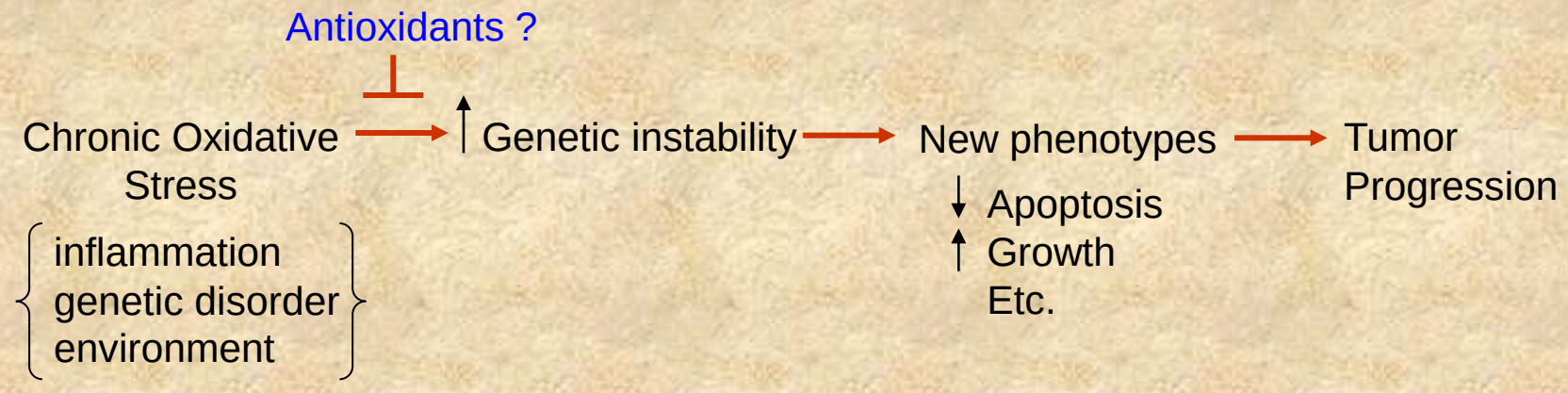
Doxorubicin
Daunorubicin
Mitomycin C
Etoposide
Cisplatin
Arsenic trioxide
Ionizing radiation
Photodynamic therapy

These anti-cancer agents depend exclusively or in part on the production of reactive oxygen species for cytotoxicity.

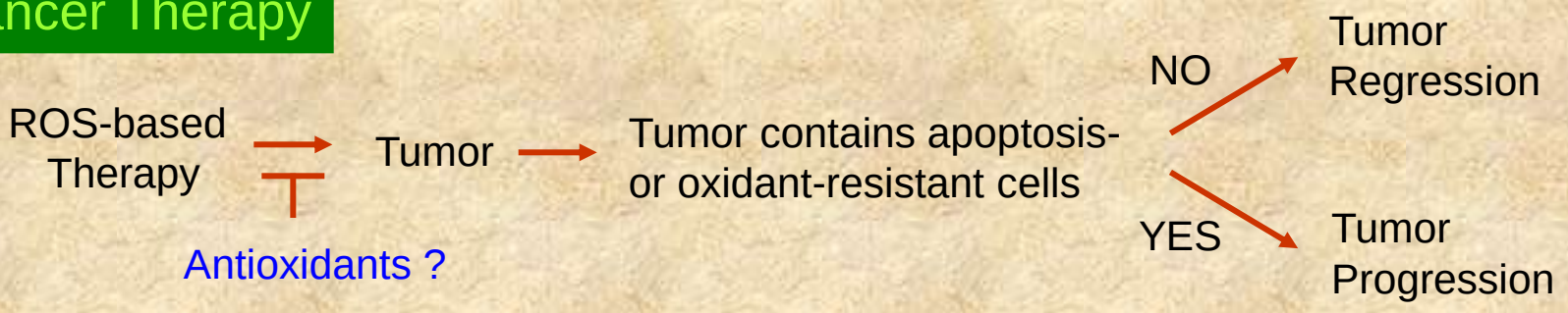
Sensitivity of tumor cells to oxidative stress and/or apoptosis may affect treatment success.

Oxidative Stress, Apoptosis and Cancer: Some Models

Carcinogenesis



Cancer Therapy




You don't have to be
great to start, but
you have to start
to be great.
-Zig Ziglar
WWW.EASYFATBURN.NET

Mechanisms of Disease

INFLAMMATION

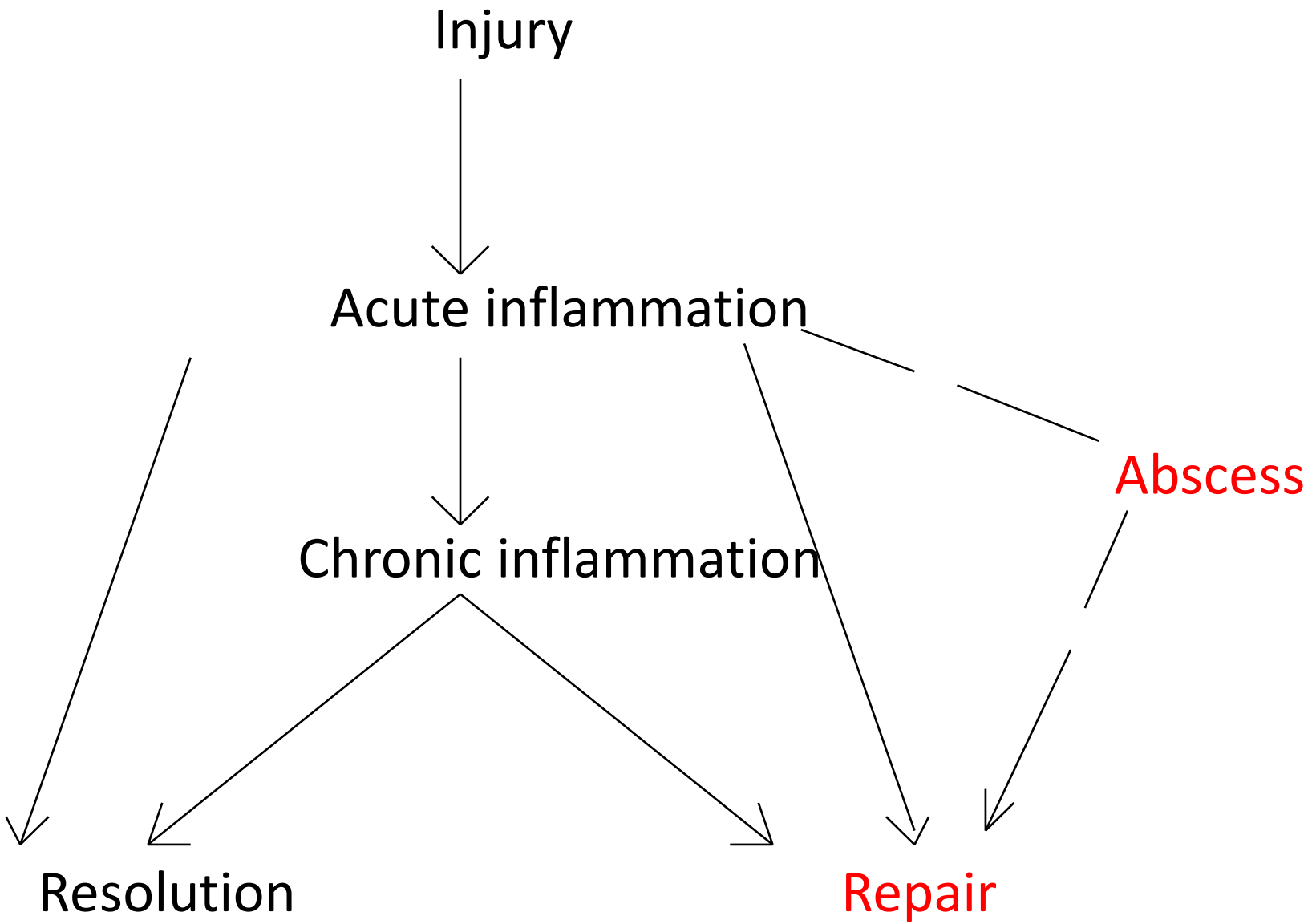
Dr. AJWADASSUMAIDAEE Ph. D

قال الامام علي (عليه السلام):

أكرم ضيفك وان كان حقيراً

وقم على مجلسك

لأبيك ومعلمك وان كنت اميراً .


Injury
Acute inflammation
Chronic inflammation
Abscess
Resolution
Repair

- **“Inflame” – to set fire.**
- **Inflammation is “A dynamic response of vascularised tissue to injury.”**
- **It is a protective response.**
- **It serves to bring defense & healing mechanisms to the site of injury.**

What is Inflammation?

- **A reaction of a living tissue & its micro-circulation to a pathogenic insult.**
- **A defense mechanism for survival .**

- **Reaction of tissues to injury, characterized clinically by: heat, swelling, redness, pain, and loss of function.**
- **Pathologically by : vasoconstriction followed by vasodilatation, stasis, hyperemia, accumulation of leukocytes, exudation of fluid, and deposition of fibrin.**

How Does It Occur?

- **The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.**

- **Tissue injury or death ---> Release mediators**

Etiologies

- **Microbial infections: bacterial, viral, fungal, etc.**
- **Physical agents: burns, trauma--like cuts, radiation**
- **Chemicals: drugs, toxins, or caustic substances like battery acid.**
- **Immunologic reactions: rheumatoid arthritis.**

Cardinal Signs of Inflammation

- **Redness : Hyperaemia.**
- **Warm : Hyperaemia.**
- **Pain : Nerve, Chemical mediators.**
- **Swelling : Exudation**
- **Loss of Function: Pain**

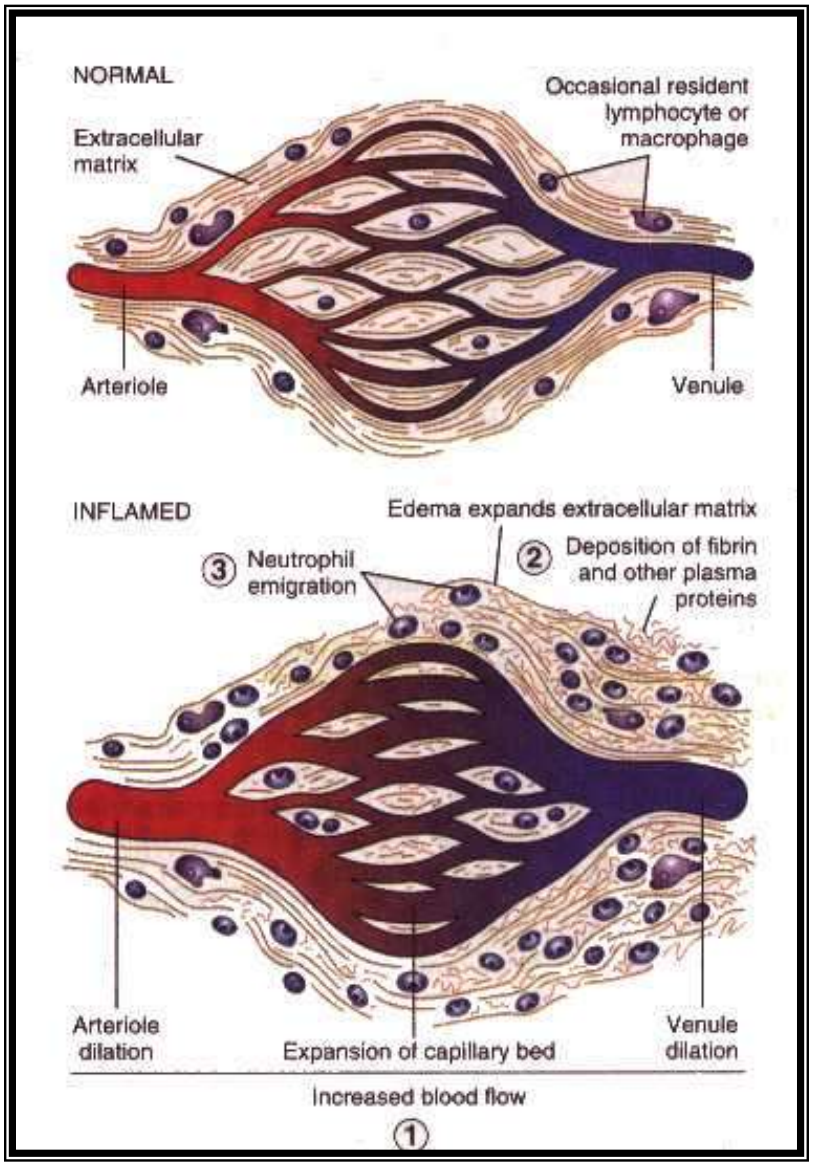
- **Time course**
  - **Acute inflammation: Less than 48 hours**
  - **Chronic inflammation: Greater than 48 hours (weeks, months, years)**
- **Cell type**
  - **Acute inflammation: Neutrophils**
  - **Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).**

Pathogenesis:

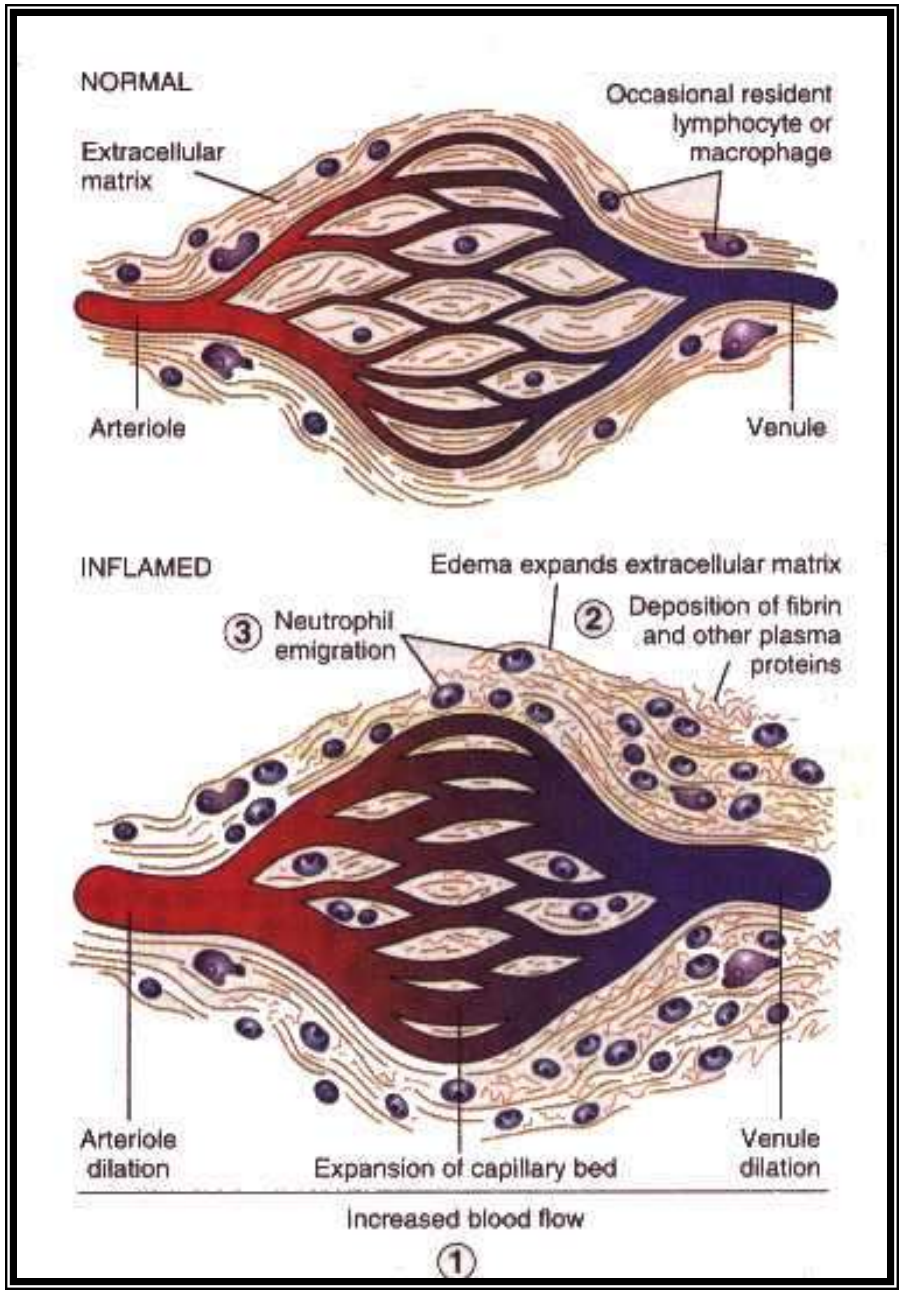
Three main processes occur at the site of inflammation, due to the release of chemical mediators :

- **Increased blood flow (redness and warmth).**
- **Increased vascular permeability (swelling, pain & loss of function).**
- **Leukocytic Infiltration.**

Mechanism of Inflammation



1. Vaso dilatation
2. Exudation - Edema
3. Emigration of cells
4. Chemotaxis



The major local manifestations of acute inflammation, compared to normal.

(1) Vascular dilation and increased blood flow (causing erythema and warmth).

(2) Extravasation and deposition of plasma fluid and proteins (edema).

(3) leukocyte emigration and accumulation in the site of injury.

Changes in vascular flow (hemodynamic changes)

- Slowing of the circulation
  - outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood.
- Leukocyte margination
  - Neutrophi become oriented at the periphery of vessels and start to stick.

Lymphatics in inflammation:

- **Lymphatics are responsible for draining *edema*.**

<u>Edema:</u> An excess of fluid in the interstitial tissue or serous cavities; either a *transudate* or an *exudate*

<u>Transudate</u>:

An ultrafiltrate of blood plasma

permeability of endothelium is usually normal.

low protein content (mostly albumin)

Exudate:

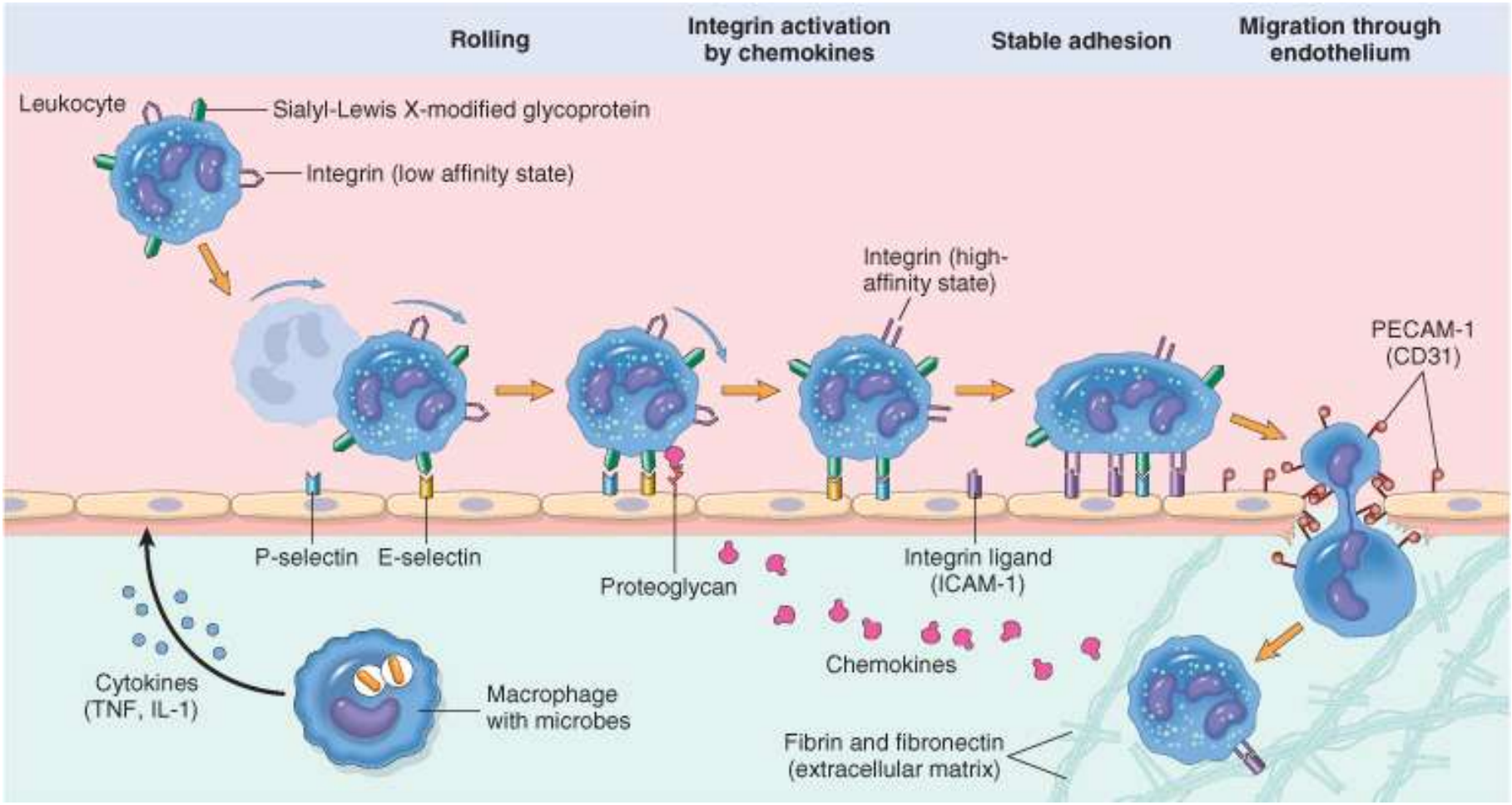
- **A filtrate of blood plasma mixed with inflammatory cells and cellular debris.**
  - **– permeability of endothelium is usually altered**
  - **– high protein content.**

Pus:

A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.

Leukocyte exudation

- **Divided into 4 steps**
  - Margination, rolling, and adhesion to endothelium
  - Diapedesis (trans-migration across the endothelium)
  - Migration toward a chemotactic stimuli from the source of tissue injury.
  - Phagocytosis


Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Sialyl-Lewis X-modified glycoprotein
Integrin (low affinity state)
Integrin (high-affinity state)
PECAM-1 (CD31)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
Chemokines
Cytokines (TNF, IL-1)
Macrophage with microbes
Fibrin and fibronectin (extracellular matrix)

Phagocytosis

- 3 distinct steps
  - Recognition and attachment
  - Engulfment
  - Killing or degradation

PHAGOCYTOSIS

Recognition and attachment

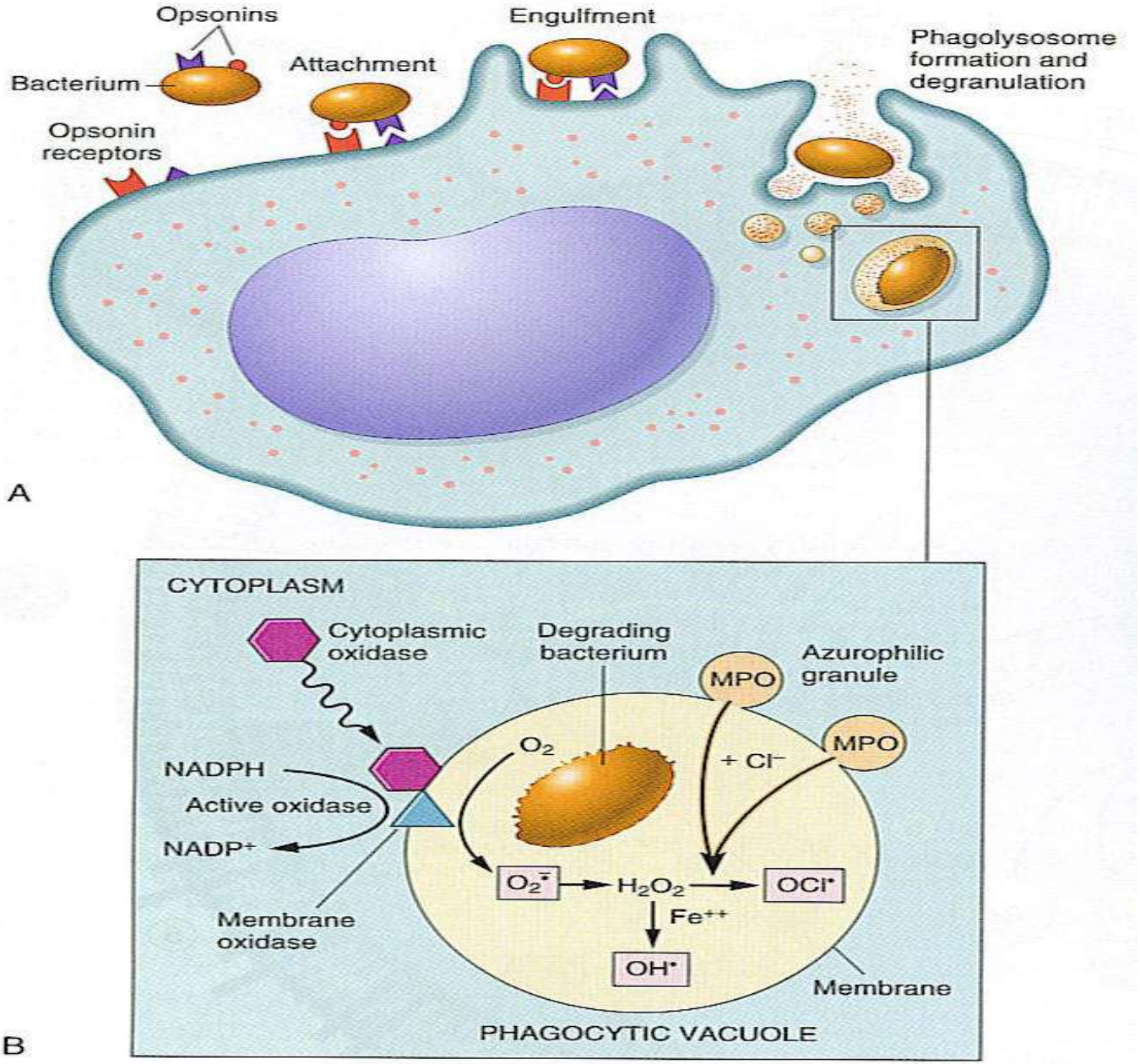
Foreign objects coated with opsonins IgG and C3b which attach to receptors on polymorph surface.

Engulfment

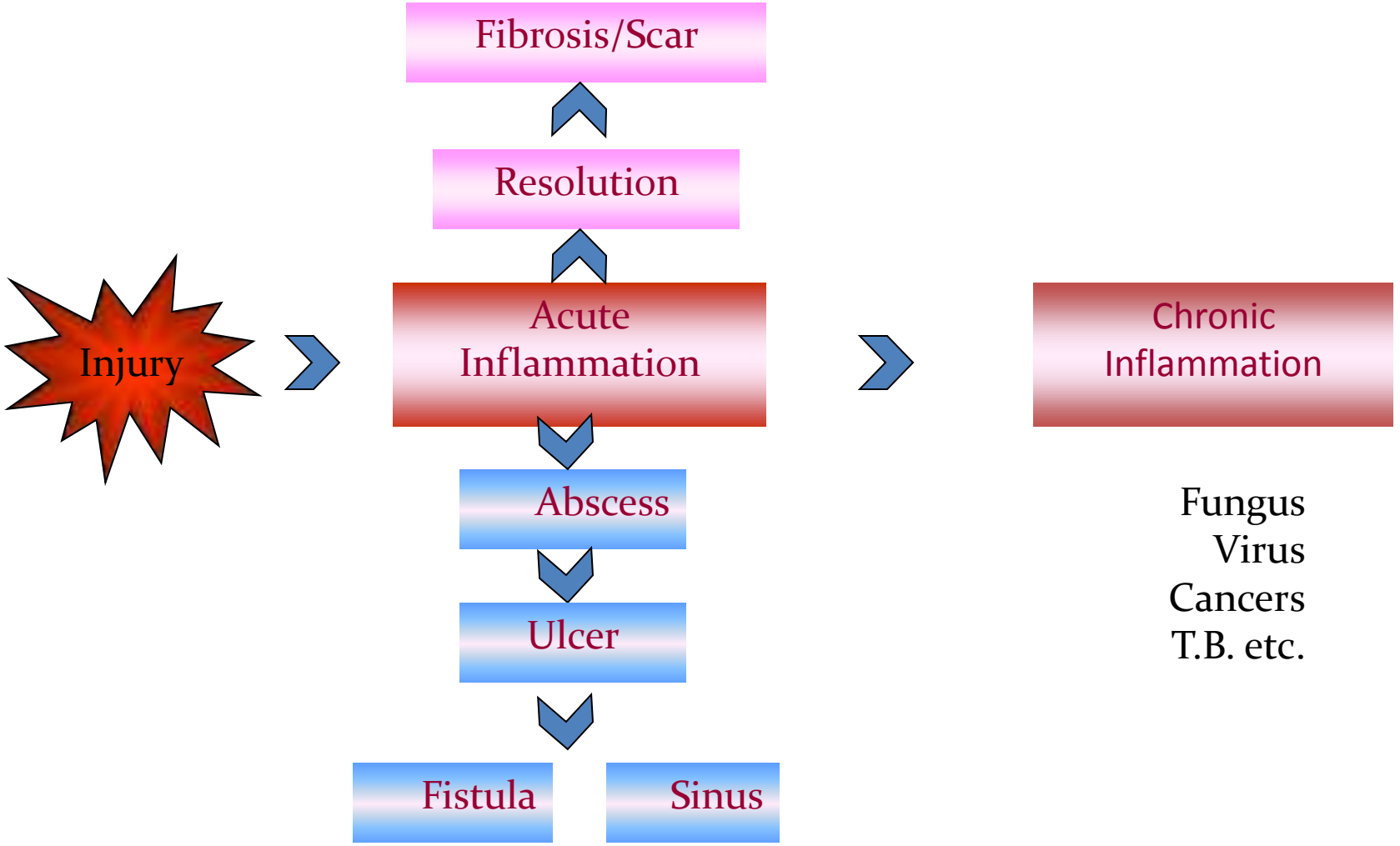
Cell membrane fuses around an object: at the same time lysosomes empty into the vacuole, often before vacuole has time to seal - this gives rise to 'regurgitation during feeding' and enzymatic damage to surrounding tissue.

Killing or degradation

H_2O_2, hypohalous acid (HOC1) produced by myeloperoxidase and superoxides kill bacteria. Lysozyme digests them.


Opsonins
Bacterium
Opsonin receptors
Attachment
Engulfment
Phagolysosome formation and degranulation
A
CYTOPLASM
Cytoplasmic oxidase
Degrading bacterium
Azurophilic granule
MPO
MPO
NADPH
Active oxidase
NADP+
O2
+ Cl−
O2−
H2O2
OCl•
Fe++
OH•
Membrane oxidase
Membrane
PHAGOCYTIC VACUOLE
B

Inflammation Outcome



Chemical Mediators:

Chemical substances synthesised or released and mediate the changes in inflammation.

- ***Histamine*** **by mast cells - vasodilatation.**
- ***Prostaglandins*** **– Cause pain & fever.**
- ***Bradykinin*** **- Causes pain.**

Chemical mediators of inflammation

- **Vasoactive amines**
  - **Histamine**
  - **Serotonin (5-HT)**
- **Neuropeptides**
  - **Substance P**
- **Plasma proteases and the complement system**
  - **Action of Hageman factor**
- **Arachidonic acid metabolites**
  - **Prostaglandins**
  - **Leukotrienes**
  - **Lipoxins**
- **Cytokines**
  - **IL-1, TNF etc.**
- **Chemokines (CXC and CC)**
- **Nitric oxide and oxygen-derived free radicals**

Chemical mediators of inflammation

- ***PREFORMED***

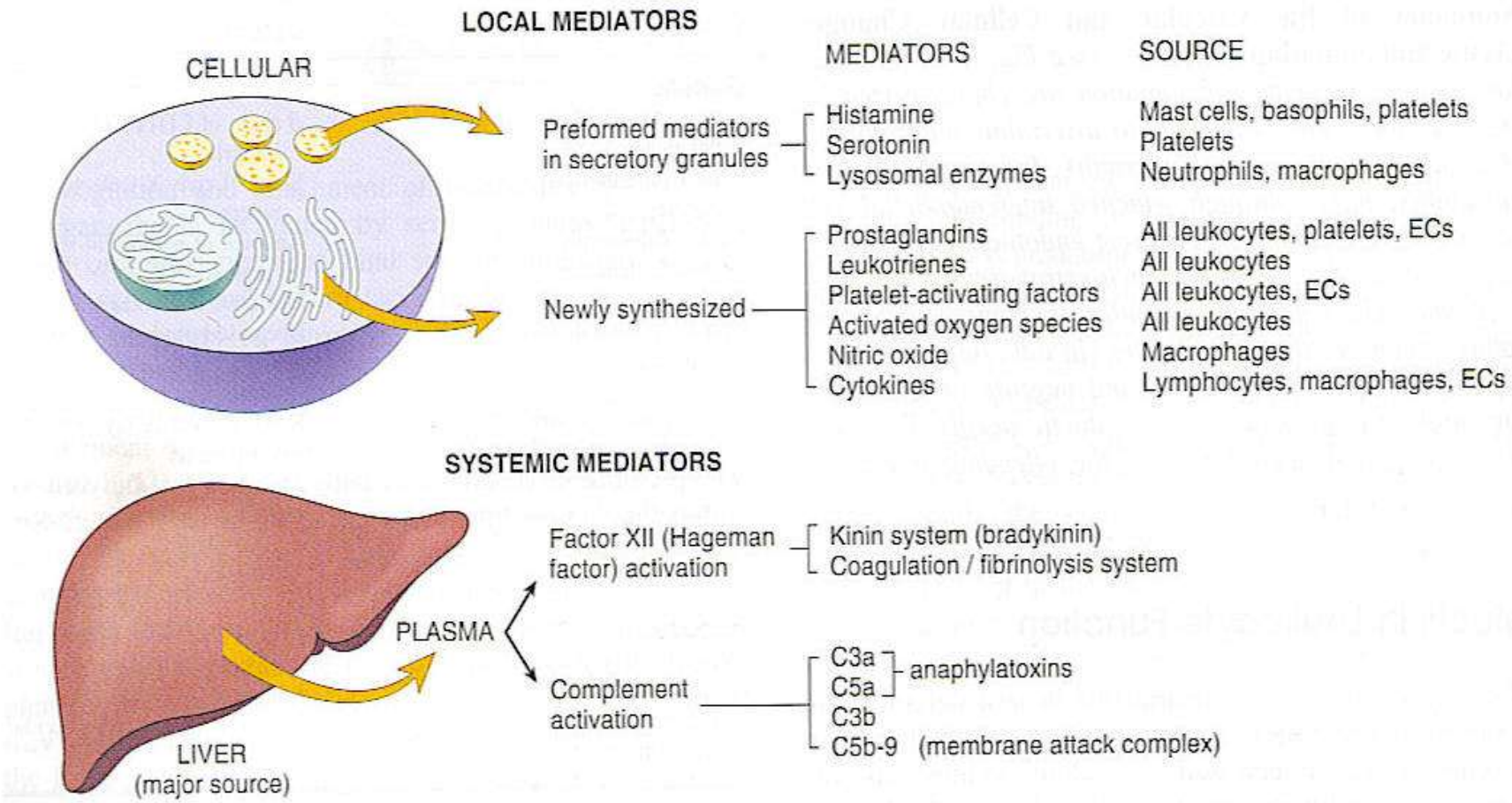
Histamine, Serotonin

- ***NEWLY SYNTHESISED***

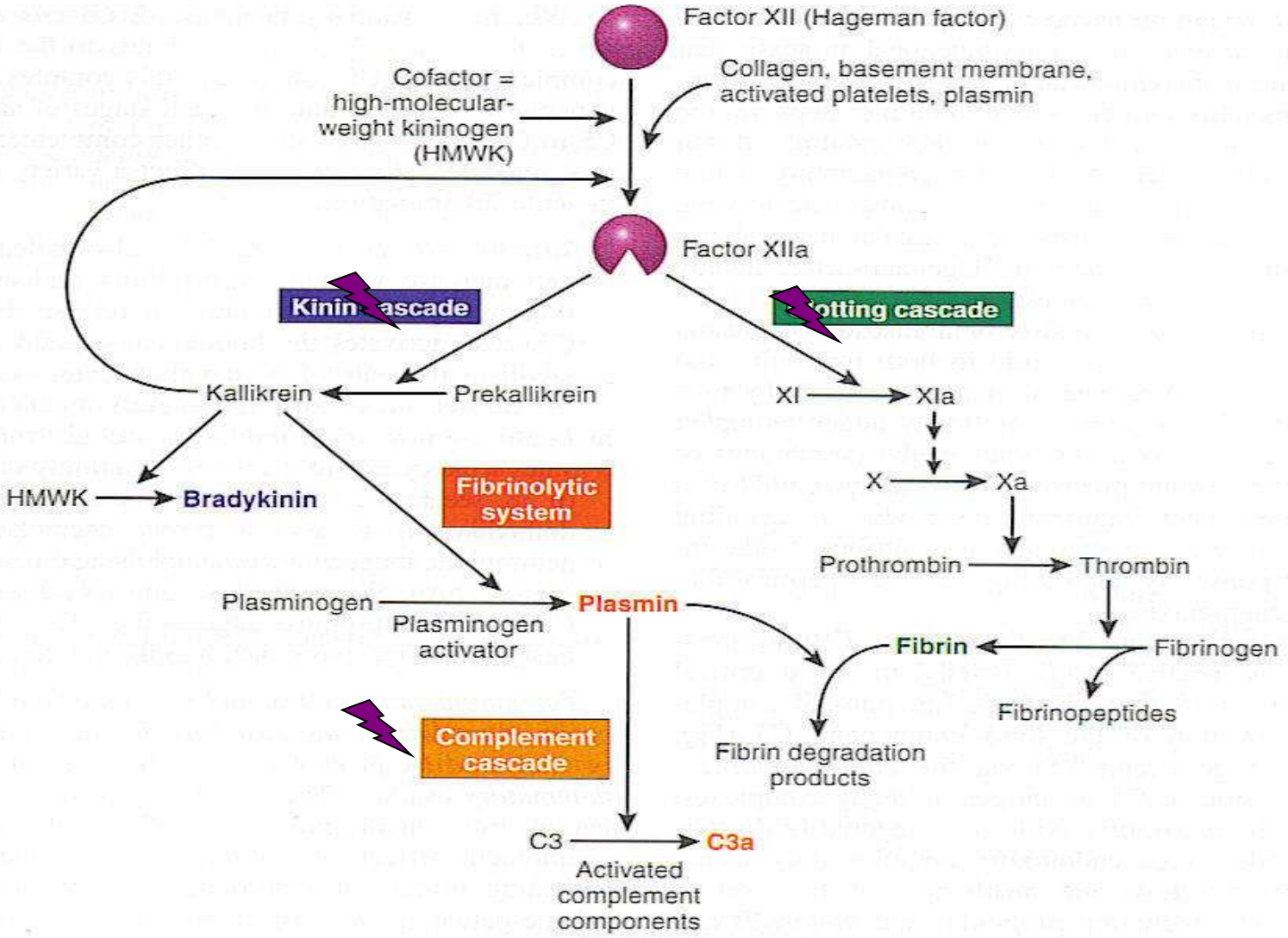
Prostaglandins
Leucotrienes
Platelet activating factor
Cytokines
Nitric oxide

- ***LOCAL AND SYSTEMIC***

Chemical mediators of inflammation (local and systemic)



Plasma proteases



Effects of mediators of inflammation

Vasodilation:

Prostaglandins, NO

Increased vascular permeability:

Histamine, serotonin, C3a, C5a, bradykinin,
Leukotrienes C4, D4, E4, platelet activating factor

Chemotaxis, leukocyte activation:

C5a, leukotriene B4, bacterial products, chemokines (IL-8)

Fever:

IL-1, IL-6, TNF, prostaglandins

Pain:

Prostaglandins, bradykinin

Tissue damage:

Neutrophil and macrophage lysosomal enzymes, oxygen metabolites
NO

Morphologic types of acute inflammation

- **Exudative or catarrhal Inflammation: excess fluid. TB lung.**
- **Fibrinous – pneumonia – fibrin**
- **Membranous (fibrino-necrotic) inflammation**
- **Suppuration/Purulent – Bacterial - neutrophils**

- **Serous – excess clear fluid – Heart, lung**
- **Allergic inflammation**
- **Haemorrhagic – b.v. damage - anthrax.**
- **Necrotising inflammation.**

Acute inflammation has one of four outcomes:

- **Abscess formation**
- **Progression to chronic inflammation**
- **Resolution--tissue goes back to normal**
- **Repair--healing by scarring or fibrosis**

Abscess formation:

- **"A localized collection of pus (suppurative inflammation) appearing in an acute or chronic infection, and associated with tissue destruction, and swelling.**

- **Site: skin, subcutaneous tissue, internal organs like brain, lung, liver, kidney,…….**
- **Pathogenesis: the necrotic tissue is surrounded by pyogenic membrane, which is formed by fibrin and help in localize the infection.**

Carbuncle

- It is an extensive form of abscess in which pus is present in multiple loci open at the surface by sinuses.

- Occur in the back of the neck and the scalp.

Furuncle or boil

- It is a small abscess related to hair follicles or sebaceous glands, could be multiple furunclosis.

Cellulitis

- **It is an acute diffuse suppurative inflammation caused by streptococci, which secrete hyaluronidase & streptokinase enzymes that dissolve the ground substances and facilitate the spread of infection.**
- **Sites:**
  - **Areolar tissue; orbit, pelvis, …**
  - **Subcutaneous tissue**

Features of acute inflammation

- Main clinical signs:
  - RUBOR
  - TUMOR
  - CALOR
  - DOLOR

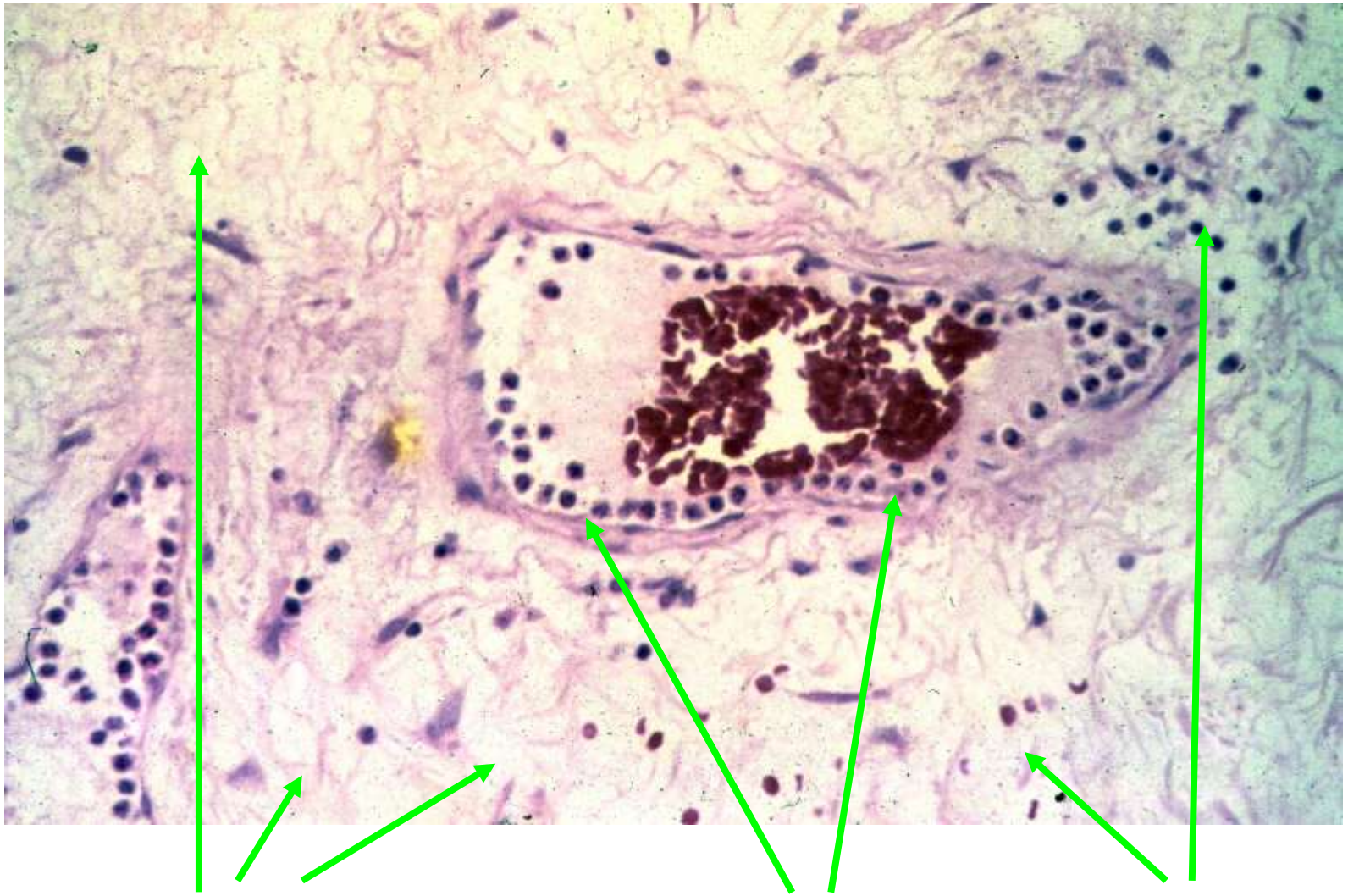
    & Functio laesa

- Also described in terms of the ‘triple response’: brief blanching, followed by REDDENING, FLARE and WHEAL.

Microscopic changes

- Dilatation of vessels
- Sludging of rbcs
- Fluid leaks into interstitium (Implies increased permeability of vessels) (**not** to water but to **protein)**.

- Cells move into interstitium


Tissue oedema
Neutrophil margination …. And emigration

PART 1: THE FLUID

- **A TRANSUDATE has a low protein content, usually caused by alterations in hydrostatic or oncotic pressure. Implies a hydrostatic (pressure) problem.**

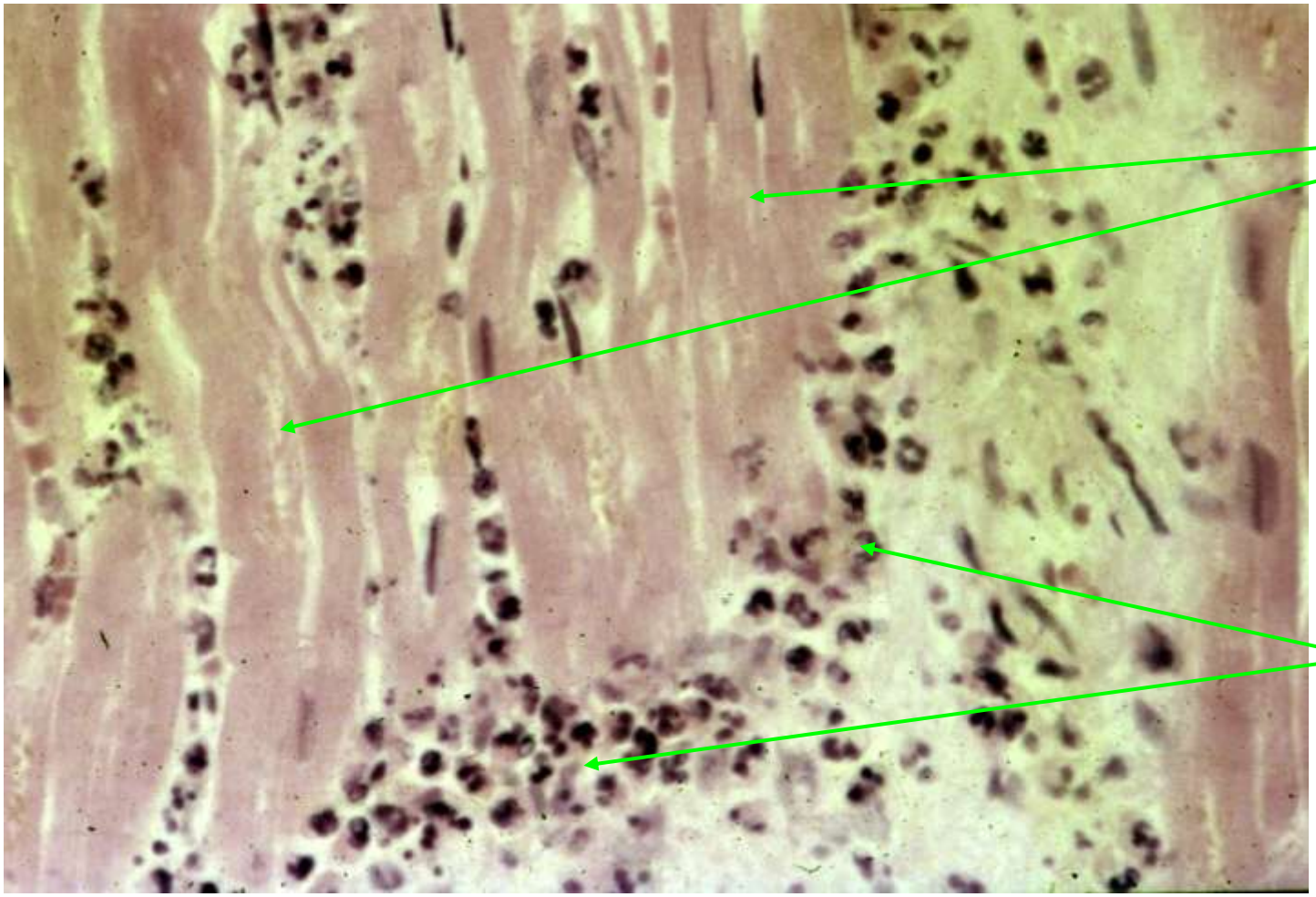
- **An EXUDATE has a high protein content, caused by increased vascular permeability.**
  Implies an inflammatory process.

PART 2: THE CELLS

White blood cells MARGINATION and EMIGRATION.

Implies binding to endothelium then directional ameboid movement through vessel wall towards injured area (mediated by chemotaxis).

Myocardial infarct - neutrophil infiltration



How do these changes combat injury?

- **Vasodilatation:**
  - **Increases delivery, increases temperature, removes toxins.**
- **Exudate:**
  - **Delivers immunoglobulins etc., dilutes toxins, delivers fibrinogen, increases lymphatic drainage.**
- **Increased lymphatic drainage:**
  - **Delivers bugs to phagocytes and antigens to immune system.**
- **Cells:**
  - **Removes pathogenic organisms, necrotic debris etc.**
- **Pain and loss of function:**
  - **Enforces rest, reduces chance of further traumatic damage.**
- **How is all this brought about?**

What are the mechanisms? CHEMICAL MEDIATORS.

Three phases:

1) Immediate early response ($^1/_2$ hr):

- **HISTAMINE**
  - **Released from mast cells, basophils and platelets, in response to many stimuli: physical damage, immunologic reactions, C3a, C5a, IL1, factors from neutrophils and platelets**
  - **Effects: Largely vascular. Pain. Not chemotactic.**

2) Immediate sustained response:

(Not always seen. Due to direct damage to endothelial cells.)

3) Delayed response: (Peaks about 3hrs):

Many and varied chemical mediators, interlinked and of varying importance
Incompletely understood.

IMPORTANT because of possibility of therapeutic intervention

Chemical mediators of acute inflammation

- **Proteases**
  - **Kinins (Bradykinin and Kallekrein)**

The kinin–kallikrein system or simply kinin system consists of blood proteins that play a role in inflammation, blood pressure control, coagulation and pain. Its important mediators bradykinin and kallidin are vasodilators and act on many cell types.

- **Contents**
  - **Complement system**
  - **Coagulation / fibrinolytic system**
- **Prostaglandins / Leukotrienes**
  - **Numerous metabolites of arachidonic acid**
  - **Synthesis blocked by NSAIDs, e.g. aspirin**
- **Cytokines / chemokines**
  - **Many and varied! Interleukins, PAF, TNF alpha, PDGF.**

Other inflammatory mediators:

- **PRODUCTS FROM PLATELETS**
  - **5-hydroxy tryptamine, histamine, ADP...**
  - **Platelet-derived growth factor, coagulation proteins...**
- **PRODUCTS FROM NEUTROPHILS**
  - **Lysosomal constituents**
  - **Products released on neutrophil death**
- **PRODUCTS FROM ENDOTHELIUM**
  - **PGI_2 (prostacyclin)**

  It is a recently discovered prostaglandin that affects many organ systems. It is both a potent inhibitor of platelet aggregation and a powerful vasodilator. The recent demonstration that it is the main prostaglandin synthesized by the blood vessel wall suggests that it may play an important role in limiting platelet-mediated thrombosis
  - **Nitric oxide (NO)**
  - **Endothelin**
- **Plasminogen activators / inhibitors**

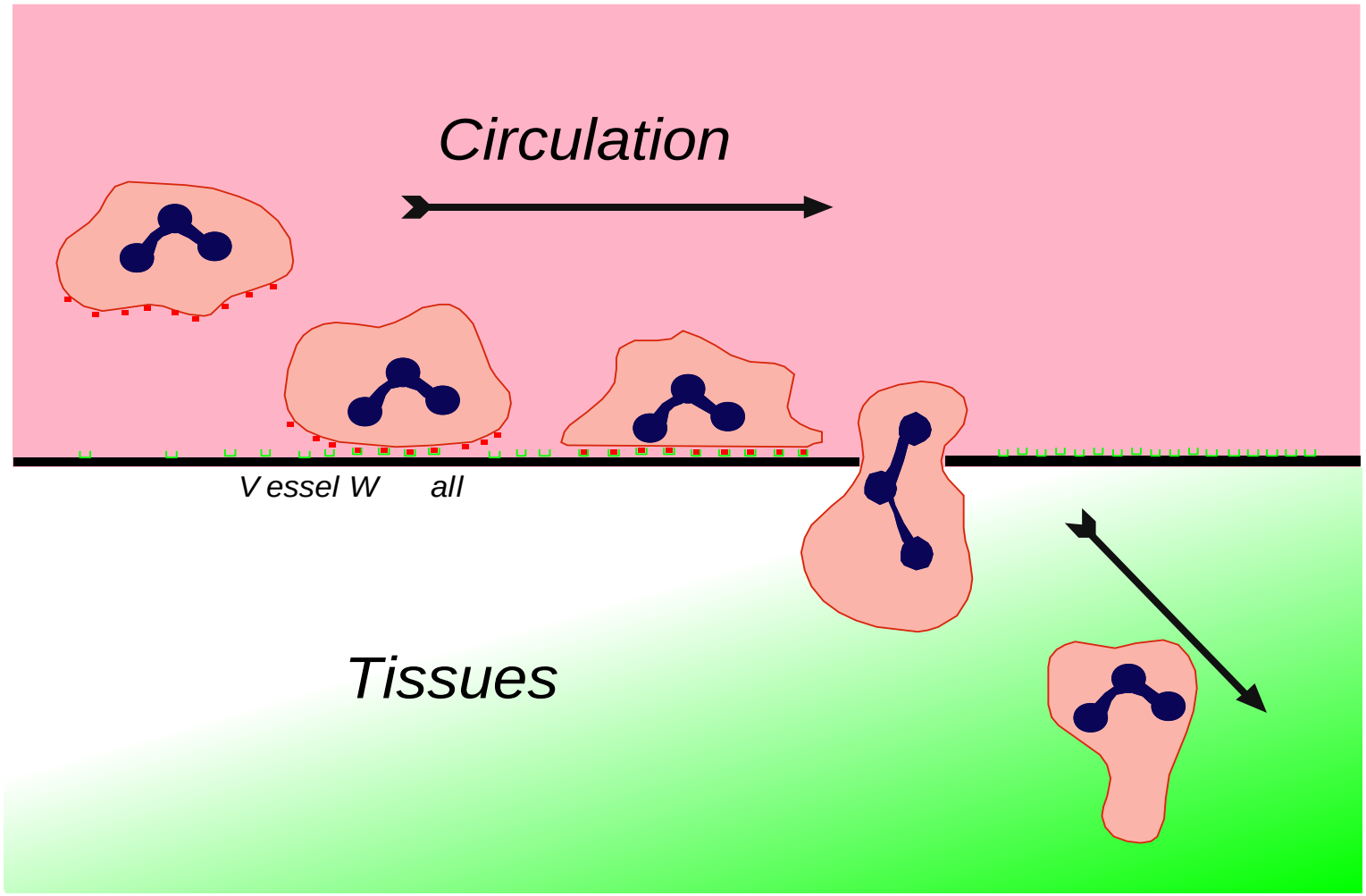
- **OXYGEN DERIVED FREE RADICALS**
  - **Endothelial damage, inactivation of antiproteases, injury to other cells.**

THE PHAGOCYTES

- **Margination**
  - **Endothelium-phagocyte interactions; adhesion molecules.**
    - **Histamine & thrombin activate P-selectin on endothelium (minutes)**

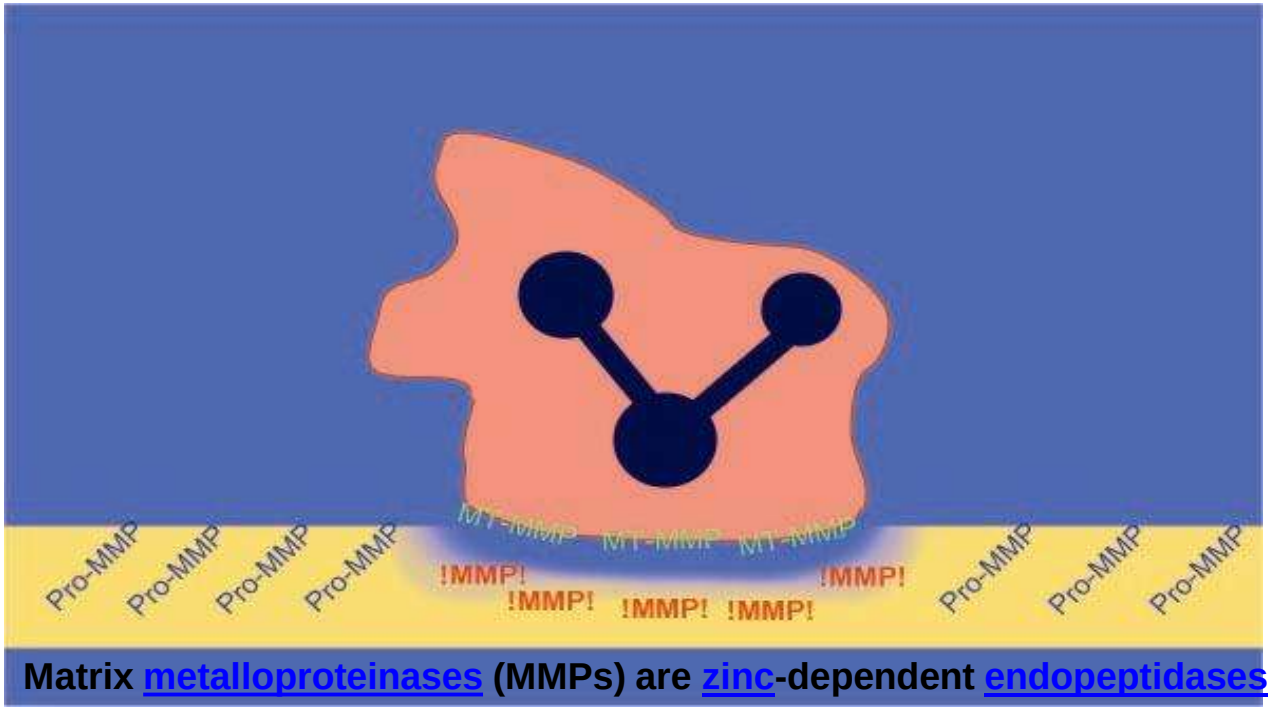
    P-selectin functions as a cell adhesion molecule (CAM) on the surfaces of activated endothelial cells, which line the inner surface of blood vessels, and activated platelets. In unactivated endothelial cells, it is stored in granules called Weibel-Palade bodies, and α-granules in unactivated platelets.
    - **IL-1, TNF activate E selectin(endothelial-leukocyte adhesion molecule 1 (ELAM-1)) on endothelium (hours)**
    - **ICAM-1 (Intercellular Adhesion Molecule 1) also known as CD54 (Cluster of Differentiation 54) and VCAM-1 (Vascular cell adhesion protein 1)also known as vascular cell adhesion molecule 1 (VCAM-1) or cluster of differentiation 106 (CD106) also upregulated on endothelium**
    - **LFA-1, Lymphocyte function-associated antigen 1, is found on all T-cells and also on B-cells, macrophages and neutrophils and is involved in recruitment to the site of infection, are activated on neutrophils**

Margination, emigration, chemotaxis



How do neutrophils escape from vessels?

- **Relaxation of inter-endothelial cell junctions**
- **Digestion of vascular basement membrane by Matrix metalloproteinases (MMPs) which are zinc-dependent endopeptidases**
- **Amoeboid Movement**

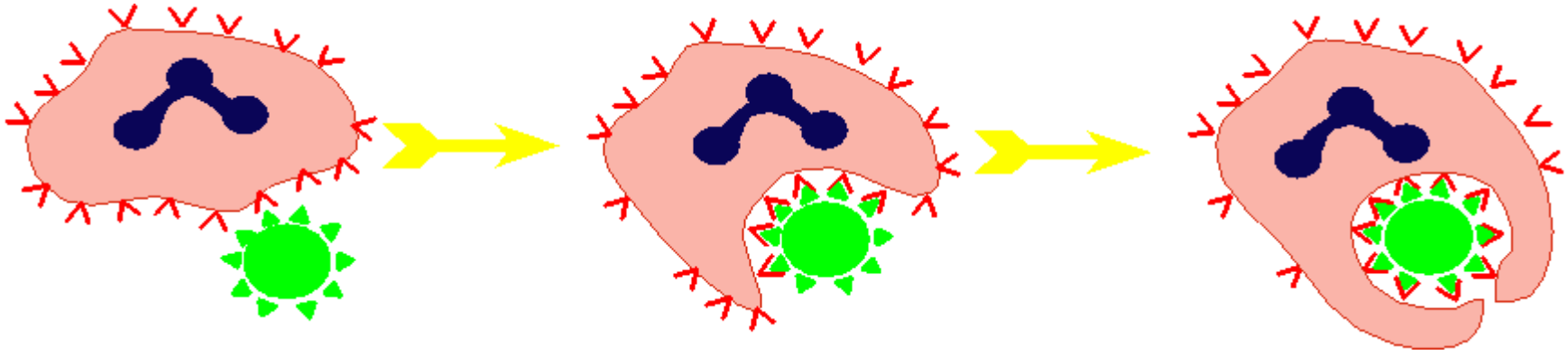


Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases

How do neutrophils move? Diapedesis and Emigration; Chemotaxis.

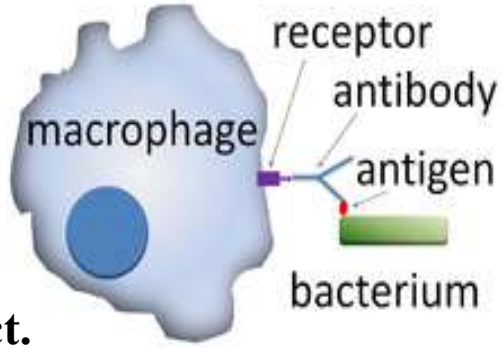
- **Chemotaxis implies detection of concentration gradients**
- **Receptor-ligand binding**
- **Phospholipase C activation**
- **Local release of free intracellular Ca+**
- **Rearrangement of cytoskeleton**
- **Production of pseudopod**

What do neutrophils do?
Phagocytosis



- **Contact, Recognition, Internalisation.**
- **Opsonins: e.g. Fc and C3b receptors**

Action of opsonins; a phagocytic cell recognises the opsonin on the surface of an antigen



- **Cytoskeletal changes (as with chemotaxis); 'zipper' effect.** ***Define???***

What do neutrophils do?
Microbial killing

- **Phagosomes fuse with lysosomes to produce secondary lysosomes.**

  Mechanisms:

- **O_2 dependent**
  - **NADPH oxidase activated; produces superoxide ion. This converts to hydrogen peroxide.**
  - **H_2O_2-Myeloperoxidase-halide system: produces $HOCl^{\cdot}$ Hypochlorous acid (i.e. bleach!)**

  - **Myeloperoxidase independent:**
  - **Uses superoxide and hydroxyl radicals. Less efficient.**

O_2 independent killing mechanisms

- **Lysozyme & hydrolases**
- **Lactoferrin- Lactoferrin is an iron-binding glycoprotein that belongs to the transferrin family. It is present in breast milk, in epithelial secretions, and in the secondary granules of neutrophils**
- **Bactericidal Permeability Increasing Protein (BPIP)**
- **Eosinophil Cationic Protein (ECP) also known as ribonuclease 3 is a basic protein located in the eosinophil primary matrix ECP is released during degranulation of eosinophils. This protein is related to inflammation and asthma because in these cases, there are increased levels of ECP in the body**
- **Major Basic Protein (MBP; Eosinophils)**

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

- **Fever**
  - 'Endogenous pyrogens' produced: IL1 and TNFα
  - IL1 - prostaglandins in hypothalamus
    hence aspirin etc. reduce fever
- **Leukocytosis**
  - IL1 and TNFα produce an accelerated release from marrow
  - Macrophages, T lymphocytes produce colony-stimulating factors
  - Bacterial infections - neutrophils, viral - lymphocytes
  - Clinically useful

SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

- **Acute phase response**
  - Decreased appetite, altered sleep patterns and changes in plasma concentrations of:
- **Acute phase proteins**:
  - C-reactive protein (CRP) (Clinically useful)
  - α_1 antitrypsin
  - Haptoglobin
  - Fibrinogen
  - Serum amyloid A protein

ACUTE INFLAMMATION: RESOLUTION.

- **What may happen after the development of acute inflammation?**

1) Complete resolution.
2) Continued acute inflammation with chronic inflammation; chronic suppuration.
3) Chronic inflammation and fibrous repair, probably with tissue regeneration.
4) Death.

RESOLUTION OF ACUTE INFLAMMATION

- Morphology

  Changes gradually reverse.

  Vascular changes stop:

  – neutrophils no longer marginate
  – vessel permeability returns to normal
  – vessel calibre returns to normal.

RESOLUTION OF ACUTE INFLAMMATION

- Therefore:
  - Exudate drains to lymphatics
  - Fibrin is degraded by plasmin and other proteases
  - Neutrophils die, break up and are carried away or are phagocytosed
  - Damaged tissue *might* be able to regenerate.

  - **Note that if tissue architecture has been destroyed, complete resolution is not possible.**

MECHANISMS OF RESOLUTION

- All mediators of acute inflammation have short half-lives.
- May be inactivated by degradation, e.g. heparinase
- Inhibitors may bind, e.g. various anti-proteases
- May be unstable e.g. some arachidonic acid derivatives
- May be diluted in the exudate, e.g. fibrin degradation products.
- Specific inhibitors of acute inflammatory changes
  - e.g. lipoxins, endothelin...

Types of acute inflammation

- **Suppurative inflammation**
- **Non-supurative inflammation**

  1-catarrhal inflammation

  2-membranous inflammation

  3-sero-fibrinous inflammation

  4-fibrinous inflammation

  5-serous inflammation

  6-haemorrhagic inflammation

  7-necrotizing inflammation

  8-allergic inflammation

Suppurative inflammation

- Sever acute inflammation characterized by pus formation
- Pus :

Pathogenesis of pus formation:

-pyogenic microorganisms cause marked tissue necrosis by it's toxins and exert strong chemotaxis

-many leucocytes are killed during their struggle witht the bacteria

-the dead leucocytes release proteolytic enzymes which cause rapid liquefction of the nercotic tissue and the fibrin threads.

- the resulting fluid material mix with the other inflammatory process forming the pus

Types of suppurative inflammation

- Localized

-abscess

-furuncle

-carbuncle

- Diffuse

-cellulitis

- suppurative appendcitis

-suppurative peritonitis

abscess

- a localizes suppurative inflammation resulting in the formation of an irregular cavity containing pus

- Commonly abscess occurs in the subcutaneous tissue,lungs ,brain,liver..etc

furuncle

- Small abscess related to a hair follicle or sebaceouos gland caused by staphylococcus aureus

- Common sites are face and back of the neck in male and axilla in females

carbuncle

- A type of localized suppurative forming multiple communicating suppurative foci in the skin and subcutaneous fat discharging pus through sevral openings

- The most common sites are the area where the skin and subcutaneous tissue are thick and tough as the back of the neck ,scalp and buttocks

diffuse

- Cellulitis :

  -acute diffuse suppurative inflamation

  - commonly found in loose connective tissue as subcutanous tissue ,facial planes,areolar tissue of the orbit ,pelvis ,scrotum and wall of the appendix.

Non-suppurative inflammation

- **Catarrhal inflammation**

-mild acute inflamation of the mucouse membranes charactrized by excess mucus secration

Gross picture:

- early the mucous membrane appears red,hot ,swollen and dry

- the excess watery mucoid discharge appears composed of inflammatory fluid exudate ,mucus small number of polymorphonuclear leucocyts and sheded epethelial cells

Non-suppurative inflammation

- **Microscopic picture**

-mucosal cells appear swollen and rounded due to mucus accumulation

- the submucosa shows hyperaemia ,inflammatory odema and mild polymorphonuclear leucocytic infiltraion.

Non-suppurative inflammation

- Membranous inflamation
- Sever acute inflammation charcterized by formation of pseudomembrane on the affected surface
- **Gross picture:**
  -early the mucosa is congested and shows small greyish yellow patches of necrosis
- -next a yelloiwsh white slightly elevated pseudomembrane is formed on the surface.

Non-suppurative inflammation

- Microscopic picture:

- the pseudomembrane is formed of necrotic mucosal cells ,bacteria,and acute inflammatory cells held together by fibrin network

- the submucosa shows hyperaemia inflammatory odema ,fibrin network and acute inflammatory cells .

Non-suppurative inflammation

- **Sero-fibrinous inflammation**

- acute inflammation charactrized by the formation of excess fluid exudate rich in fibrinogen e.g inflammation in serous sacs

gross picture:

-early the serous surfaces show many hyperaemic vessels

-next the visceral and parietal layers become thickened ,opaque ,greyish and reticulated due to fibrin deposition

- na inflammatory serous fluid collects in the serous sac

Non-suppurative inflammation

- ***Microscopic picture :***

-serosal cells lining the visceral and parietal layers swell due to degeneration and desquamate leaving bare surface.

-na inflammatory fluid exudate rich in fibrinogen pours from the bare surface

- the subserosa shows hyperaemia ,inflammatory odema ,fibrin,network and acute inflammatory cells .

Non-suppurative inflammation

- **Fibrinous inflammation**

- Acute inflammation charctrized by an exudate rich in fibrinogen e.g labor pneumonia

Non-suppurative inflammation

- **Serous inflammation**

- acute inflammation charcterized by excess serous exudate e.g mild burns and herpes simplex which show epidermal vesicles full of serous fluid containing few inflammatory cells

Non-suppurative inflammation

- **Haemorrhagic inflammation**

-acute inflammationcharcterized by cellular exudate rich in the red blood cells due to vascular damage e.g smallpox and haemolytic streptococcal infection

Non-suppurative inflammation

- **Necrotizing inflammation**

-acute inflammation charctrized by marked tissue necrosis e.g cancrum oris

Chronic inflammation

- The irritant is mild
- May follow acute inflammation
- The tissue response is gradual and prolonged
- Tissue necrosis in progressive and gradually replaced by fibrous tissue
- Vascular dilatation and congestion are mild
- The inflammatory fluid exudate is scanty

Chronic inflammation

- The exudate shows the following types of the inflammatory cells :

  - lymphocytes
  - plasma cells
  - macrophages

Types of chronic inflammation

- **Chronic non-specific inflammation**

  - different irritants produce inflammatory reactions of the same microscopic picture

  - this type may follow the acute inflammation

- **Chronic specific inflammation**

  -each irritant produces inflammationof a charcteristic microscopic picture

Granulomas

- Is a type of chronic specific inflammation characterized by focal accumulation of larg number of macrophages together with lymphocytes,plasma cells,gaint cells .
- **Types :**

-infective granuloma

-non infective granuloma

-granuloma of unknown cause

Granulomatous inflammation:

a special form of chronic inflammation

Granuloma

- Definition
  - A collection of macrophages, lymphocytes, mononuclear cells and fibroblasts with or without giant cell formation and constitutes a special form of chronic inflammation

Granulomatous inflammation

Bacterial:
TB, Leprosy, Syphillis, cat-scratch disease

Parasitic:
Schistosomiasis

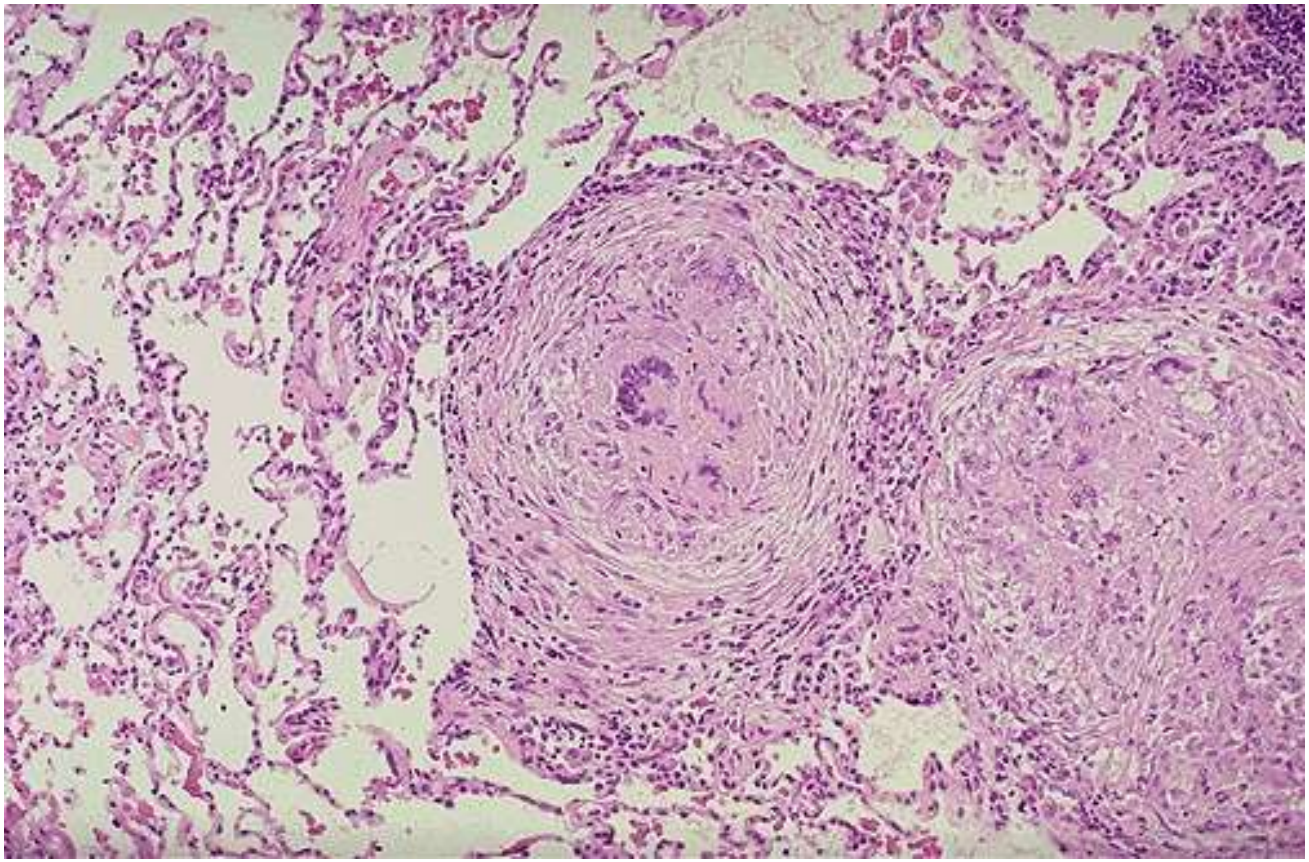
Fungal:
Histoplasma, blastomycosis, cryptococcus

Inorganics, metals, dusts:
Silicosis, berrylliosis

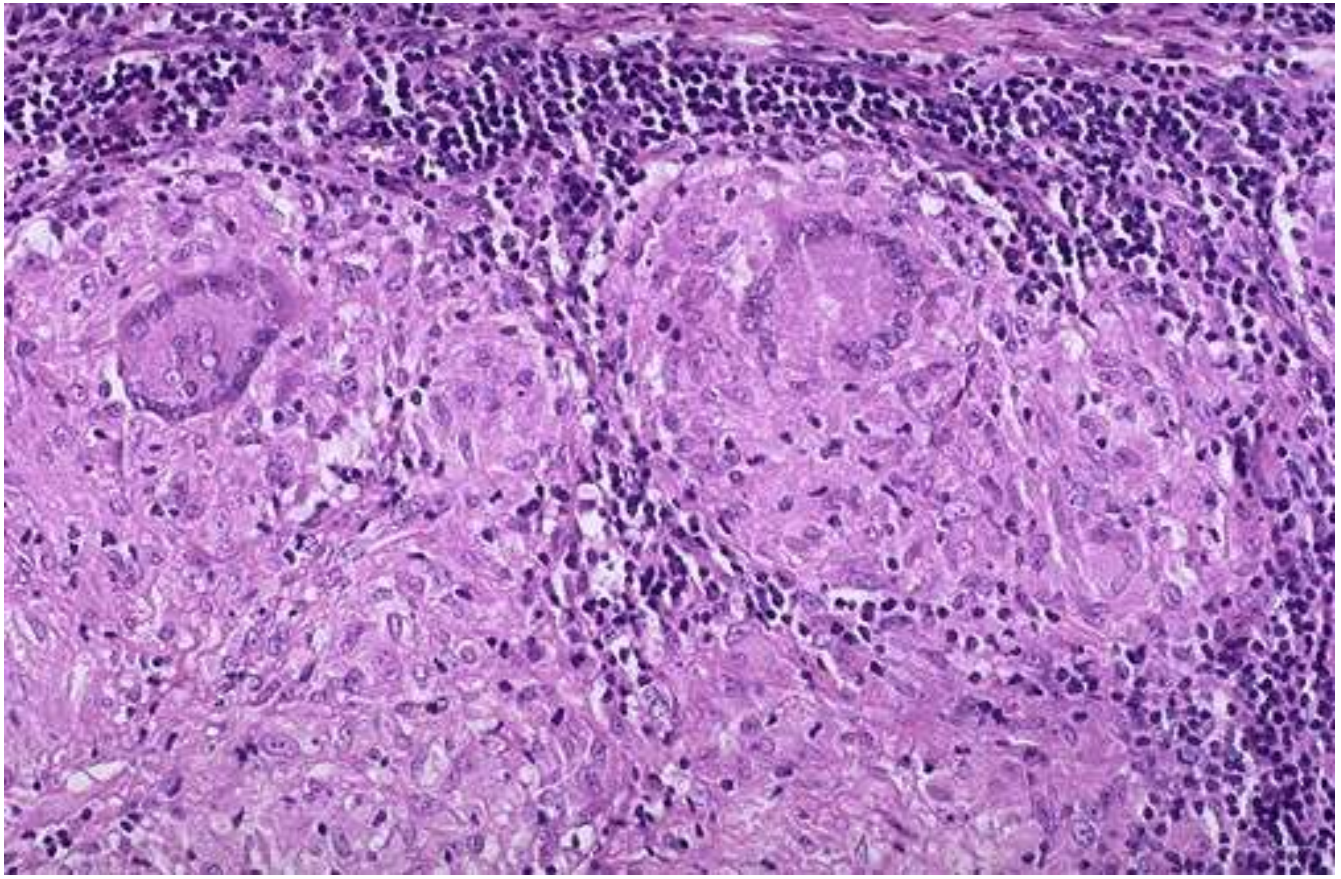
Foreign body

Unknown:
Sarcoidosis

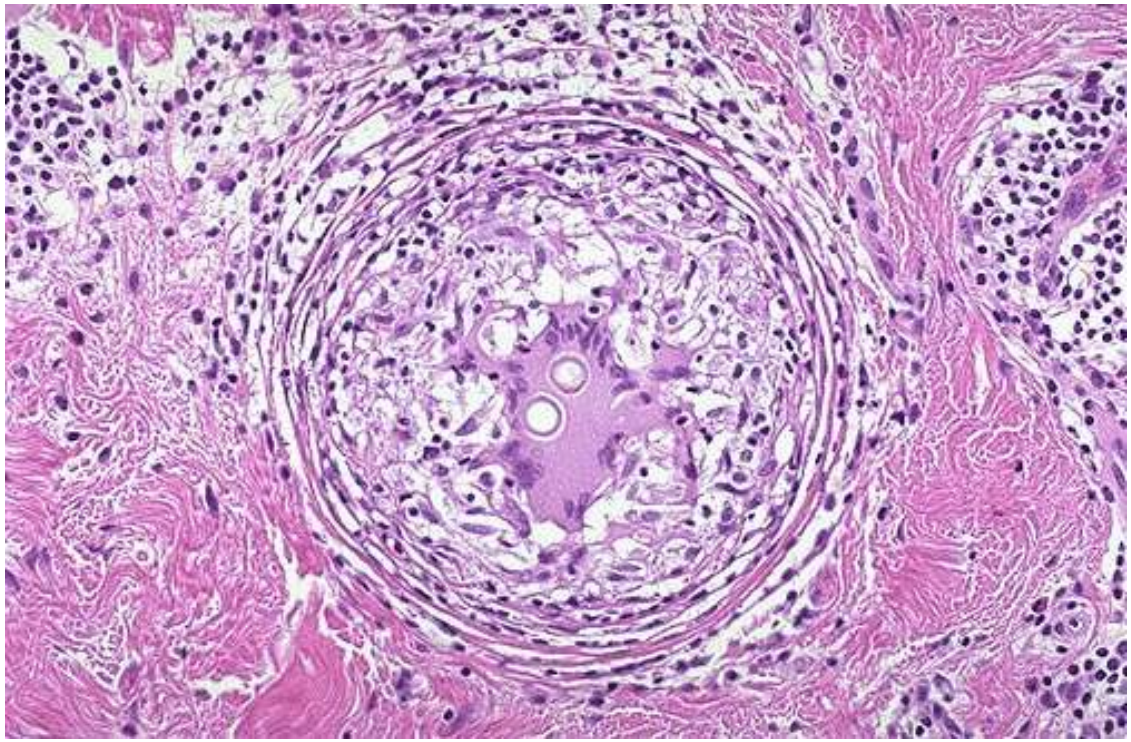
Granulomatous inflammation: tissue effects



Granulomatous inflammation: tissue effects



Granulomatous inflammation: tissue effects



The Inflammatory Response

- **Key purposes = DEFENSE**

    1. **To hunt & kill invaders**
    2. **To limit their spread**
    3. **To prepare tissue for repair**

- **Key events**

    1. **Increase of vascular permeability**
    2. **Recruitment (margination) & emigration (diapedesis) of WBC's**
    3. **Phagocytosis**

The Inflammatory Response

- **Inflammatory response = normal body defense mechanism to tissue injury**
  - » **Note: Inflammation is NOT infection**

- **Cells of the inflammatory response when get tissue injury**
  - **Main groups;**
    - **Phagocytes --- "the eaters"**
      - **Macrophages --- become active as APC's (antigen presenting cell)**
      - **Neutrophils --- "little eaters"**
      - **Monocytes --- become tissue macrophages**
    - **T- lymphocytes (helper-T) ---- produce cytokines which " call all to action"**
    - **Platelets ---- release PAF (platelet activating factor) which in turn begins call to action and release of chemical mediators**
    - **Mast cells --- release chemical mediators that begin inflammation**

Chemical Mediators

- The initial "macrophage (APC cell) – antigen complex" causes chemical mediators to be released:
  - Histamine
    - From basophils & mast cells
    - Cause vasodilation & increased permeability of vessels via release of nitric oxide
  - Prostaglandins
    - Made in mast cell membrane from fatty acid (arachidonic)
    - Cause pain & vasodilation
  - Leukotrienes
    - "bad" prostaglandins since cause symptoms of inflammation (pain & swelling)
    - Cause chemotaxis
    - Very important for causing allergies, asthma, & anaphylaxis

Chemical Mediators

- Complement
  - Coats bacterial surface; enhances phagocytosis & lyses bacteria
  - Inactive plasma proteins become activated by initial An-Ab complex
- Interferon
  - Proteins that are released by helper T's & kill viruses
- Bradykinins
  - From inactivated plasma protein
  - Cause similar effects like histamine
  - Cause pain
  - Induce WBC's into area (chemotaxis

- **Local effects of inflammation**
  - 4 cardinal signs of inflammation
    - Redness (rubor) – from increased blood supply
    - Heat (calor) – from increased blood supply
    - Swelling (tumor) – from increased permeability & increased proteins in interstitial fluid
    - Pain (dolar) – from chemical mediators
  - Also get inflammatory exudate
    - Serous – from allergic reactions & burns
    - Purulent – from infections
      - May lead to abscess
- **Systemic effects of inflammation**
  - General malaise
  - Fatigue
  - Headache
  - Fever
    - Caused by pyrogens (chemicals released from phagocytes)
    - Beneficial
      - Inhibits growth of pathogens
      - Enhances repair process via increased metabolic rate

- **Potential complications of inflammation**
  - Infection
  - Ulceration – from chronic inflammation
    - May lead to:
      - perforation of viscera
      - excess scar formation
  - Skeletal muscle spasm
  - Local tissue reactive changes
    - Joints from decreased ROM become stiff
    - Lungs cannot exchange gases

- **Diagnostic tests for inflammation**
  - Leukocytosis
  - Differential WBC count
  - ESR
  - Cell enzymes – may or may not be tissue specific
    - C-reactive protein

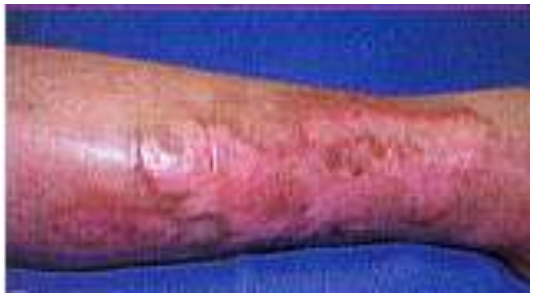
- **Chronic Inflammation**
  - The acute inflammatory reaction usually subsides within 48 –72 hours as long as the cause is removed (e.g. touching a hot stove)
  - If the cause persists, you get chronic inflammation
  - Clinically:
    - Increase in connective tissue reaction to the chronicity
      - Get more fibroblasts & more collagen
        - » Thus get more scar tissue
        - » Can get granulomas (collection of chronically inflamed tissue)

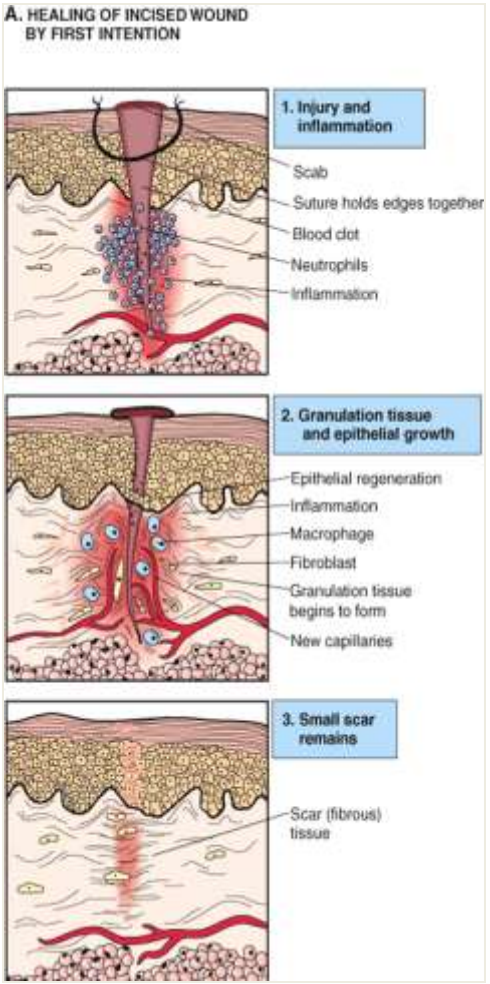
- **Treatment of inflammation**
  - Aspirin
  - NSAID's
  - Glucocorticoids
  - Heat & cold
  - Physiotherapy if chronic
    - » Prevents contractures

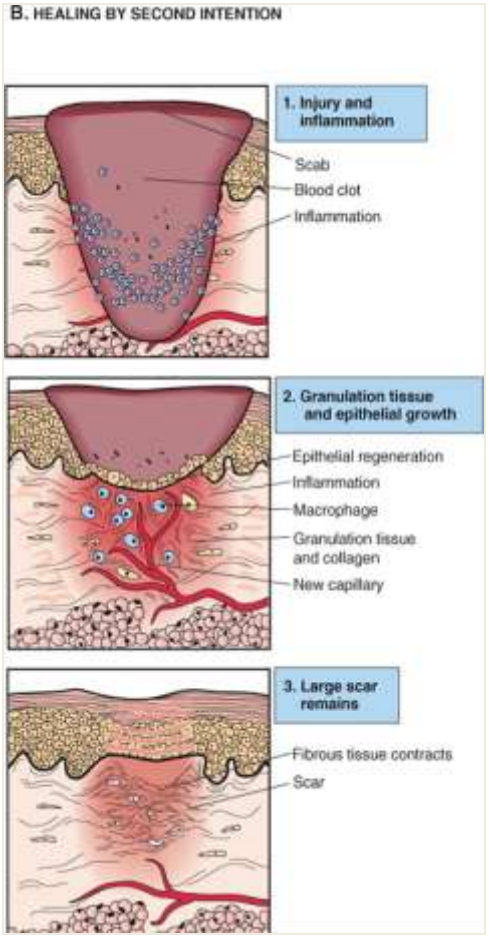
Healing

- **3 ways depending on the tissue involved & degree of injury**
  - **Resolution**
    - **Damaged cells recover in short time**
    - **Exp = mild sunburn**
  - **Regeneration**
    - **Damaged cells replaced by identical cells via mitosis**
    - **Only occurs in epithelia & connective tissue**
    - **If complex organ, some damaged tissue replaced by regeneration & some by scar**
  - **Scar formation**
    - **Key tissue = granulation tissue(highly vascular connective tissue)**
      - » **Collagen produced by fibroblasts makes granulation tissue into scar tissue**
    - **Scar tissue is non-functional**

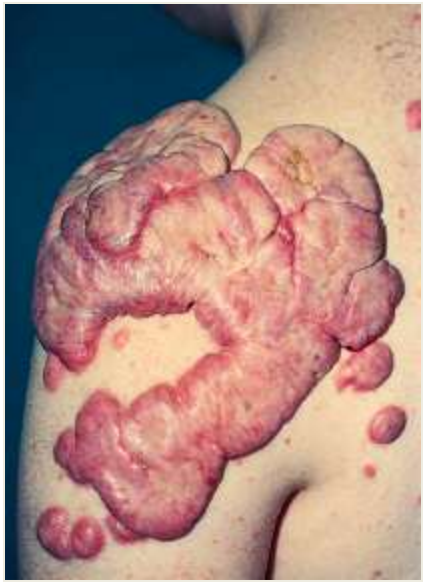
- **Healing by primary or secondary intention**
  - Depend weather edges of lesion can be brought together
    - Primary (first) intention gives small scar formation
      - Secondary intention gives large scar formation
        - Heals via granulation tissue







- **Complications from large scar formation**
  - **Loss of function**
  - **Contractures & obstructions**
    - **Can lead to stenosis**
  - **Adhesions**
  - **Ulceration**



- **Factors promoting healing**
  - **Nutrition**
  - **Blood supply**
  - **Cleanness of area**
  - **Lack of complications**
- **Factors delaying healing**
  - **Old age**
  - **Presence of foreign material**
  - **Poor blood supply**
  - **Poor nutrition**
  - **Complications (bleeding, hematoma, excessive mobility)**

Burns

- **First degree burns**
  - Superficial partial-thickness
  - Involves just epidermis
  - Get redness but no blistering
  - May peel in 1-3 days
  - Get no scarring
- **Second degree burns**
  - Deep partial-thickness
  - Involves epidermis & dermis
  - Get redness & blistering
  - Can get scarring
  - Can get some fluid loss
  - Get significant pain
- **Third degree burns**
  - Full-thickness
  - Involves all 3 layers & may involve underlying tissue
  - Get no pain
  - Get serious fluid loss

- **Rule of 9's**
  - If burn 1^{st} ,2^{nd} , or 3^{rd} & involves more than 20% ---- needs medical attention
  - If burn 2^{nd} or 3^{rd} & involves greater 20% = serious
  - If burn 2^{nd} or 3^{rd} & involves greater 40% = severe
- **Complications**
  - Fluid imbalance
  - Dehydration
  - Anemia
  - Infection
  - Excess scar formation

Pathophysiology

COLLEGE OF PHARMACY

UNIVERSITY OF BAGHDAD

GENERAL PRINCIPLES OF PATHOLOGY & PATHOPHYSIOLOGY

Dr. AJWADASSUMAIDAEE Ph. D

1- CELLULAR INJURY
2- CELLULAR ADAPTATION
3- CELLULAR DEGENERATION
4- NECROSIS & APPOPTOSIS
5- INFLAMMATION
6- CELLULAR REPAIR

Pathology and Pathophysiology

- Pathology
  - Study of diseases (structural changes) and its cause.
- Pathophysiology

  - The study of how diseases (structural changes) alter the normal physiological processes of the human body
  - Disease may include illness or injury
  - From the root “patho” meaning disease.

What is pathophysiology?

- A subject to explore the rule of origin and evolution of disease processes and the fundamental mechanisms.
- Pathophysiology – abnormal functioning of diseased organs and how it applies to medical treatment and patient care

Difference from Physiology

Also named:

- Physiopathology
- Physiology of Disease
- Physiology of Disordered Function

Difference from Pathology

- Pathology emphasizes the structural changes
- Pathophysiology focuses on the functional and metabolic alterations and the mechanisms

Why is Pathophysiology Important?

- As a bridge not between the basic science and diseases but various basic sciences .
- Enabling to understand why and how diseases develop and various clinical manifestations appear, and what are the fundamental mechanisms.

How the Teaching of Pathophysiology is Arranged?

- Introduction
- Fundamental pathological processes
- Organic pathophysiology
- Cellular and molecular pathophysiology

Major Points in Learning Pathophysiology

- The general concepts
- The etiology and pathogenesis
- The alterations in metabolism and functions
- The principles for the prevention and therapies

Conspectus of Disease

Concept of Disease

- Disease is referred as aberrant manifestation of deregulated homeostasis caused by harmful agents.

- The development of a disease is definitely a pathologic process with a characteristic set of signs and symptoms involved in the whole body or any of its parts.

Disease

loss of homeostasis, or when physical or mental capacities cannot be fully utilized (interuption, cessation or disorder in the function of an organ or system).

Categories of etiology
Etiology = cause of the disease

- **Genetic disease**– genes are responsible for a structural or functional defect
- **Congenital disease**– genetic information is intact, but the intrauterine environment interferes with normal development
- **Acquired disease** – disease is caused by factors encountered after birth (biological agents, physical forces, and chemical agents)

Etiology-

Idiopathic- cause is unknown

Iatrogenic- results from a treatment, procedure, or medical error

Examples: bladder infection after catheterization; damage due to a prescribed drug……

Clinical manifestations – indications that the person is sick

Symptoms – unobservable effects of a disease reported by the patient

Signs – observable or measurable traits

Syndrome - a characteristic combination of signs and symptoms associated with a particular disease.

Signs vs. Symptoms

- **Signs**= objective (What the Dr. See's)-felt, heard or seen
  - Ex. Lesions, redness, swelling
- **Symptoms**= subjective (what the patient experiences) not visible outwards to others
  - Ex. Nausea, headache

-Syndrome- collection of signs and symptoms that occur together.

More Specific Terms

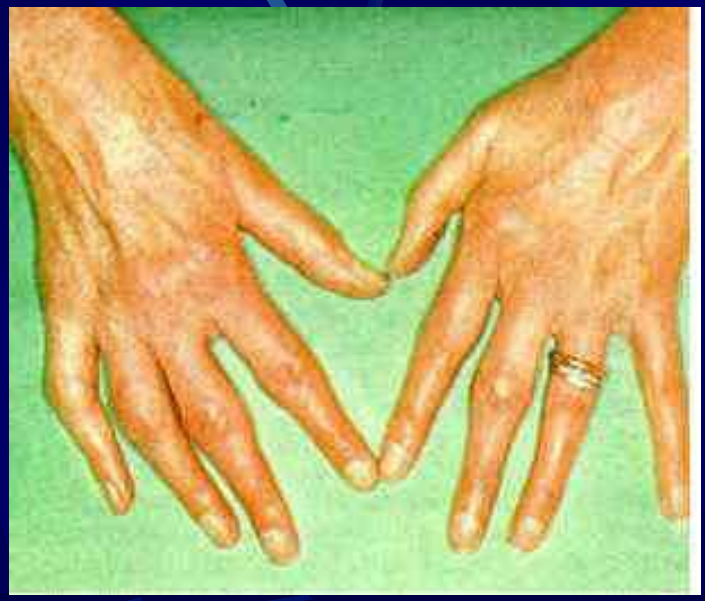
- **Pathogenesis- the development of the disease or the sequence of events involved in the tissue changes related to the specific disease process.**
- **Onset**
  - **Acute – sudden/quick**
  - **Insidious – gradual/slow**
- **Chronic- on-going**
- **Sub-clinical** – (flies under the radar), no obvious manifestations are exhibited

- **Latent**- incubation period "silent period"

Most infectious in some viruses

Course of Disease Terms

- **Remission**- manifestations subside
- **Exacerbation**- manifestations increase
- Example: Arthritis
- (COULD BE BOTH?



Precipitating factors- condition that triggers an acute episode.

How is that different than a predisposing factor?

Complications- secondarily arise after initial disease begins but while the disease is still manifested.

Sequelae- secondarily arise after disease has gone away.

Last bit of disease terminology:

- Prognosis- likelihood of outcome
- Morbidity- incidence w/in a group
- Mortality- death rate
- Epidemiology- study the occurrence of disease
- Epidemics- many cases in an area
- Pandemics- world-wide
- Prevelance- # new cases
- Incidence- # new + old (total # cases)

Pathogenesis - sequence of events in the of development of a disease

Sequelae – lesions or impairments resulting from a disease

Acute conditions – rapid onset, develop quickly, usually of short duration

Chronic conditions – longer duration

onset may be sudden or **insidious**

Distribution of lesions may be:

- **Local – confined to one area of the body**
- **Systemic – widely distributed throughout the body**

Within an organ damage can be:

- **Focal if there are only one or more distinct sites of damage**
- **Diffuse if the damage is uniformly distributed**

Concept of Health

- **Health** is the state of the organism when it functions optimally without evidence of disease.
-
- **The definition of health from WHO:**

Health indicates not only without any evidence of disease, but also a state of complete well-being physically, psychologically and socially.

Etiology of disease

- Etiology is used to study the causative agents including microorganisms, environmental, social factors and personal habits as contributing factors that causes disease.
- Answer the question why disease happens.

Etiological factors

Extrinsic Factors

- Biological agents
- Chemical agents
- Physical agents
- Nutritional imbalance

Etiological factors

Intrinsic Factors

- Genetic factors
- Congenital factors
- Immunological factors
- Psychological factors

Predisposing factors

- Genetic constitution
- Physiological diathesis
- Psychological characteristics

Precipitating Factors

- Natural conditions
- Physical condition
- Social condition

Pathogenesis of disease

- Disruption of homeostasis
- Process of damage and anti-damage
- Reversal role of cause and result
- Correlation between systemic and local regulations

Outcome of disease

- Complete recovery
- Incomplete recovery
- Death

How Cells Respond to Change and Injury

Cellular and Tissue Alteration

- Body tends to maintain a constantly balanced environment and to adapt (correct or compensate) for any change that disturbs the balance
- Cellular adaptation
  - Cells adapt to their environment to avoid and protect themselves from injury
  - Adapted cells are neither normal or injured (they are somewhere between these two states)

Adaptation to Environmental Stresses

- 2 cellular reactions happen:
- Hyperfunctioning
- Hypofunctioning

Cellular Changes
6 types

cellular changes photo.jpg

- **1. Atrophy**- decrease in cell size
- **2. Hypertrophy**- increase in cell size (increase muscle mass due to exercise)
- **3. Hyperplasia**- increased number of cells (glandular proliferation of breast during pregnancy)

- 4. Metaplasia- one form changes to another (cells look different than before)

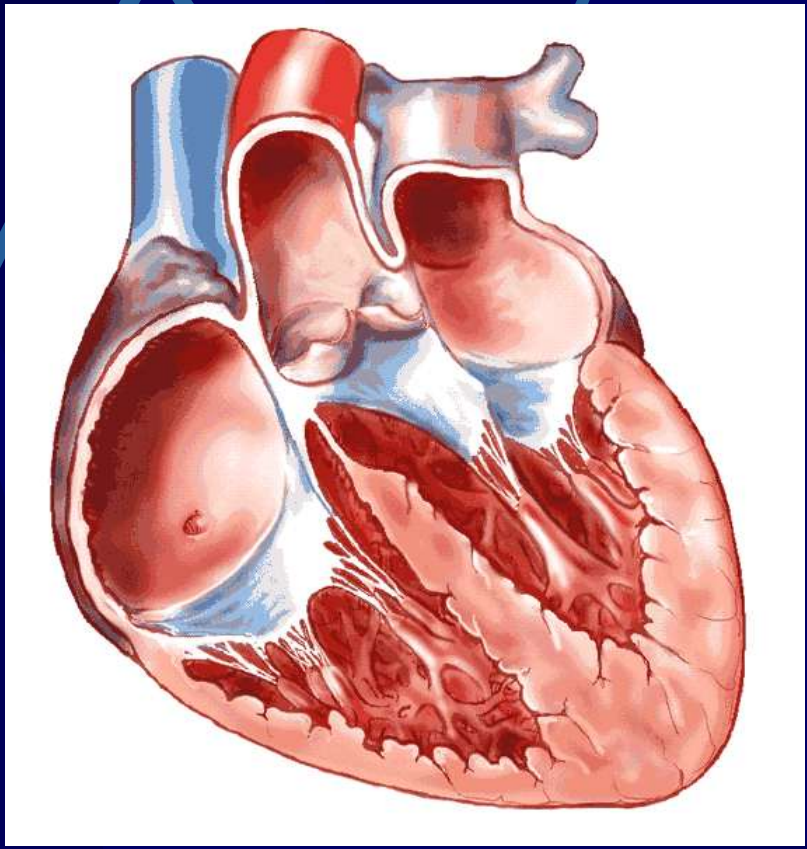
- 5. Dysplasia- cells vary in shape and size
  - Usually results from chronic infection or irritation
  - Pre-cancerous cells are detected
- 6. Neoplasia= causes tumors

Cellular Adaptation

- Cells, tissues, organs, and organ systems can adapt to both normal and injurious conditions.
- Adaptation to external stressors results in alteration of structure and function.
- Examples:
  - Growth of the uterus during pregnancy, dilation of the left ventricle after an MI.

Types of Cellular Adaptations

- Atrophy—decreased size resulting from a decreased workload.
- Hypertrophy—an increase in cell size resulting from an increased workload.



Types of Cellular Adaptations

- Hyperplasia—An increase in the number of cells resulting from an increased workload.
- Metaplasia—Replacement of one type of cell by another type of cell that is not normal for that tissue.
- Dysplasia—A change in cell size, shape, or appearance caused by an external stressor.

Cell Injury and Cell Death

Objectives

- *Upon completion of this lecture you will be able to*:
  - Define 4 types of cellular adaptation to physiologic and pathologic conditions.
  - List 7 common causes of cell injury.
  - Explain the difference between reversible and irreversible cell injury.
  - Explain the difference between necrosis and apoptosis.
  - Describe patterns of necrosis In tissues or organs.

Important Terms

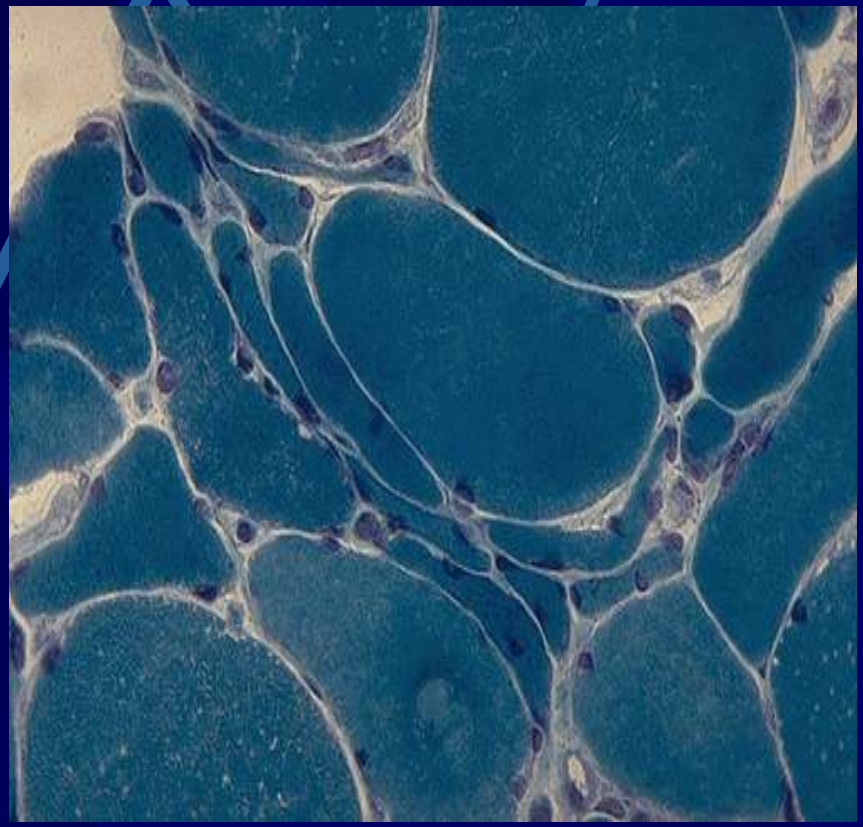
- Cellular Adaptation
- Cell Injury
- Necrosis
- Apoptosis
- Atrophy
- Hypertrophy
- Hyperplasia
- Metaplasia
  - For more details see Cotran, R. S., Kumar, V., Collins, T. (1999). Pathologic Basis of Disease (6th ed.). Philadelphia, PA:

- Cells are the structural and functional units of tissues and organs. They are capable of adjusting their structure and functions in response to various physiological and pathological conditions. This capability is called **cellular adaptation**.

- Cellular adaptations include:
  - **Atrophy**--shrinkage of cells
  - **Hypertrophy**--increase in the size of cells which results in enlargement of the organs
  - **Hyperplasia--**increased number of cells in an organ or tissue
  - **Metaplasia**--transformation or replacement of one adult cell type with another

Atrophy

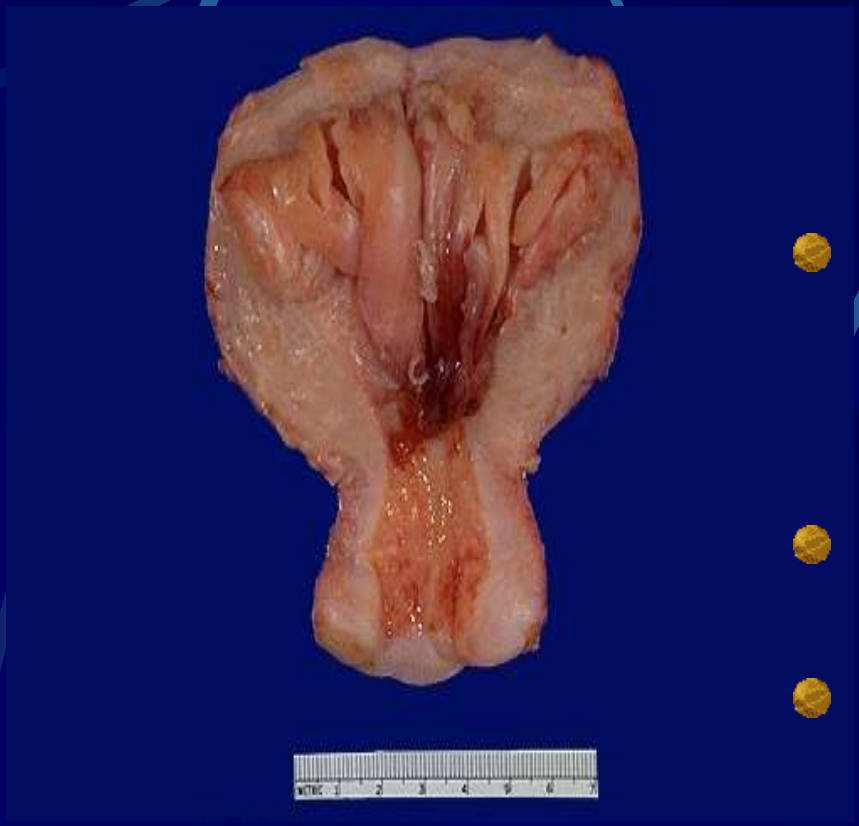
- There are some muscle fibres here that show atrophy.
- The number of cells is the same as before the atrophy occurred, but the size of some fibres is reduced.
- This is a response to injury by "downsizing" to conserve the cell.
- In this case, innervation of the small fibres in the centre was lost.
- This is a trichrome stain.



Hypertrophy

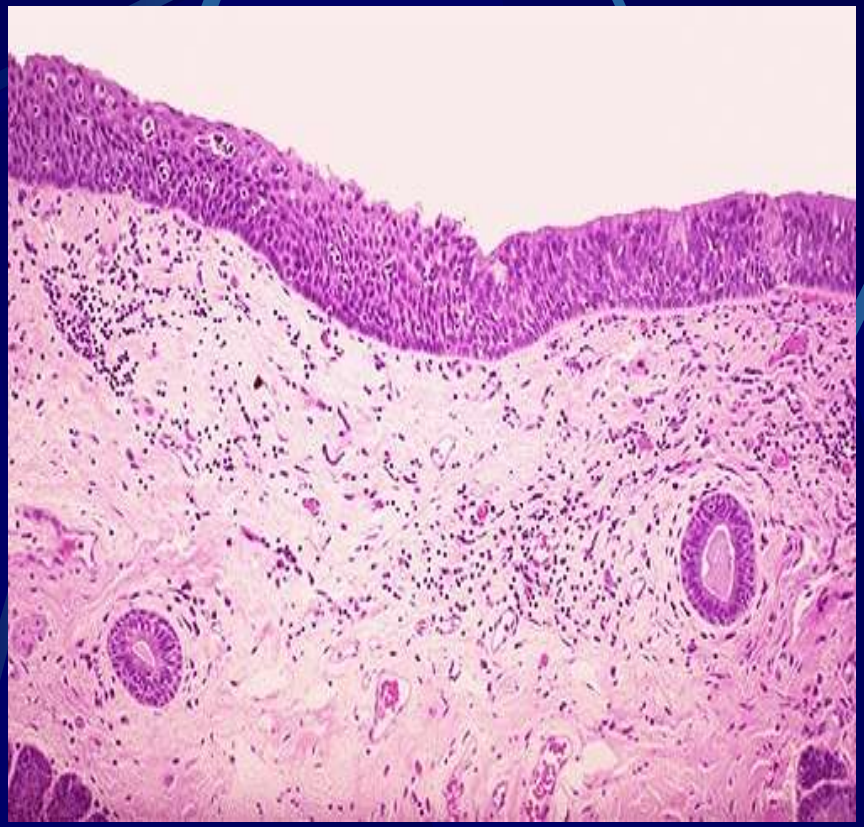
- This is cardiac hypertrophy involving the left ventricle.
- The number of myocardial fibres does not increase, but their size can increase in response to an increased workload, leading to the marked thickening of the left ventricle in this patient with systemic hypertension.

Hyperplasia



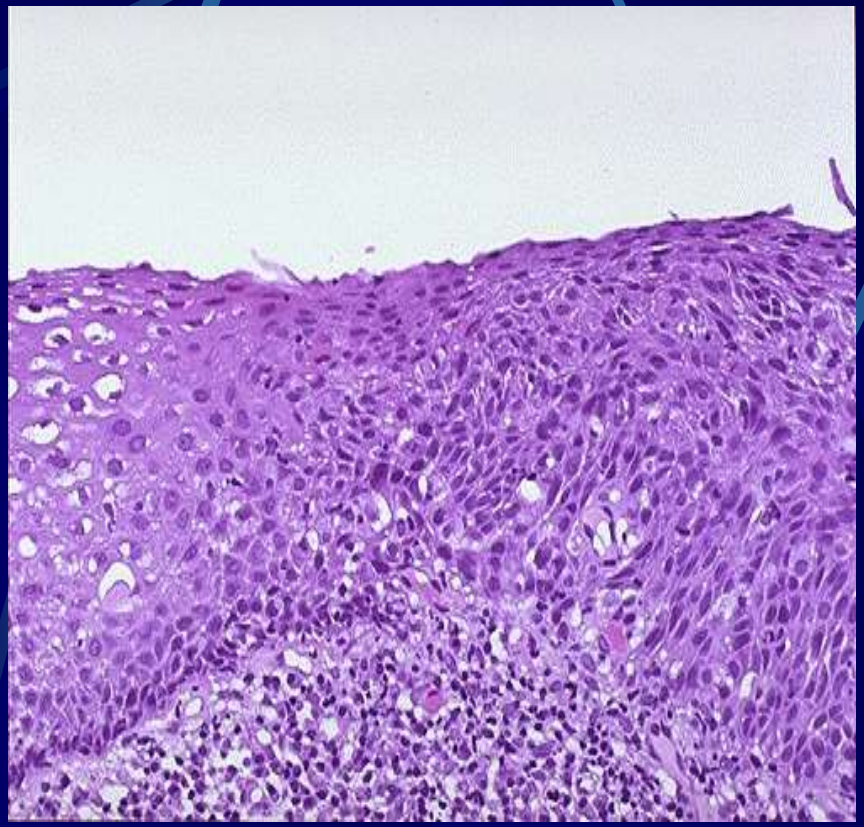
- The prominent folds of endometrium in this uterus opened to reveal the endometrial cavity are an example of hyperplasia.
- Cells forming both the endometrial glands and the stroma have increased in number.
- As a result, the size of the endometrium has increased.
- This increase is physiologic with a normal menstrual cycle.

Metaplasia



- Metaplasia of laryngeal respiratory epithelium has occurred here in a smoker.
- The chronic irritation has led to an exchanging of one type of epithelium (the normal respiratory epithelium at the right) for another (the more resilient squamous epithelium at the left).
- Metaplasia is not a normal physiologic process and may be the first step toward neoplasia.

Dysplasia



- This is dysplasia. The normal cervical squamous epithelium has become transformed to a more disorderly growth pattern, or dysplastic epithelium.
- This is farther down the road toward neoplasia, but dysplasia is still a potentially reversible process.

Various Types of Adaptations

- Cells may undergo various adaptations in physiological and pathological conditions. These are controlled by complex molecular mechanisms.

Atrophy-

- -shrinkage of cells; classified as:
  - Physiologic--due to decreased work load (e.g., decreased size of uterus following child birth, or disease)
  - Pathologic--primarily due to denervation of muscle, diminished blood supply, nutritional deficiency

Hypertrophy-

- Increase in the size of cells which results in enlargement of the organs.
- It is mostly seen in cells that cannot divide, such as:
  - skeletal muscle (pumping iron),
  - cardiac muscle (hypertension).
- These changes usually revert to normal if the cause is removed.
- Hypertrophy is mediated by different mechanisms.

Hyperplasia-

- Increased number of cells in an organ or tissue. Hyperplasia may sometimes co-exist with hypertrophy. Hyperplasia can be classified as:
  - **physiologic**--hormonal (e.g., breast and uterus during pregnancy)
  - **compensatory**--regeneration of liver following partial hepatectomy. Various growth factors and interluekins are important in such hyperplasia.
  - **pathologic**--excessive hormonal stimulation, viral infection (papilloma viruses); neoplasms

Metaplasia -

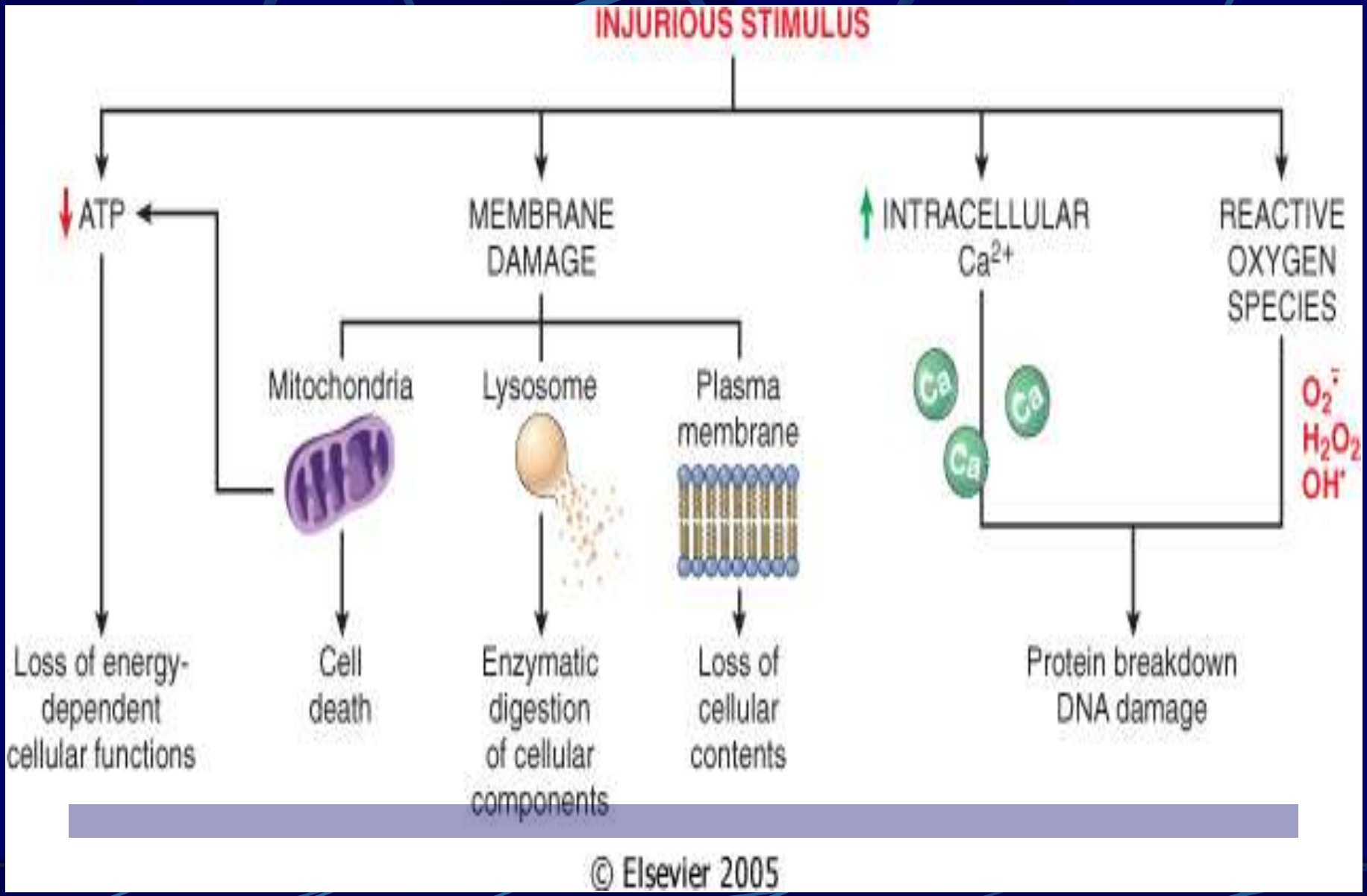
- Transformation or replacement of one adult cell type to another adult cell type
  - (e.g., the change from columnar to squamous cells in respiratory tract, from squamous to columnar in Barrett esophagitis).
  - Metaplasia also occurs in mesenchymal tissue (e.g., formation of bone in skeletal muscle).
- Metaplastic changes usually result from chronic irritation.
- Metaplastic changes seem to precede the development of cancer, in some instances.
- Metaplasia is thought to arise from reprogramming of stem or undifferentiated cells that are present in adult tissue.

Cell Injury

- If the cells fail to adapt under stress, they undergo certain changes called cell injury. The affected cells may recover from the injury (reversible) or may die (irreversible).
- Causes of Cell Injury
  - oxygen deprivation (anoxia)
  - physical agents
  - chemical agents
  - infections agents
  - immunologic reactions
  - genetic defects
  - nutritional imbalances

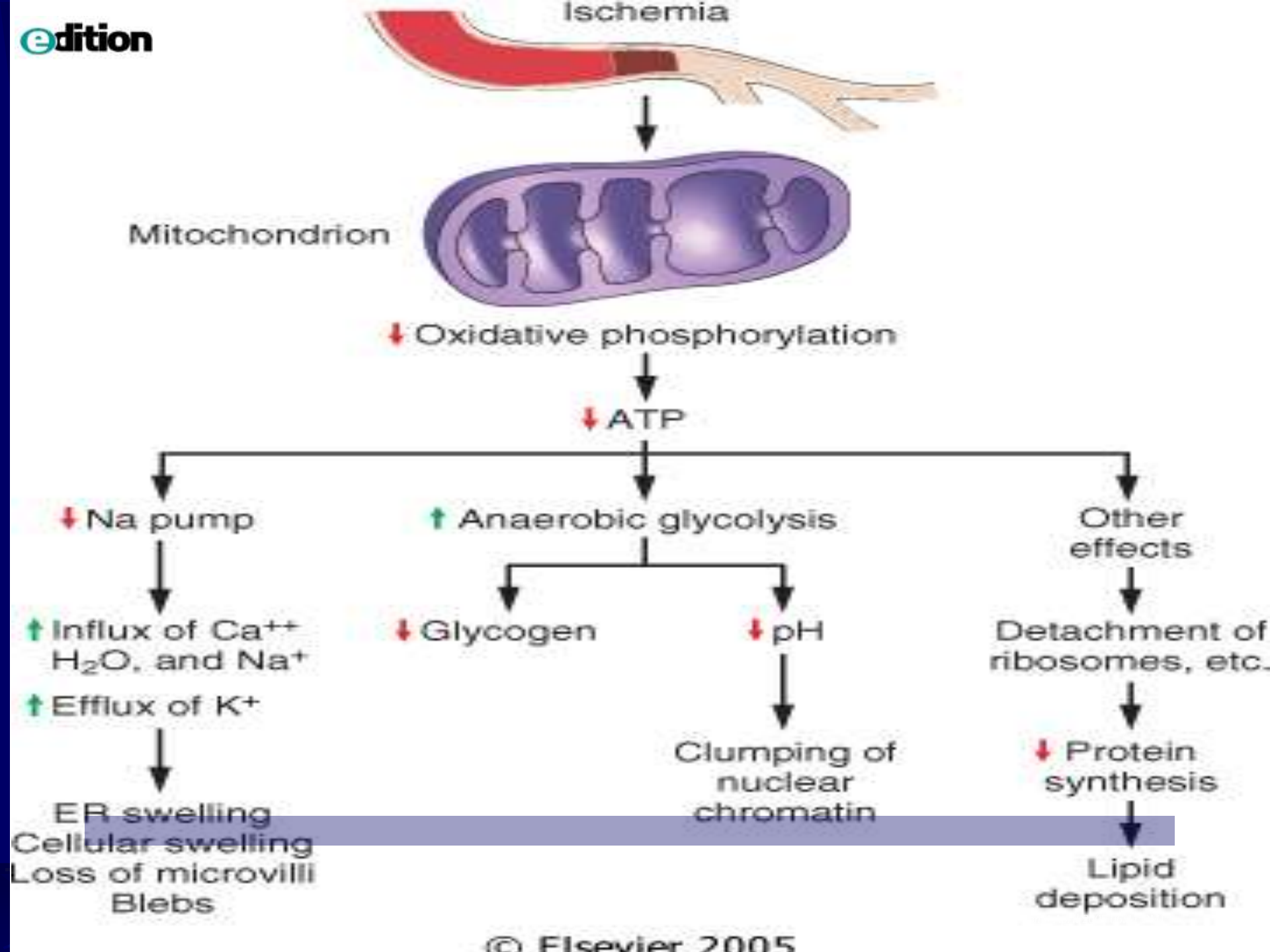
IMPORTANT TARGETS OF CELL INJURY

- Aerobic respiration –
  - ATP depletion or decreased synthesis.
- Cell membranes - plasma membranes, mitochondrial, lysosomal and other organelle membranes.
- Protein synthesis.
- Cytoskeleton.
- Genetic apparatus.



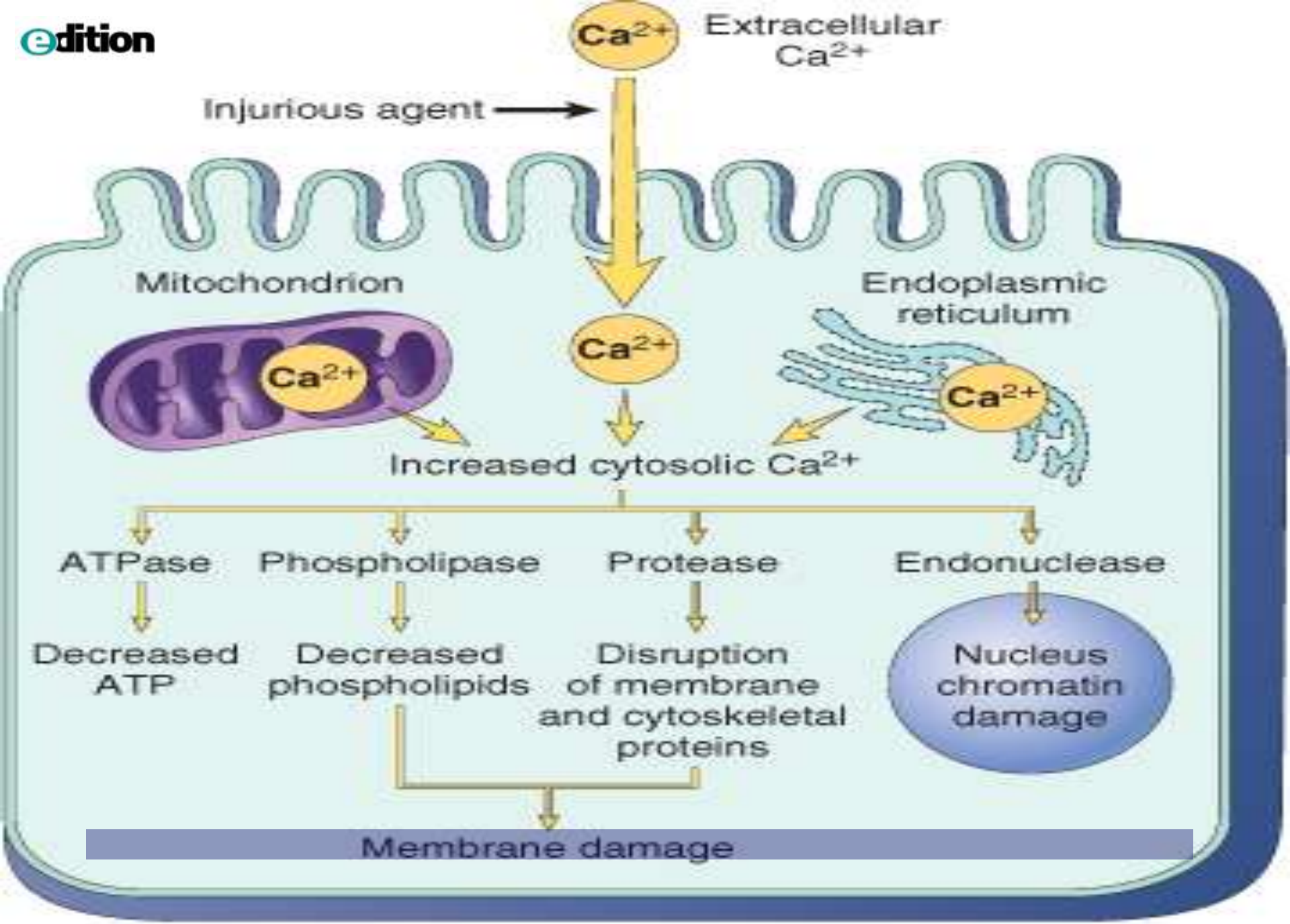
ATP DEPLETION - HYPOXIA/ISCHAEMIA

- Mitochondria - reduced oxidative phosphorylation.
- Cell membrane - reduced sodium pump.
- Sodium and water enter the cell; potassium exits.
- Endoplasmic reticulum dilates, the cell swells, blebs appear.
- Anaerobic glycolysis occurs with loss of glycogen, accumulation of lactic acid, acid pH which interferes with enzymes.
- Failure of the calcium pump leads to influx of Ca++ into the cell, activate various enzymes to the detriment of the cell.
- RER loses ribosomes and protein synthesis falls - structural proteins (membranes, cytoskeleton) and enzymes.
- Misfolded proteins lead to the unfolded protein response which may further injure the cell.



THE IMPORTANCE OF CALCIUM

- Influx of calcium to the cytosol comes from the extracellular fluid and stores in mitochondria and endoplasmic reticulum.
- Ca++ activates **phospholipases** (damages cell membranes),**proteases** (damages cell membranes and cytoskeleton) and **endonucleases** (damages DNA).
- This is one of the main mechanisms of cell death, either through severe damage to membranes of lysosomes and leakage of lysosomal enzymes or triggering apoptosis.
- Occurs particularly in hypoxia and ischaemia and with certain toxins. Preventing the rise in Ca++ or restoring to normal levels prevents cell death.

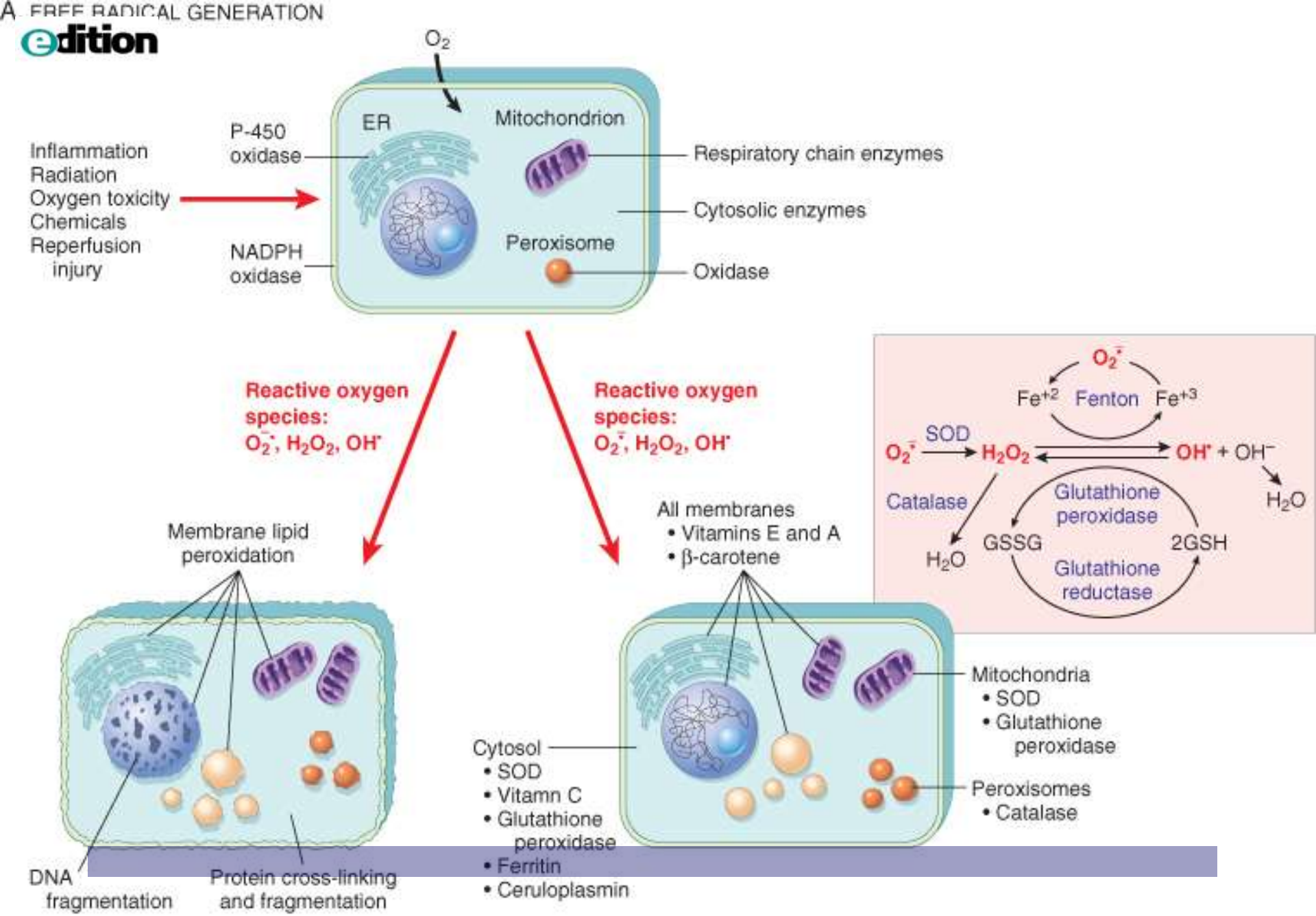


THE IMPORTANCE OF FREE RADICALS

- Free radicals have a single unpaired electron in the outer orbit. They are highly reactive with adjacent molecules.
- Are usually derived from oxygen to produce reactive oxygen species, superoxide, hydroxyl radicals,H2O2,etc.
- Are normally produced during cellular respiration. Protective molecules include superoxide dismutase, glutathione peroxidase, vitamin E, vitamin C, catalase.
- Produced in excess, they react with, and damage proteins, lipids, carbohydrates, nucleic acids.
- These damaged molecules may themselves be reactive species with a chain reaction being set up with widespread damage.

FREE RADICALS

- In addition to oxygen-derived free radicals, nitric oxide (NO) can act as a free radical and be converted to an even more reactive anion.
- Iron and copper catalyze free radical formation and are thus important in the generation of reactive oxygen species.
- Binding to molecules such as transferrin, ferritin and ceruloplasmin is protective.
- Free radicals cause lipid peroxidation in cell membranes, oxidation of amino acids and proteins resulting in fragmentation, and protein-protein cross linkages. Altered proteins are acted on by the proteosomes with further cell damage.



FREE RADICALS AND DISEASE

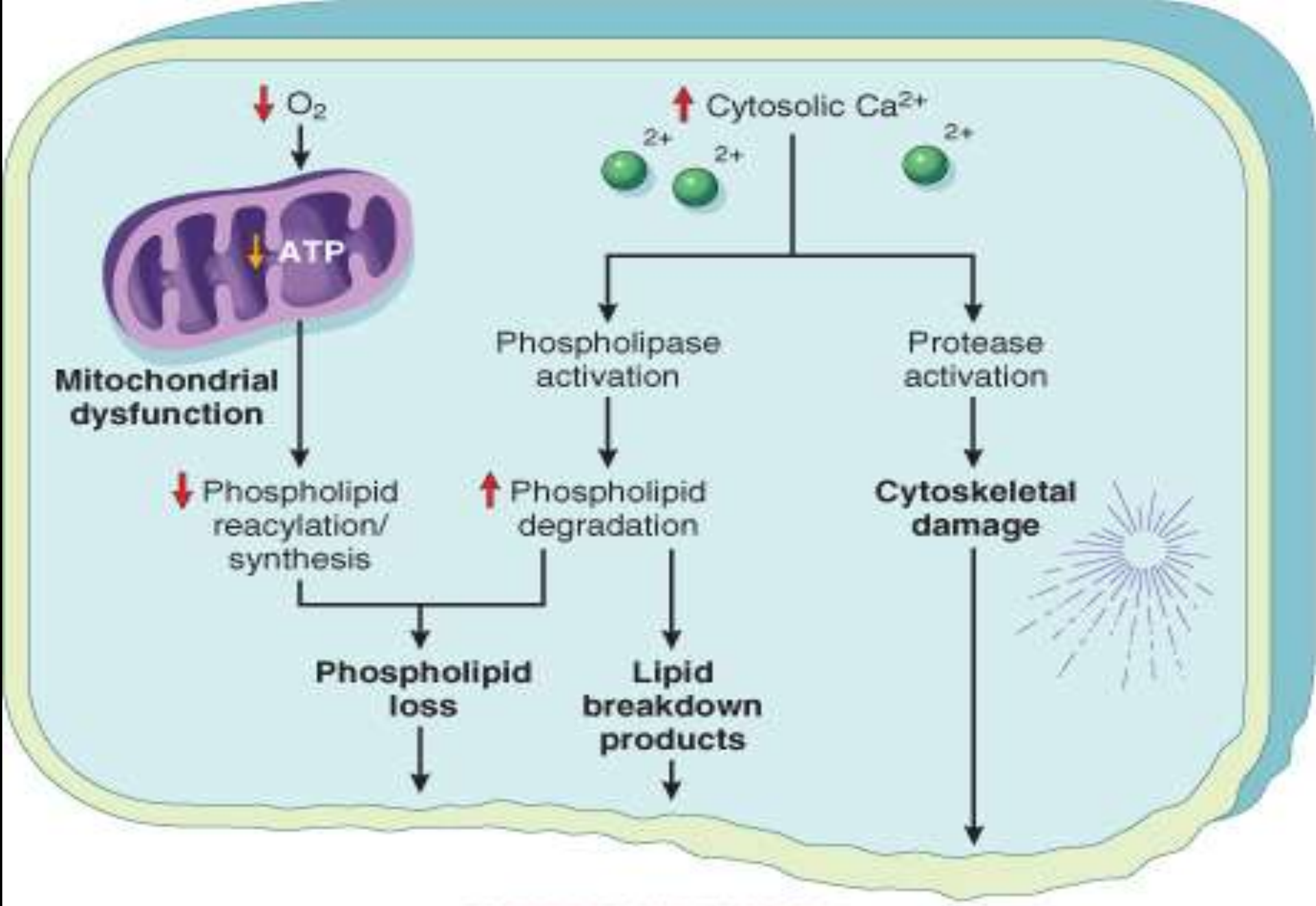
- Free radicals may be a common pathway for most types of cell damage, particularly oxygen-derived free radicals (oxidative stress).
- Some examples are:-
  - oxygen toxicity, ischaemia/reperfusion injury, radiation injury (hydrolyses H_2O to OH & H), metabolism of drugs, toxins, pollutants (eg Paracetamol to reactive metabolite;CCl_4 to CCl_3,cigarette smoke);
  - leukocyte killing of bacteria or in non-bacterial inflammations, release of iron in haemorrhages enhances oxidative stress (important in CNS),
  - lipid peroxidation of low-density lipoproteins in atherosclerosis, cancer production (damage to DNA), ageing.
- Therapies for combating oxidative stress are available for prevention or treatment with antioxidants and/or free-radical scavengers.

ISCHAEMIA/REPERFUSION INJURY

- If cells are reversibly injured due to ischaemia, complete recovery occurs following restoration of blood flow.
- However, reperfusion can result in more damage including cell death.
- This is due to incompletely metabolised products producing reactive oxygen species on re-introduction of oxygen
  - (especially damaging to mitochondria;
  - loss of anti-oxidants during ischaemia;
  - inflow of calcium with the renewed blood flow;
  - recruitment of leukocytes to the injured area.
- Reperfusion injury is especially important in ischaemic damage to the heart and brain and in organ transplantation.
- Various therapies and preventive measures are in use.

MEMBRANE DAMAGE

- Mitochondria –
  - mitochondrial permeability transition;
  - this non-selective pore may be reversible or become permanent leading to cell death.
  - Leakage of cytochrome c can trigger apoptosis.
- Plasma membrane –
  - mechanisms include those occurring with hypoxia/ischaemia and free radicals, but also
  - immune mechanisms as with complement activation and
  - perforin from lymphocyte attack on cells infected with a virus.
- All membranes may be damaged and ruptured by
  - mechanical force as in trauma, or by
  - ice crystals as in extreme cold.
- Damage to lysosomal membranes can lead to cell death by necrosis.



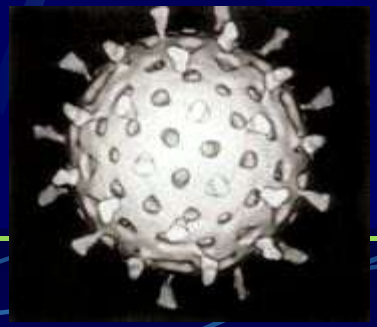
MEMBRANE DAMAGE

CHEMICAL & BIOLOGICAL AGENTS

- Chemical agents - direct effects, e.g. cyanine on cytochrome oxidase, HgCl on sulphydryl groups of proteins, ricin on ribosomes, cytotoxic effects of chemotherapy & antibiotics.
  - -indirect effects via free radicals.

CHEMICAL & BIOLOGICAL AGENTS

- Biological agents - direct effects of bacterial toxins; cytopathic effects of viruses and other actions such as:
  - interfering with DNA,RNA, proteins, cell membranes or
  - inducing apoptosis.
  - -indirect effects via the host immune reaction.



Causes of degeneration
External 1- Physical heat, cold,
radiations. 2- Toxic chemicals 3- Infective
agents
Internal
1- Dietary, vitamins deficiency
4- Genetic defects.
3- Increase in endogenous toxins e.g. cholesterol
or uric acid.
2.Hypoxia deficiency in the amount of oxygen
reaching the tissues. e.g. anemia, respiratory
failure, or ischaemia.
4
Types of degeneration Depending upon the nature
of the metabolite that accumulates within the
cell. 6
Common in Cause Characters of metabolites accumulate Type
The mildest but the most common one Destruction of mitochondria No ATP no Na pump Na H2O Absorption swelling Granulation deposition of protein and lipids Swelling and cloudy cytoplasm with granulation 1. Cloudy Parenchmatous
Scar formation Pancreas in Diabetes Uterus in menopause Deposition of Hyaline (protein) from inside or outside the cell. Hyaline with glassy appearance, due to degeneration of cell protein. 2. Hyaline
Striated muscles. Some infections as Diphtheria typhoid. A Special type of hyaline. The striated muscles become waxy, homogenous and structureless. 3. Waxy Zenkers

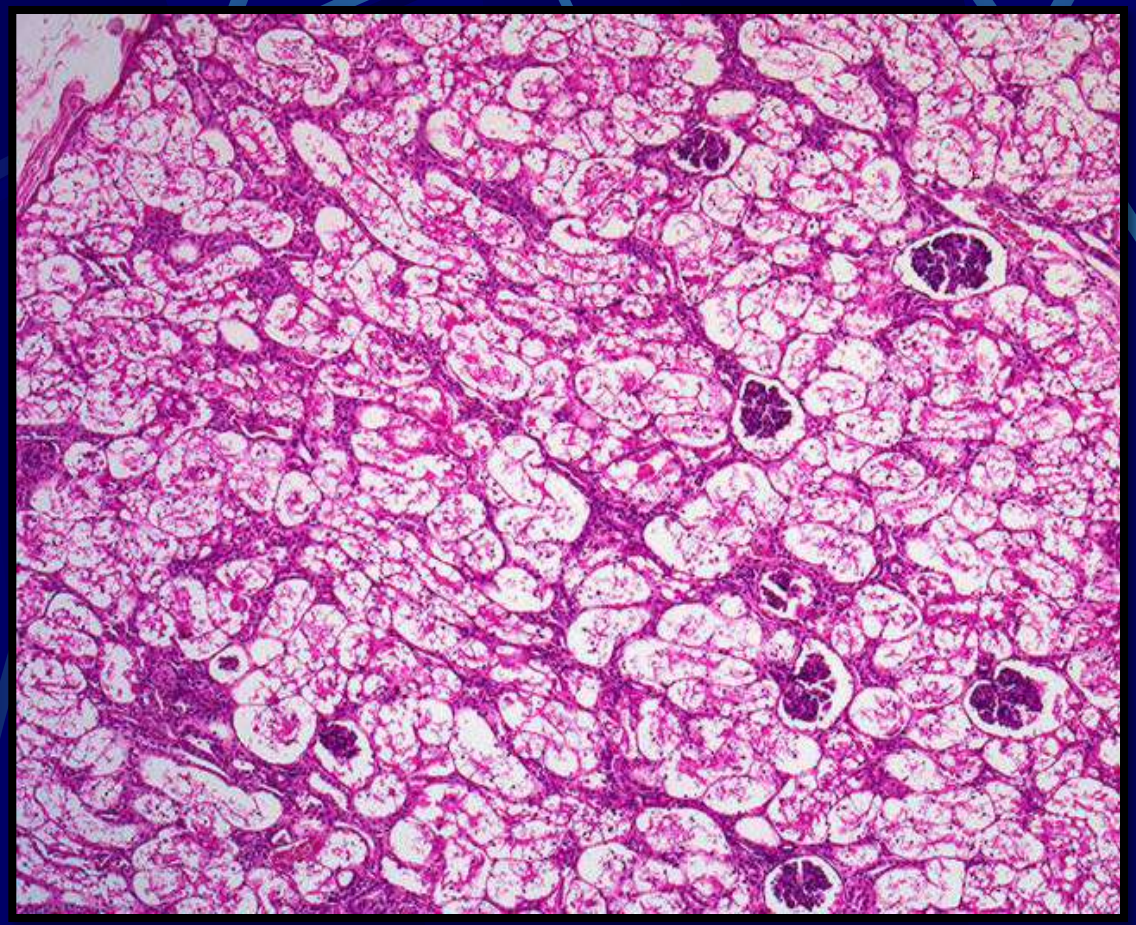
Types of degeneration
1- Cloudy swelling Hydropic degeneration
2- (Parenchymatous degeneration)
3- Waxy degeneration (zenkers degeneration)
4- Hyaline degeneration
5- Amyloid degeneration.
6- Mucoid degeneration.
7- Fatty degeneration
8-Fibrinoid degeneration

Types of degeneration cont.
Common in Cause Characters of metabolites accumulate Type
Tongue macroglossia Liver spleen in tuberculosis. Antigen- Antibody reactions Deposition of Amyloid material Carbohydrates Protein Mucopolysaccharide 4.Amyloid
between skeletal muscles Excessive secretion retention of mucous. Mucoid or mucous accumulation transformation of tissues into a jelly-like structure.
5. Mucoid
Liver, kidney and heart. Sever Bacterial toxins e.g. Diphtheria Alcoholism O2 deficiency Deficiency in lipotropic factors. Disturbance in fat metabolism Deposition of Fat, accumulation due to inability of the cell to metabolise fat.

Morphology of Cell Injury

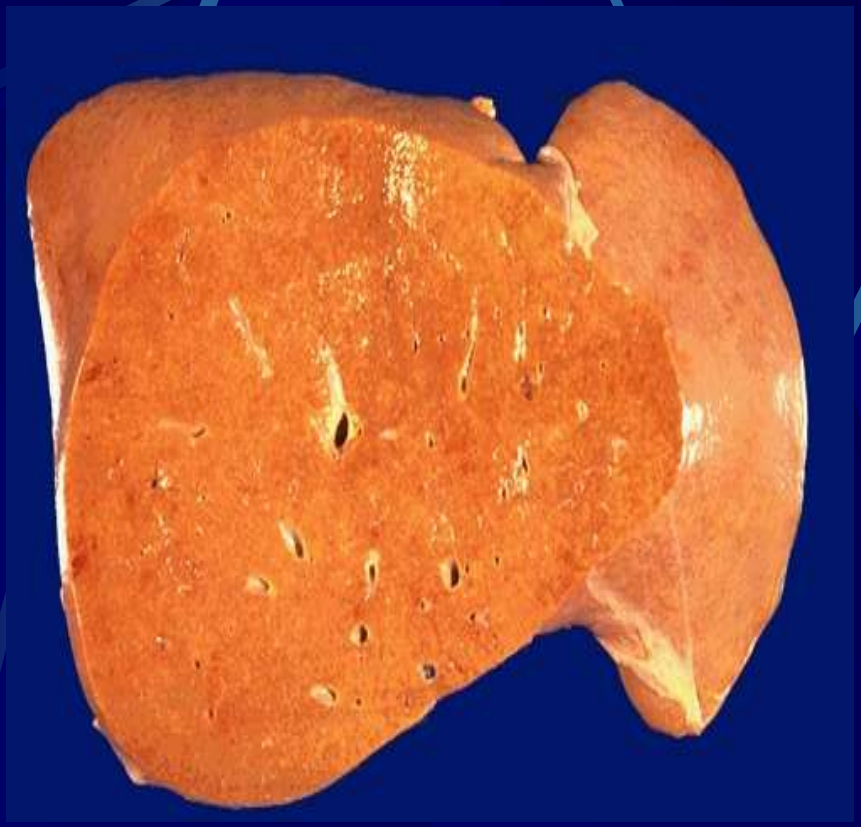
- *Reversible*:
  - Cellular swelling and vacuole formation (Hyodropic changes)
  - Changes at this stage are better appreciated by EM that may show blebbing of the plasma membrane, swelling of mitochondria and dilatation of ER
  - Fatty changes

Hydropic Change



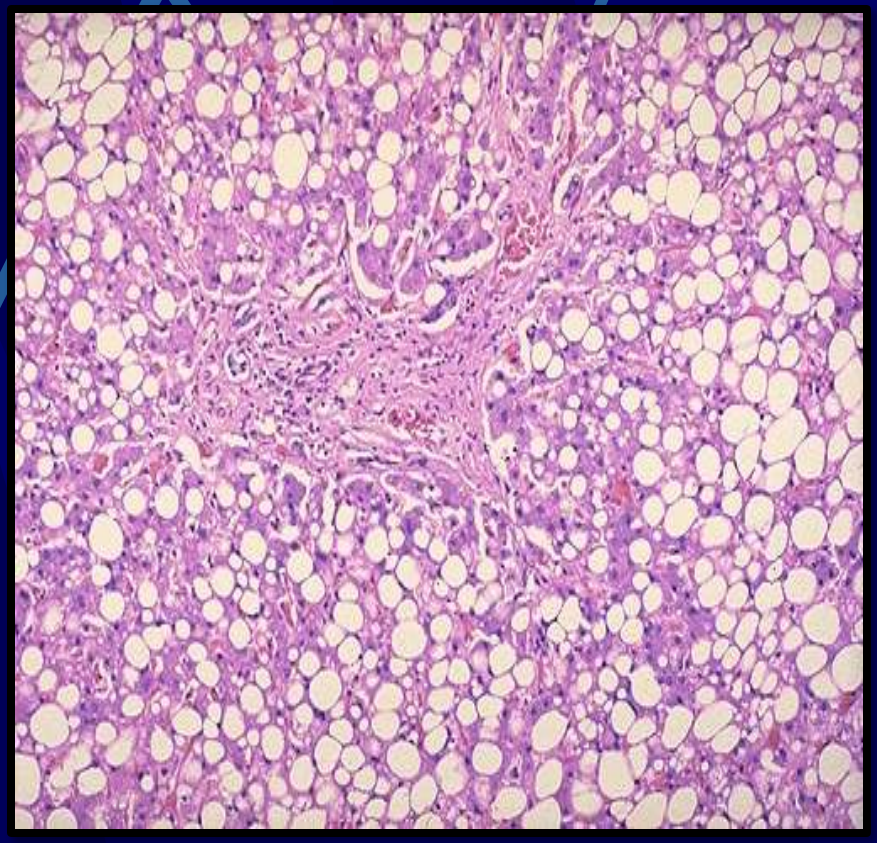
- Hydropic change is one of the early signs of cellular degeneration in response to injury.
- refers to the accumulation of water in the cell. This is clearly seen in this slide.
- The accumulation of water in the tubular cells is usually due to hypoxia of the tissue with a resultant decrease in aerobic respiration in the mitochondria and a decreased production ATP.

Fatty Change



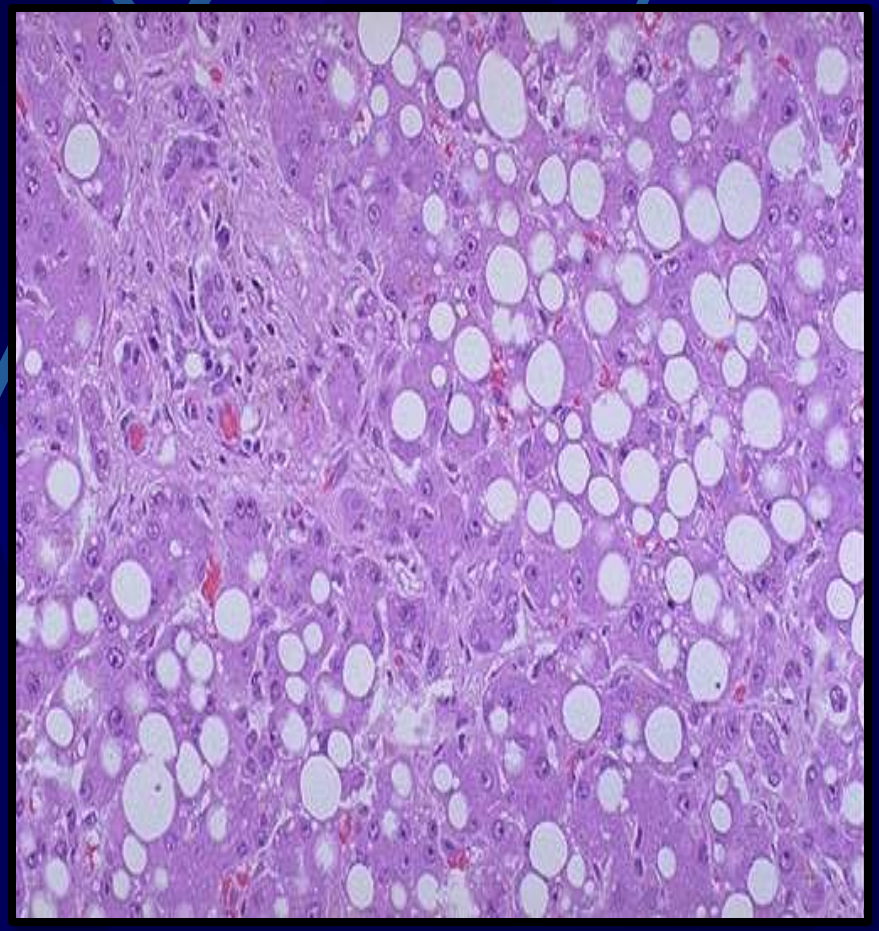
- This liver is slightly enlarged and has a pale yellow appearance, seen both on the capsule and cut surface. This uniform change is consistent with fatty metamorphosis (fatty change).

- This is the histologic appearance of hepatic fatty change. The lipid accumulates in the hepatocytes as vacuoles.
- These vacuoles have a clear appearance with H&E staining.
- The most common cause of fatty change in developed nations is alcoholism.
- Diabetes mellitus, obesity, and severe gastrointestinal malabsorption are additional causes.



Fatty Change

- Here are seen the lipid vacuoles within hepatocytes.
- The lipid accumulates when lipoprotein transport is disrupted and/or when fatty acids accumulate.
- Alcohol, the most common cause, is a hepatotoxin that interferes with mitochondrial and microsomal function in hepatocytes, leading to an accumulation of lipid.



Morphology of Cell Injury

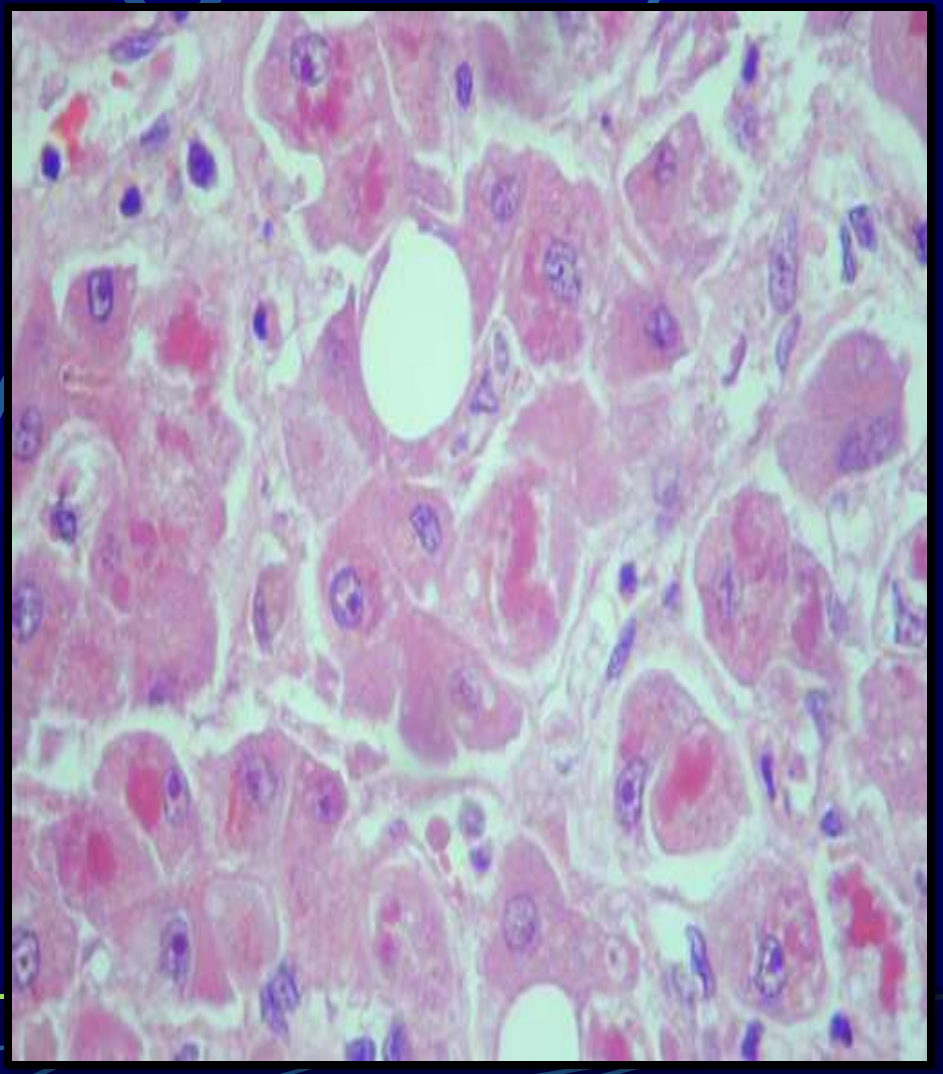
- *Irreversible/Necrosis*
  - **The changes are produced by enzymatic digestion of dead cellular elements, denatunation of proteins and autolysis (by lysosomal enzymes)**
  - **Cytoplasm - increased eosinophilia**
  - **Nucleus - nonspecific breakdown of DNA leading to**
    - **pyknosis (shrinkage),**
    - **karyolysis (fading) and**
    - **karyorrhexis (fragmentation).**

Chronic Cell Injury

- Non-lethal injury may cause subcellular changes some of which are characteristically seen in certain pathologic conditions. The following are examples of some of these changes:
  - Changes in mitochondria seen in various conditions in some of which there is an increase in the number of mitochondria with various morphological abnormalities.
  - Cytoskeletal changes with formation of distinctive intracellular inclusions such as Mallory body Neurofibrillary tangles, or Lewy body.

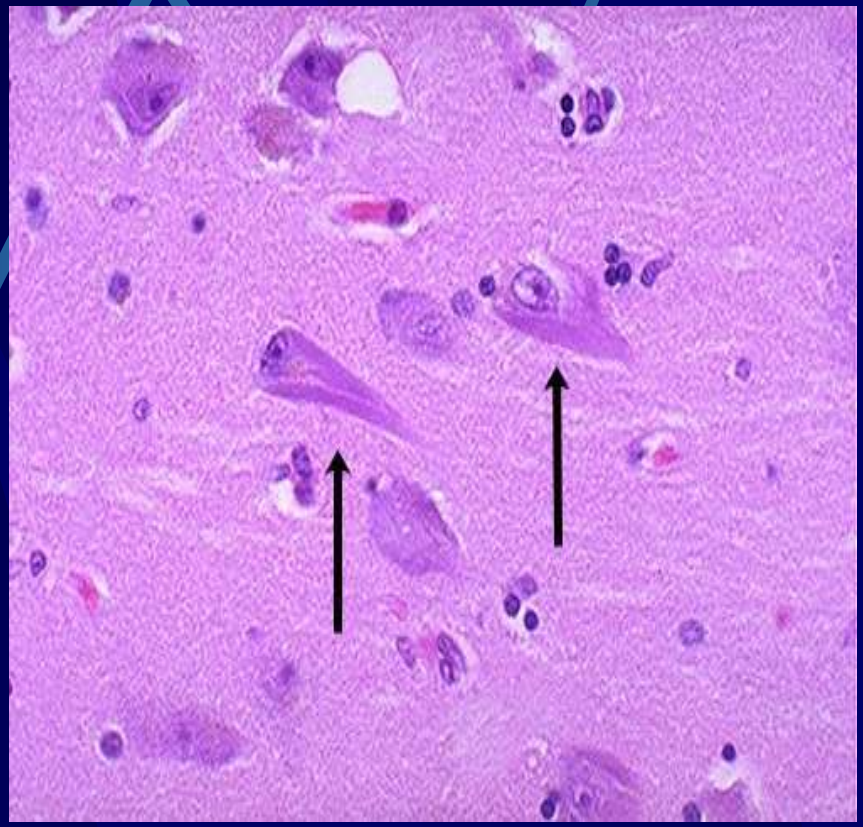
Mallory Bodies

- Cytoplasmic organelle damage leads to a variety of injury patterns, most of which are best seen by electron microscopy.
- Acute injuries tend to damage an entire cell, so specific organelle damage is beside the point.
- However, in some cases the damage can be cumulative over many years.
- Here are Mallory bodies (the red globular material) composed of cytoskeletal filaments in liver cells chronically damaged from alcoholism.
- These are a type of "intermediate" filament between the size of actin (thin) and myosin (thick).



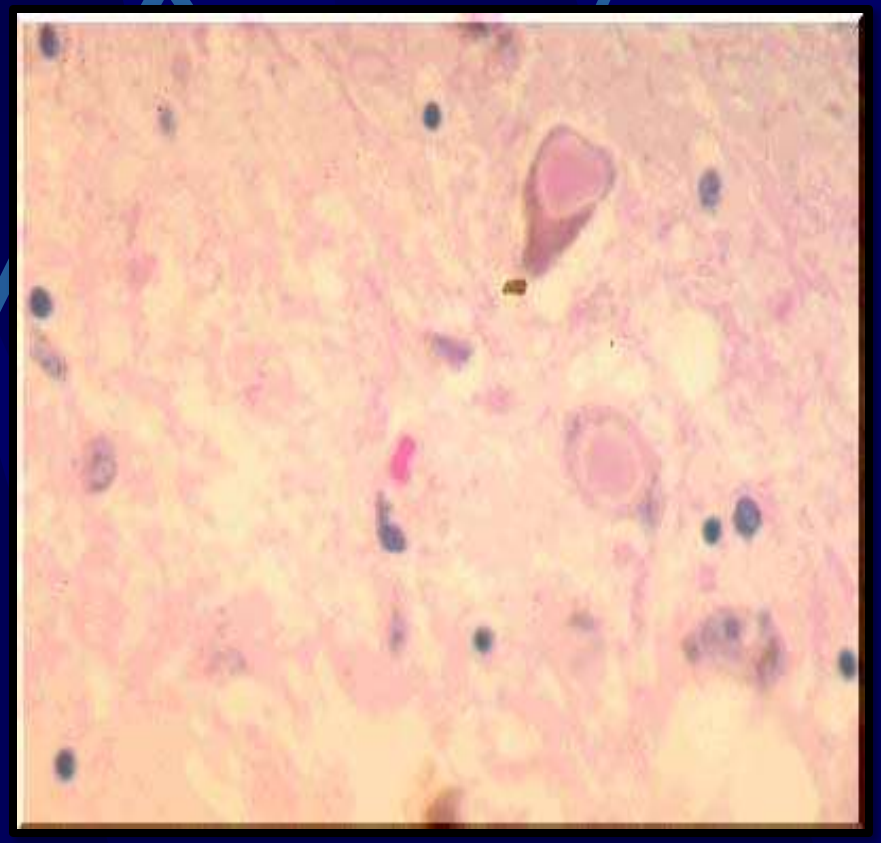
Neurofibrillary Tangles

- Here are neurofibrillary tangles in neurons of a patient with Alzheimer's disease.
- The cytoskeletal filaments are grouped together in the elongated pink tangles.



Lewy bodies

- Lewy bodies in the image above are the intracytoplasmic, eosinophilic inclusions with a clear halo around.
- Lewy bodies are abnormal aggregates of protein that develop inside nerve cells.



Cell Death

- Death of cells occurs in two ways:
  - **Necrosis**--(irreversible injury) changes produced by enzymatic digestion of dead cellular elements
  - **Apoptosis**--vital process that helps eliminate unwanted cells--an internally programmed series of events effected by dedicated gene products

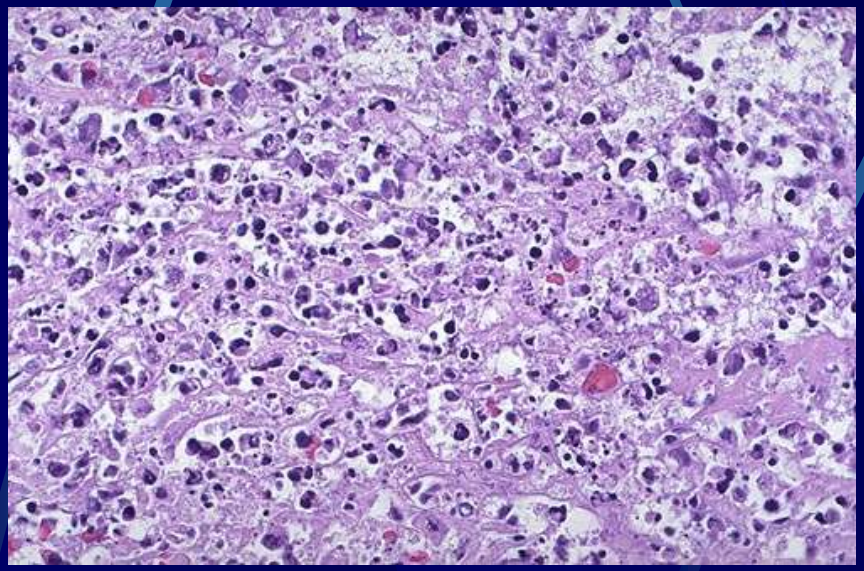
Mechanisms of Cell Death

- Mechanisms of cell death caused by different agents may vary. However, certain biochemical events are seen in the process of cell necrosis:
  - ATP depletion
  - Loss of calcium homeostasis and free cytosolic calcium
  - Free radicals: superoxide anions, Hydroxyl radicals, hydrogen peroxide
  - Defective membrane permeability
  - Mitochondrial damage
  - Cytoskeletal damage

Patterns of Necrosis In Tissues or Organs

- As a result of cell death the tissues or organs display certain macroscopic changes:
  - **Coagulative necrosis**:
    - typically seen in hypoxic environments
    - the outline of the dead cells are maintained and the tissue is somewhat firm.
    - Example: myocardial infarction
  - **Liquifactive necrosis**: the dead cells undergo disintegration and affected tissue is liquified.
    - Example: cerebral infarction.
    - usually associated with cellular destruction and pus formation (e.g. pneumonia).
    - ischemia (restriction of blood supply) in the brain produces liquefactive rather than coagulative necrosis.

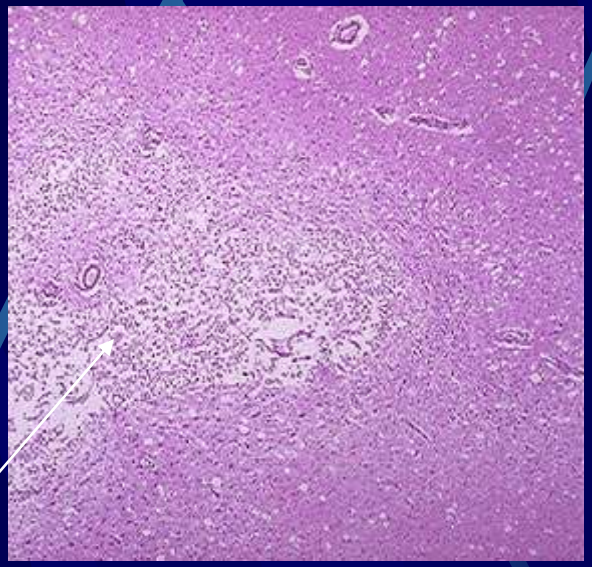
Coagulative Necrosis

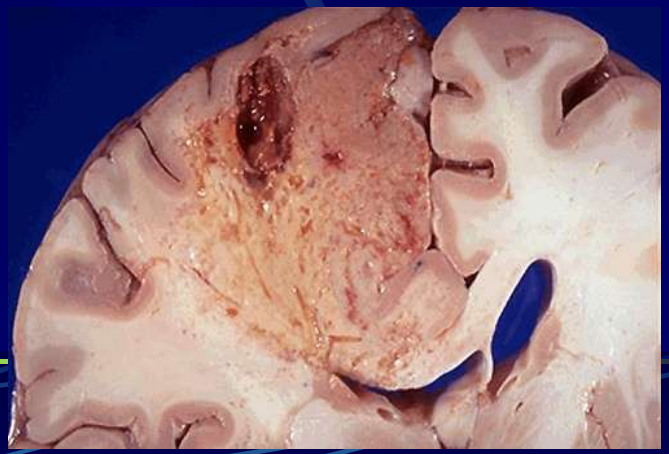


- When there is marked cellular injury, there is cell death. This microscopic appearance of myocardium is a mess because so many cells have died that the tissue is not recognizable. Many nuclei have become pyknotic (shrunken and dark) and have then undergone karorrhexis (fragmentation) and karyolysis (dissolution). The cytoplasm and cell borders are not recognizable.

Liquefactive necrosis

- This is liquefactive necrosis in the brain in a patient who suffered a "stroke" with focal loss of blood supply to a portion of cerebrum. This type of infarction is marked by loss of neurons and neuroglial cells and the formation of a clear space at the centre left.

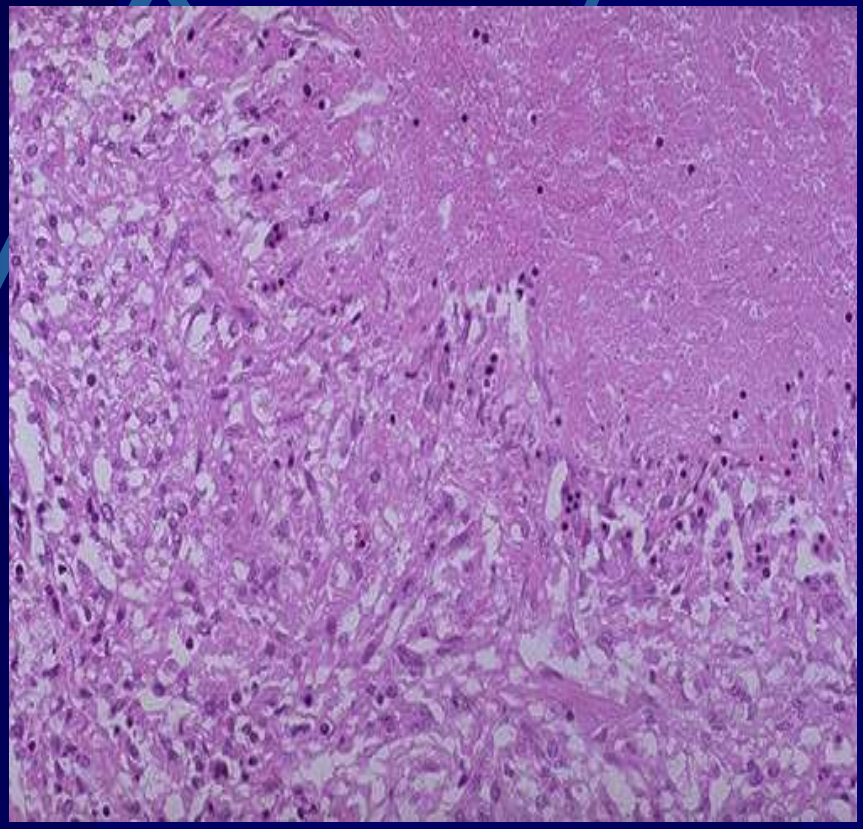




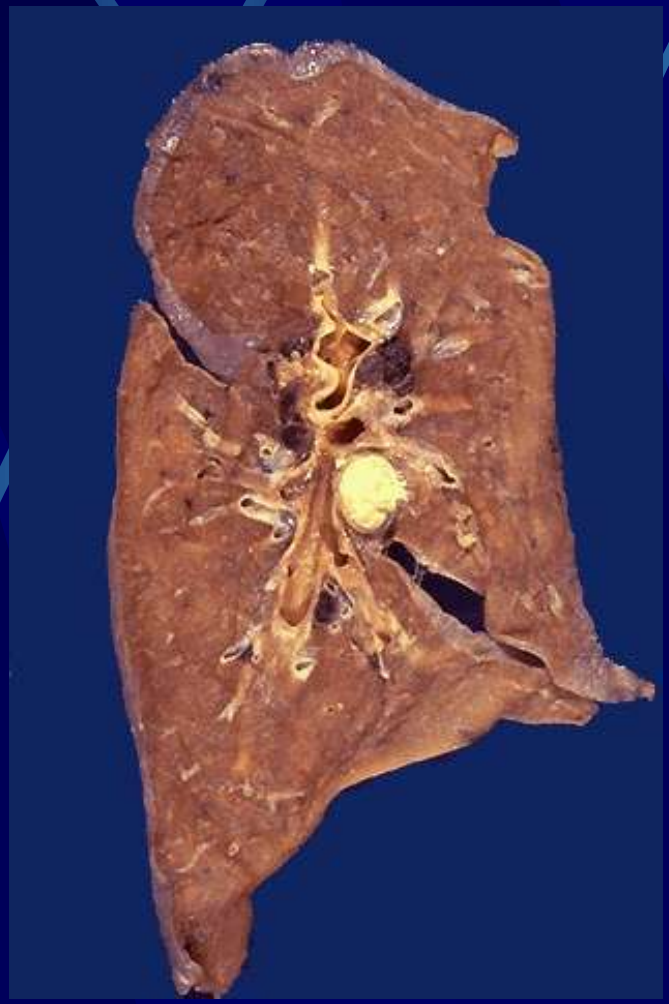
- **Caseous necrosis**:
  - specific form of coagulation necrosis typically caused by mycobacteria (e.g. tuberculosis).
  - a form of coagulative necrosis (cheese-like).
  - Example: tuberculosis lesions.
- **Fat necrosis**:
  - enzymatic digestion of fat.
  - Example: necrosis of fat by pancreatic enzymes.
- **Gangrenous necrosis**:
  - Necrosis (secondary to ischemia)
  - usually with superimposed infection.
  - Example: necrosis of distal limbs, usually foot and toes in diabetes.

Caseous Necrosis

- Microscopically, caseous necrosis is characterized by acellular pink areas of necrosis, as seen here at the upper right, surrounded by a granulomatous inflammatory process.

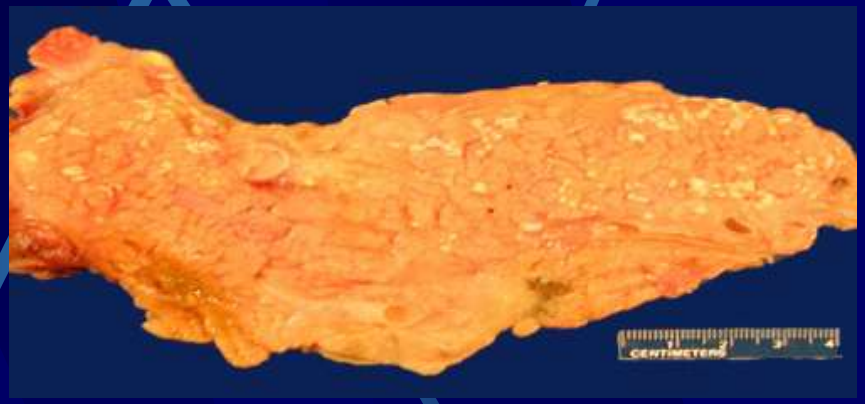


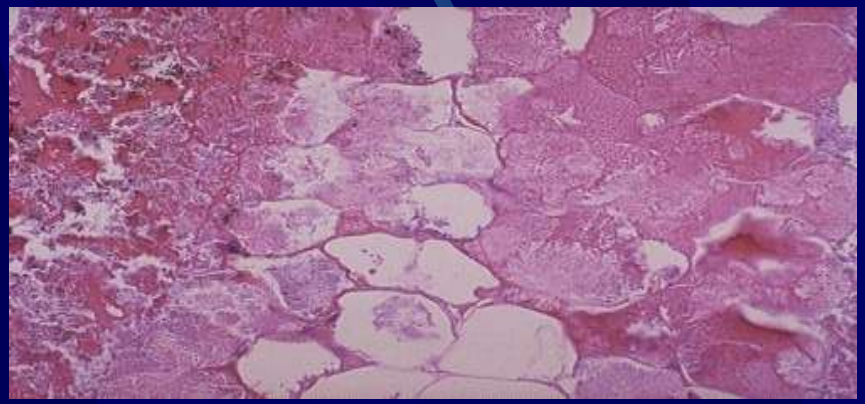
- Caseous necrosis hilar lymph node lung



Fat Necrosis

- This is fat necrosis of the pancreas. Cellular injury to the pancreatic acini leads to release of powerful enzymes which damage fat by the production of soaps, and these appear grossly as the soft, chalky white areas seen here on the cut surfaces.





Gangrenous Necrosis

- In this case, the toes were involved in a frostbite injury. This is an example of "dry" gangrene in which there is mainly coagulative necrosis from the anoxic injury.

- Gummatous necrosis is restricted to necrosis involving spirochaetal infections (e.g. syphilis).
- Haemorrhagic necrosis is due to blockage of the venous drainage of an organ or tissue (e.g. in testicular torsion).
- Fibrinoid necrosis is caused by immune-mediated vascular damage. It is marked by deposition of fibrin-like proteinaceous material in arterial walls, which appears smudgy and eosinophilic on light microscopy.

Morphological Forms of Programmed Cell Death

Type I = Apoptosis
Type II = Autophagic Cell Death
Type III = Non-lysosomal

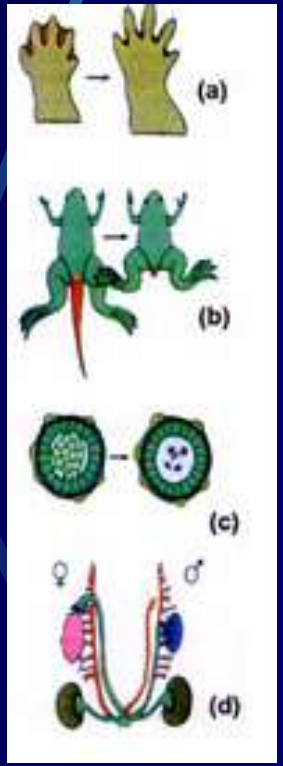
Kerr, Wyllie, and Currie, 1972; Schweicheland Merker, 1973; Clarke 1990Kerr, Wyllie, and Currie, 1972; Schweicheland Merker, 1973

Apoptosis

- This process helps to eliminate unwanted cells by an internally programmed series of events effected by dedicated gene products. It serves several vital functions and is seen under various settings.
  - During development for removal of excess cells during embryogenesis
  - To maintain cell population in tissues with high turnover of cells, such as skin, bowels.
  - To eliminate immune cells after cytokine depletion, and autoreactive T-cells in developing thymus.
  - To remove damaged cells by virus
  - To eliminate cells with DNA damage by radiation, cytotoxic agents etc.
  - Hormone-dependent involution - Endometrium, ovary, breasts etc.
  - Cell death in tumours.

Apoptosis

- In the human body ~ 100,000 cells are produced every second by mitosis and a similar number die by apoptosis.
- Development and morphogenesis
  - During limb formation separate digits evolve
  - Ablation of cells no longer needed (tadpole)
- Homeostasis
  - Immune system
  - >95% T and B cells die during maturation (negative selection)
- Deletion of damaged/ dangerous cells

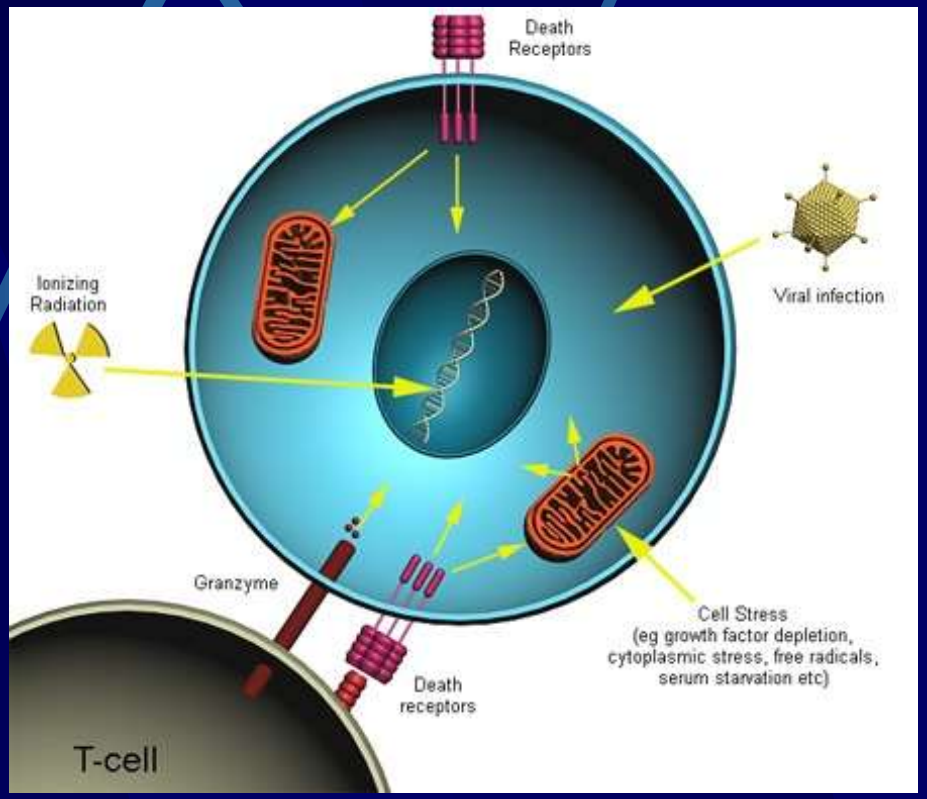


Mechanisms of Apoptosis

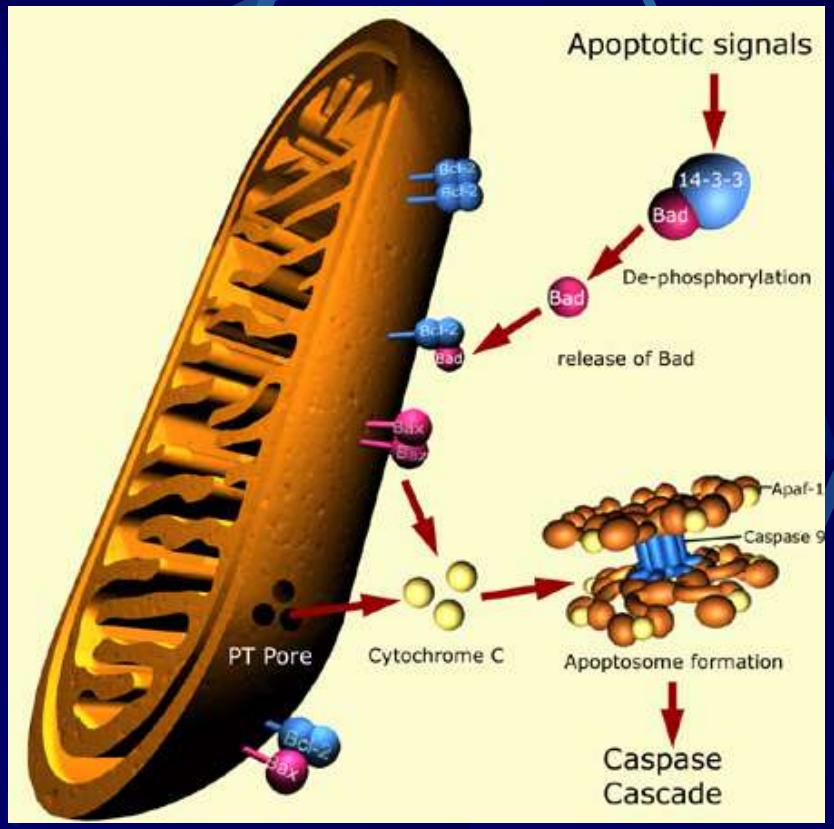
- Apoptosis can be induced by various factors under both physiological and pathological conditions:
- It is an energy-dependent cascade of molecular events which include protein cleavage by a group of enzymes (caspases), protein cross-linking, DNA breakdown.
- Apoptosis is regulated by a large family of genes some of which are inhibitory (bcl-2) and some are stimulatory (bax).

Apoptosis

- There are a number of mechanisms through which apoptosis can be induced in cells.
- The sensitivity of cells to any of these stimuli can vary depending on a number of factors such as:
  - the expression of pro- and anti-apoptotic proteins (eg. the Bcl-2 proteins or the Inhibitor of Apoptosis Proteins),
  - the severity of the stimulus and
  - the stage of the cell cycle.



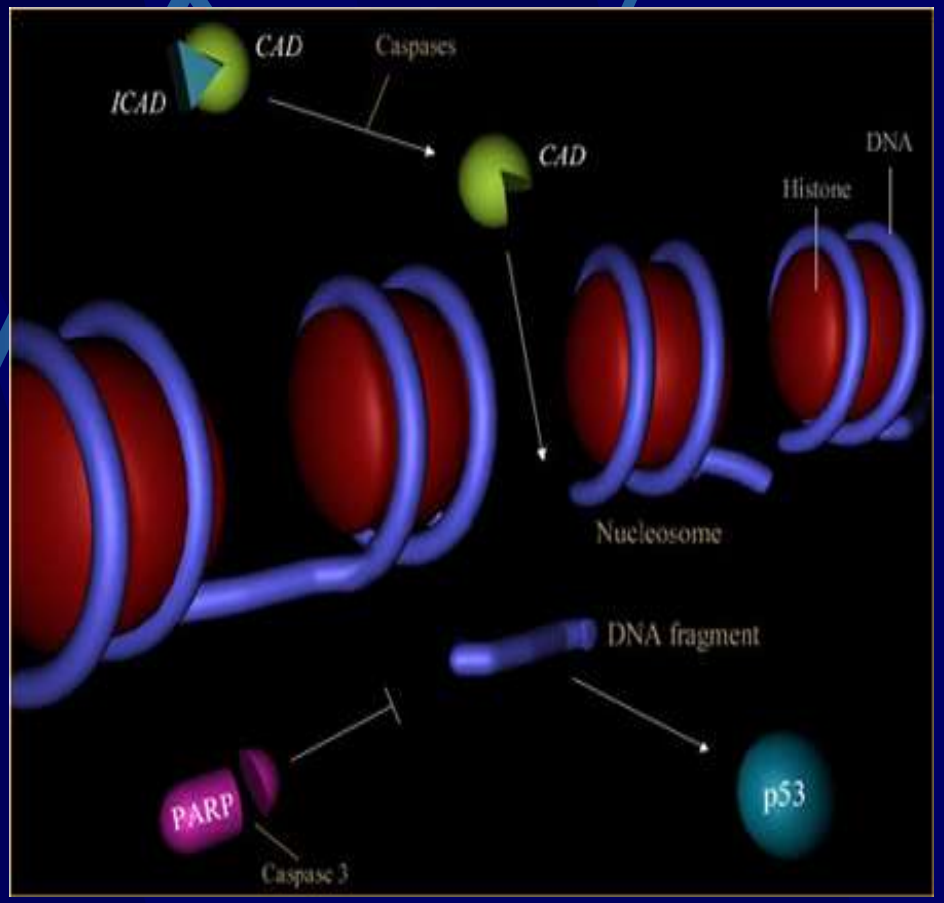
Role of mitochondria in apoptosis



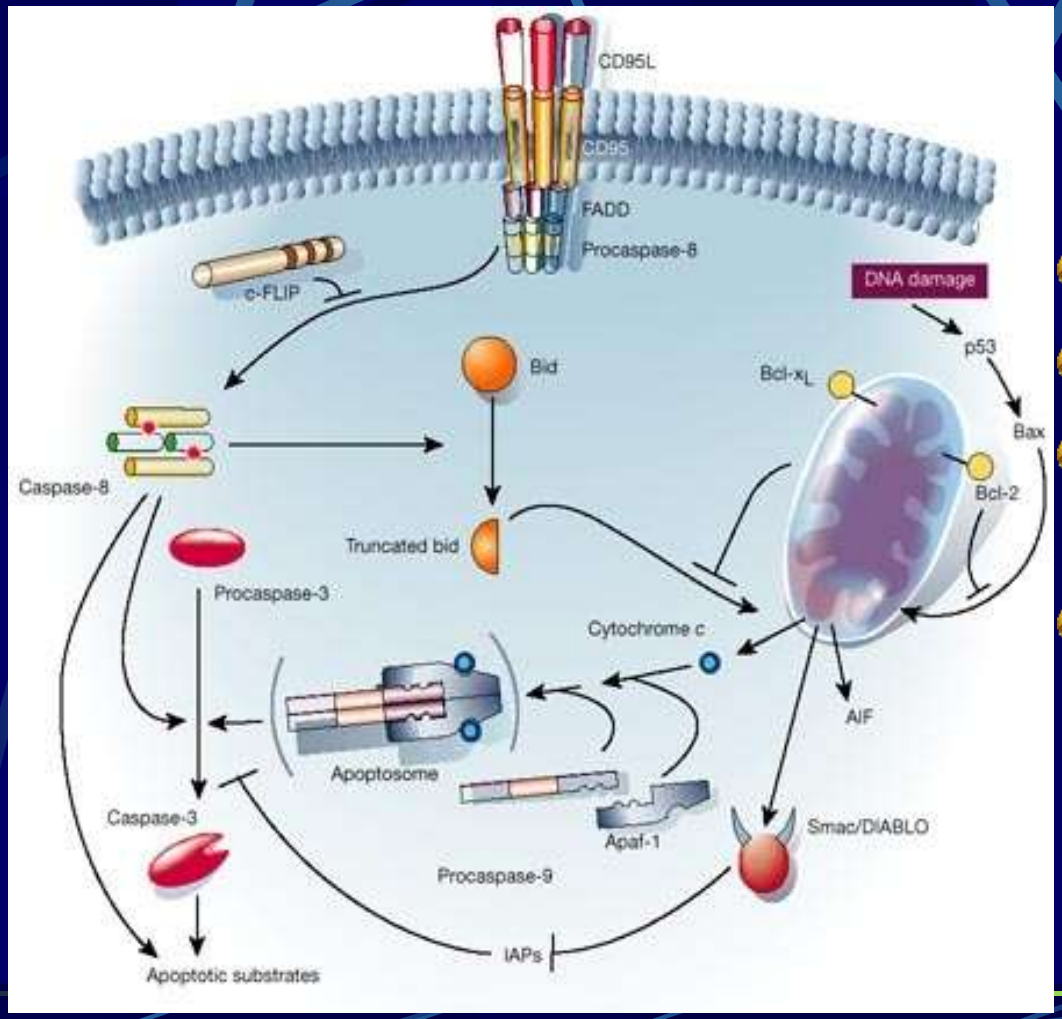
- The pro-apoptotic bcl-2 proteins are often found in the cytosol where they act as sensors of cellular damage or stress.
- Following cellular stress they relocate to the surface of the mitochondria where the anti-apoptotic proteins are located.
- This interaction between pro- and anti-apoptotic proteins disrupts the normal function of the anti-apoptotic bcl-2 proteins and can lead to the formation of pores in the mitochondria and the release of cytochrome C and other pro-apoptotic molecules from the intermembrane space.
- This in turn leads to the formation of the apoptosome and the activation of the caspase cascade.
- The release of cytochrome C from the mitochondria is a particularly important event in the induction of apoptosis.
- Once cytochrome C has been released into the cytosol it is able to interact with a protein called Apaf-1. This leads to the recruitment of pro-caspase 9 into a multi-protein complex with cytochrome C and Apaf-1.

Caspases and Apoptosis

- One of the hallmarks of apoptosis is the cleavage of chromosomal DNA into nucleosomal units.
- The caspases play an important role in this process by activating DNases, inhibiting DNA repair enzymes and breaking down structural proteins in the nucleus.



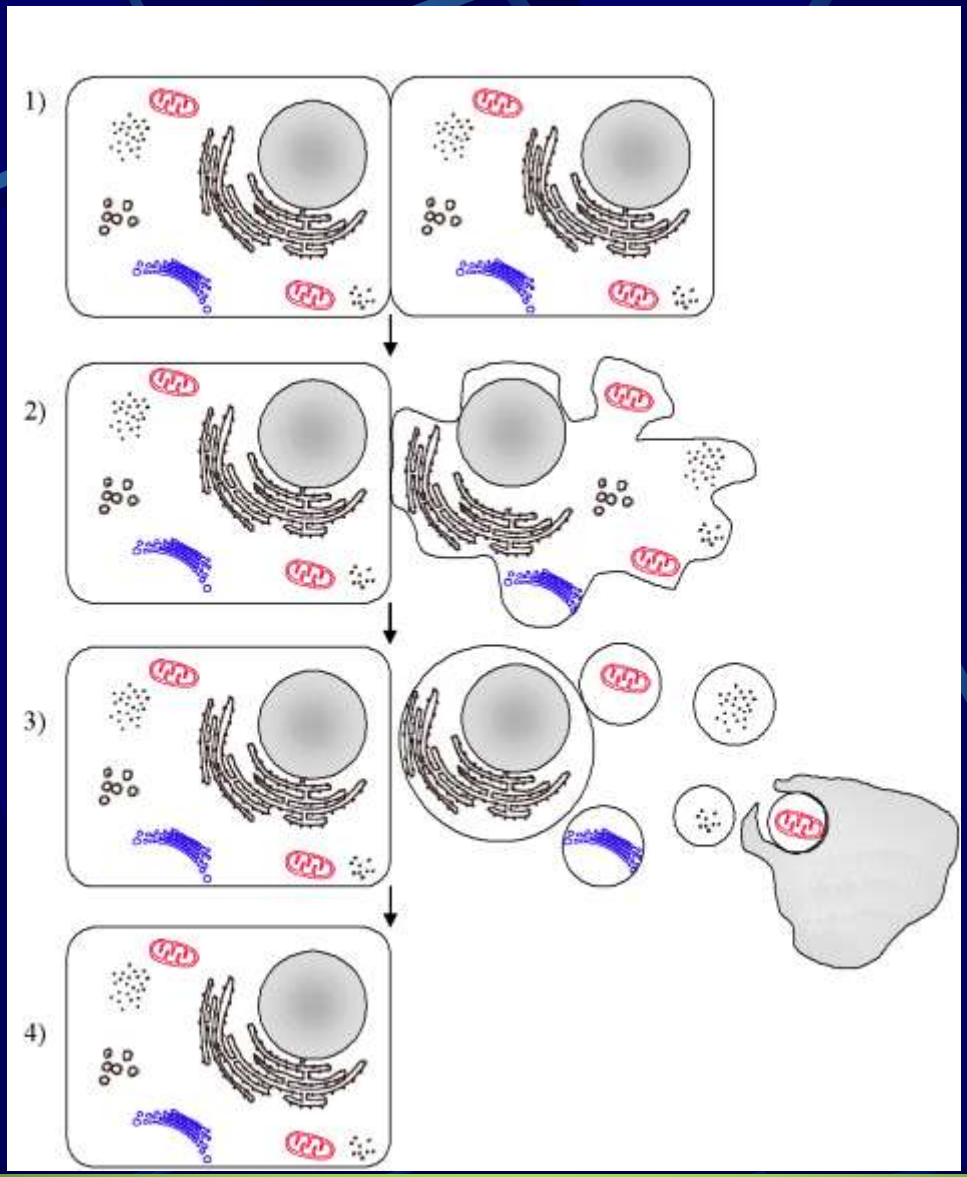
2 pathways



- Death receptor (left)
- Mitochondrial (right)
- Both Converge
  - Caspase 3 activation
- Then branch causing eventual cell death

Morphology of Apoptosis

- Shrinkage of cells
- Condensation of nuclear chromatin peripherally under nuclear membrane
- Formation of apoptotic bodies by fragmentation of the cells and nuclei. The fragments remain membrane-bound and contain cell organelles with or without nuclear fragments.
- Phagocytosis of apoptotic bodies by adjacent healthy cells or phagocytes.
- Unlike necrosis, apoptosis is not accompanied by inflammatory reaction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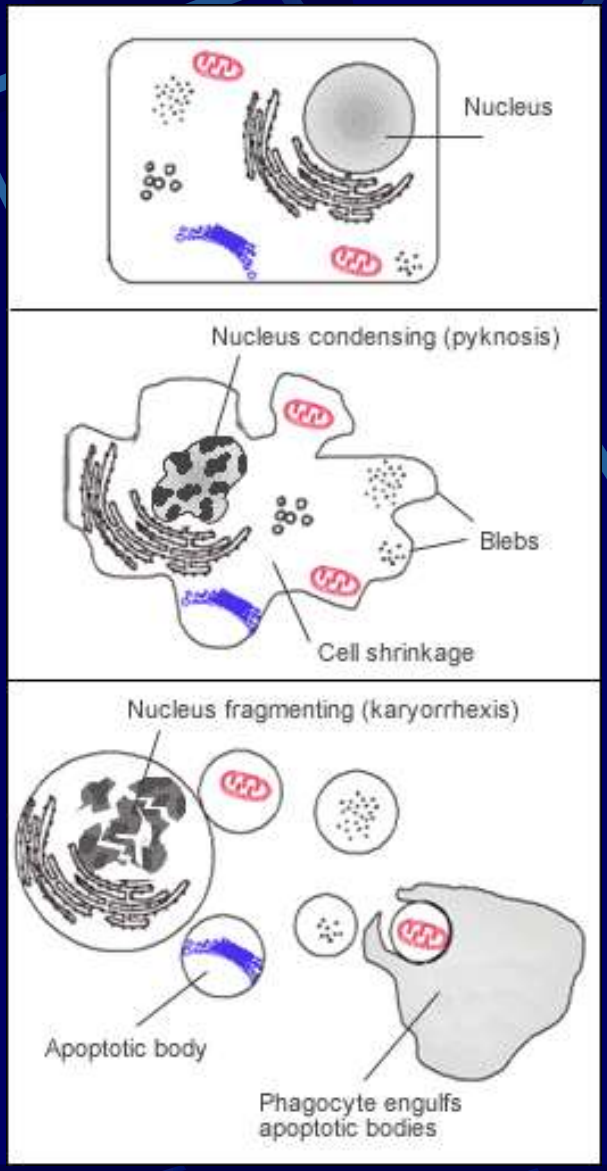
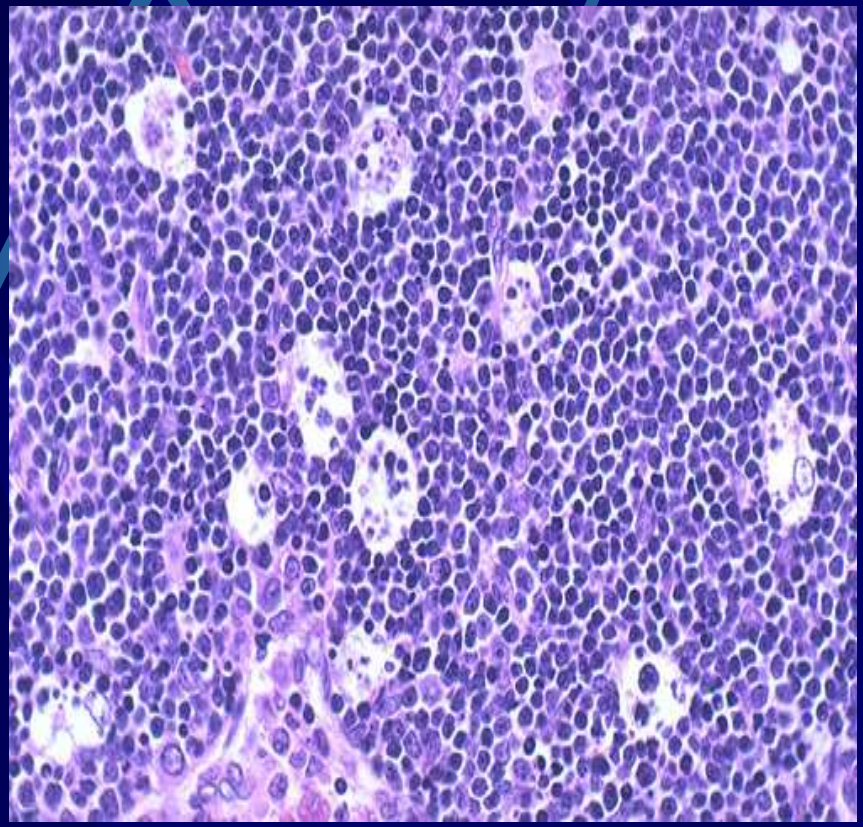

Nucleus
Nucleus condensing (pyknosis)
Blebs
Cell shrinkage
Nucleus fragmenting (karyorrhexis)
Apoptotic body
Phagocyte engulfs
apoptotic bodies

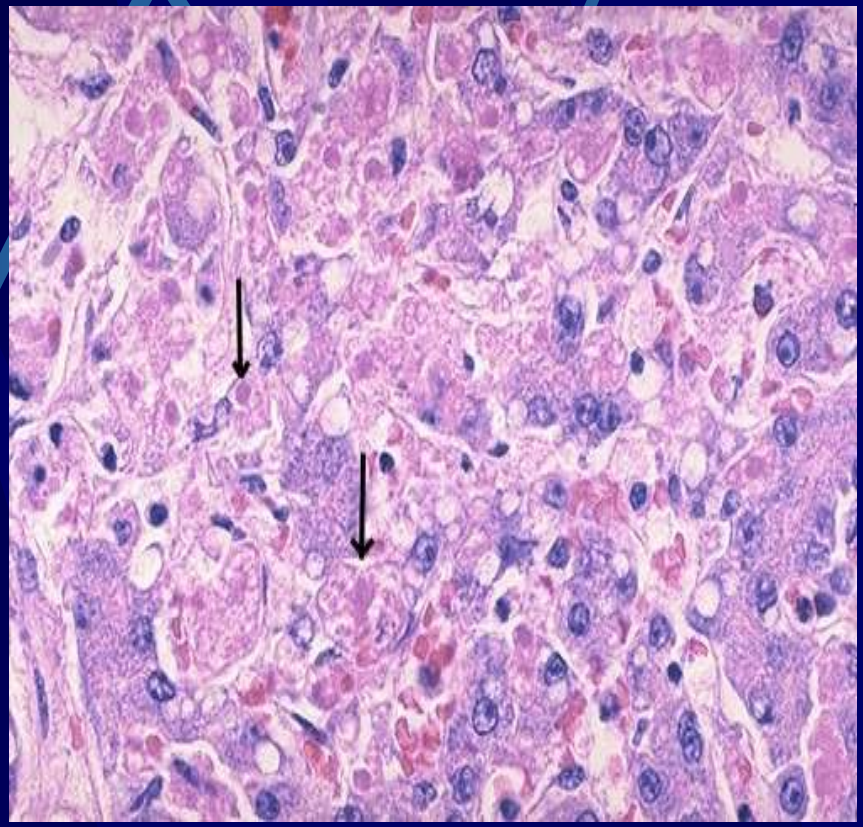
Apoptosis

- In this fetal thymus there is involution of thymic lymphocytes by the mechanism of apoptosis.
- Individual cells fragment and are consumed by phagocytes to give the appearance of clear spaces filled with cellular debris.
- Apoptosis is controlled by many mechanisms.
- Genes such as Bcl-2 are turned off and Bax genes turned on.
- Proteolytic enzymes called caspases produce much cellular breakdown.



Apoptosis

- Apoptosis is a more orderly process of cell death in which there is individual cell necrosis, not necrosis of large numbers of cells.
- In this example, liver cells are dying individually (arrows) from injury by viral hepatitis.
- The cells are pink and without nuclei.



Autophagy

- When cells are faced with an inadequate supply of nutrients in their extracellular fluid (ECF), they may begin to cannibalize some of their internal organelles (e.g. mitochondria) for re-use of their components.

- Autophagy refers to a set of diverse processes whereby intracytoplasmic material is delivered to lysosomes.

Autophagy

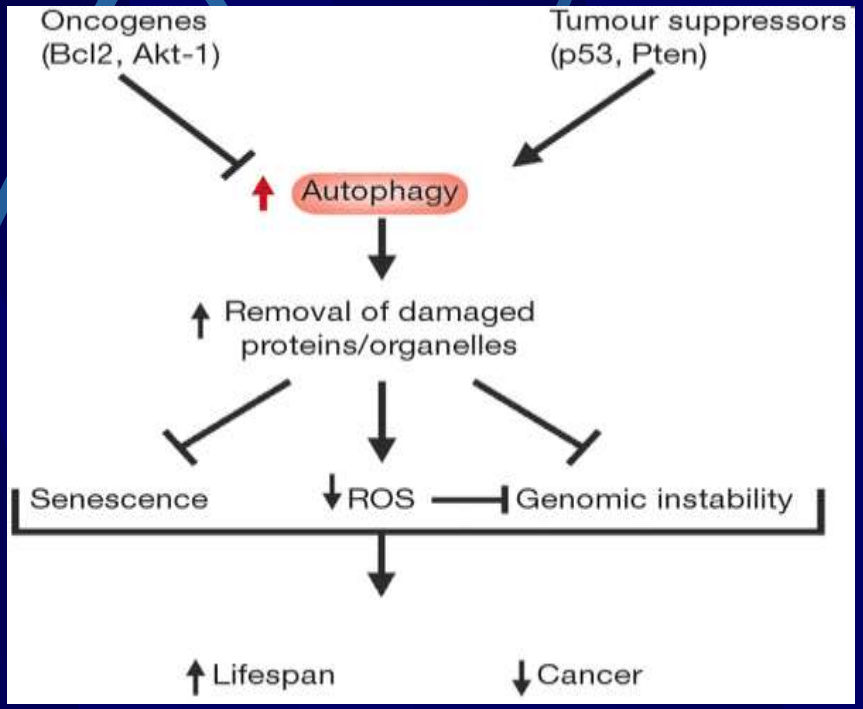
Autophagy is a regulated process for the removal of damaged proteins and organelles.

Autophagy occurs under basal conditions and is stimulated by environmental factors such as starvation.

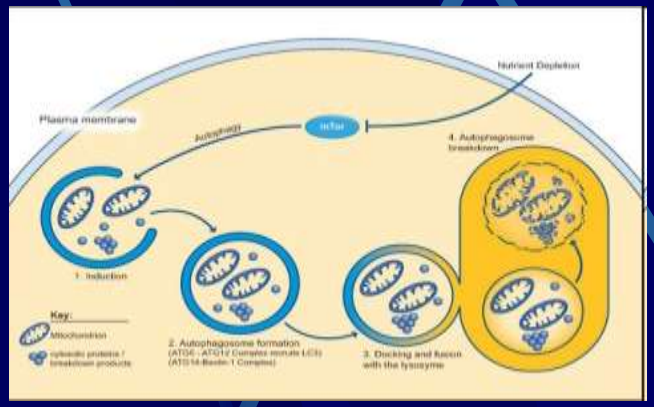
There is evidence that proteins that are linked to tumorigenesis can regulate the rate of autophagy, with oncogenes in general blocking and tumour suppressors stimulating the process.

The removal of damaged cellular components, especially damaged mitochondria, might decrease the level of reactive oxygen species (ROS), which in turn might reduce genomic instability or forestall cellular senescence.

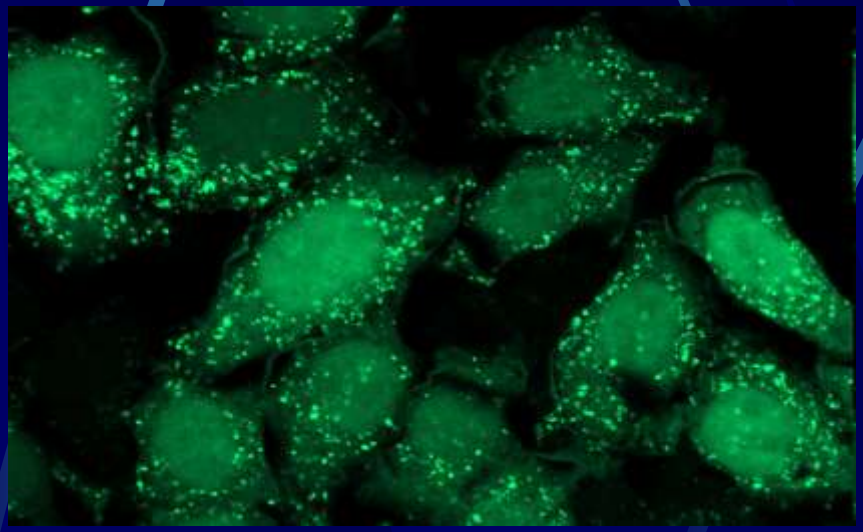
Such mechanisms might allow moderate increases in autophagy to reduce the incidence of cancer and prolong lifespan.



Autophagy involves:



- formation of a double membrane within the cell which envelops the materials to be degraded into a vesicle called an **autophagosome**.
- The autophagosome then fuses with a lysosome forming an **autolysosome** whose hydrolytic enzymes degrade the materials.



- The confocal microscopy image shows stable HeLa cells expressing EGFP-LC3.
- Treatment with an autophagy-inducing small molecule increases the formation of autophagosomes (green punctate structures) in these cells.

- Sarkar *et al.* Nature Chemical Biology 3(6):331-338 (2007).

Cellular Injury

- Hypoxic
- Chemical
- Infectious
- Immunologic/ Inflammatory
- Physical agents
- Nutritional balances
- Genetic factors

Types of insult - hypoxia

- Ischaemia
  - Local e.g. embolus
  - Systemic e.g. cardiac failure
- Hypoxaemia
  - Oxygen problems e.g. altitude
  - Haemoglobin problems e.g. anaemia
- Oxidative phosphorylation
  - E.g. cyanide poisoning

Types of insult - chemical

- Many of the common poisons (arsenic, cyanide, mercury) interfere with cellular metabolism. If ATP levels drop below critical levels, affected cells will die.

- The list of pharmaceuticals that may have toxic effects on cells is enormous. Some act directly, but most have their effect through breakdown metabolites. Metabolism of alcohol (a type of drug) to acetaldehyde is one example.

Types of insult - infections

- Fungi, Rickettsiae, Bacteria and Viruses
  - E.g. viruses can take over protein translation machinery and subvert it entirely to the production of new virions.

Types of insult - Physical

- Direct Physical Effects
  - Exposure of tissue to extreme heat or cold results in direct injury that is often irreversible, resulting in a pattern of coagulative necrosis (see later).
  - Sudden changes in pressure can cause cellular disruption (e.g. a hammer blow to the thumb).
  - Electrical currents can cause direct breakdown of cellular membranes that may be irreversible.

Types of insult –immune

- Inflammatory mediators such as *interferons* and *interleukins*
  - can alter both gene expression and cellular metabolism. The effects are designed to help cells combat an infectious process, but the resulting stress to the cells can be highly injurious and sometimes deadly.
- Activation of *complement*
  - can result in direct attack on a cell's surface membrane.
- Cytotoxic T-cells and NK cells
  - can mediate a direct attack on a target cell's and initiate the self-destruct cascade within a target cell.

Types of insult - nutrition

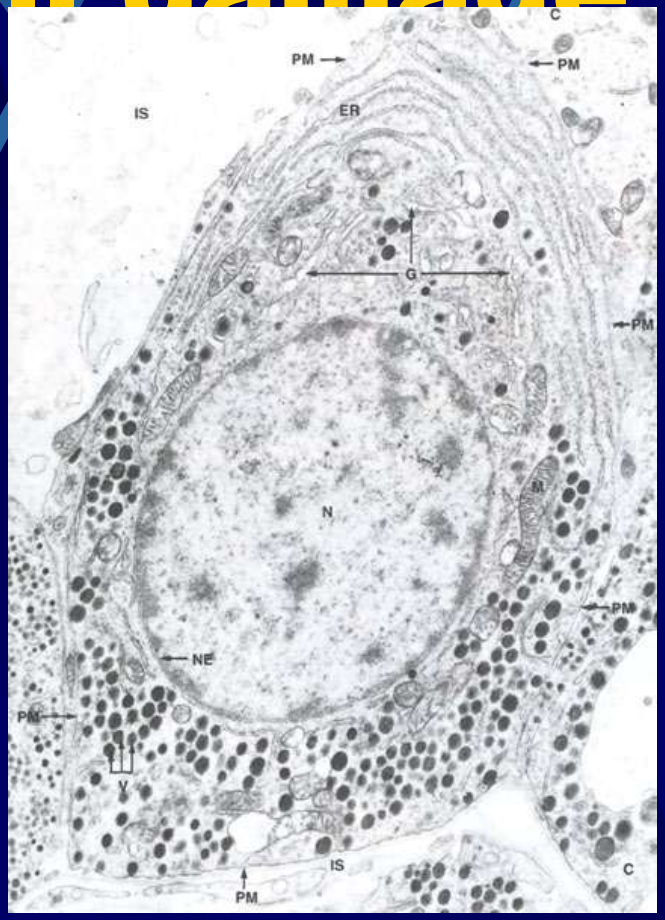
- Dietary insufficiency
  - of protein, vitamins and/or minerals can lead to injury at the cellular level due to interference in normal metabolic pathways.
- Dietary excess
  - can likewise lead to cellular and tissue alterations that are detrimental e.g. fat is the biggest offender, or excess ingestion of "health supplements"

Causes of cell injury - summary

- Hypoxia
- Chemical
- Physical
- Infection
- Immune
- Nutritional deficiency (or excess!)

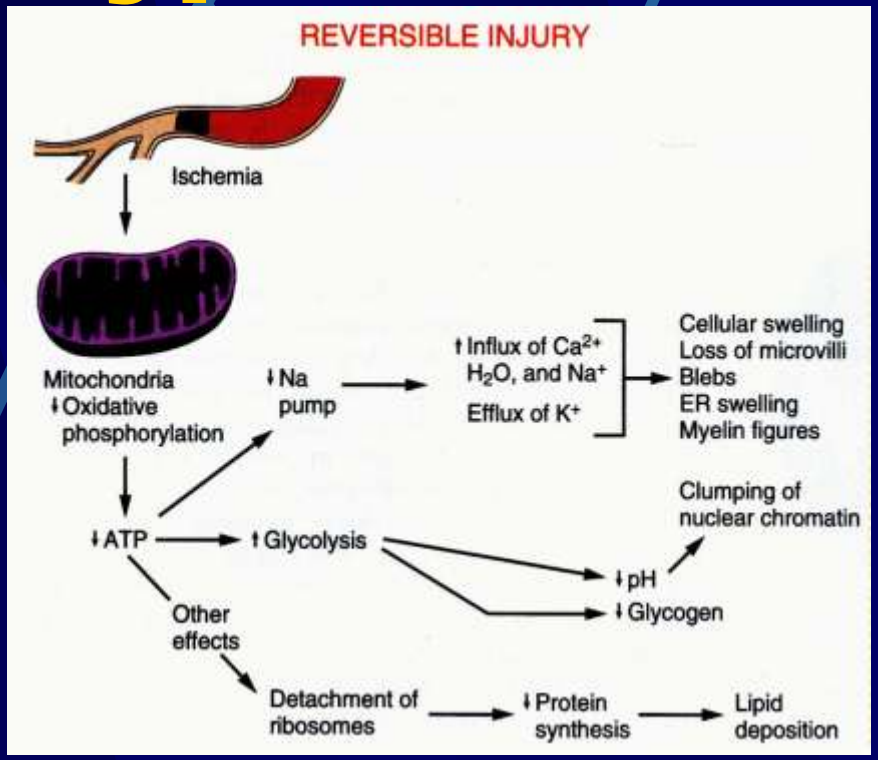
Principle structural targets for cell damage

- Cell membranes
  - Plasma membrane
  - Organelle membranes
- DNA
- Proteins
  - Structural
  - Enzymes
- Mitochondria
  - oxidative phosphorylation



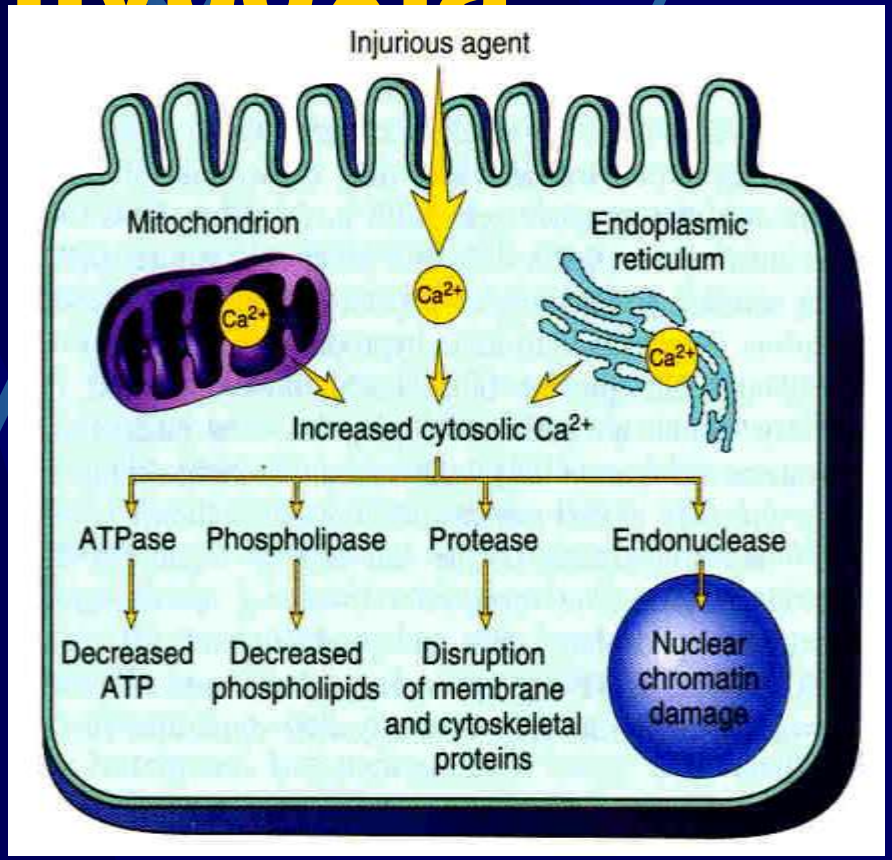
Pathogenesis of cell injury - hypoxia

- Reversible
  - Loss of ATP
    - Failure of Na/K pump
  - Anaerobic metabolism
    - Increased lactic acid and phosphate
  - Reduced protein synthesis



Pathogenesis of cell injury - hypoxia

- Irreversible
  - Massive intra-cytoplasmic calcium accumulation
  - Enzyme activation



Pathogenesis of cell injury - general

- Reduced ATP synthesis/mitochondrial damage
- Loss of calcium homeostasis
- Disrupted membrane permeability
- Free radicals

Free radicals

- Highly reactive, unstable chemicals
- Associated with cell injury
  - Chemicals/drugs, reperfusion injury, inflammation, irradiation, oxygen toxicity, carcinogenesis

Free radicals

- Free radical generation occurs by….
  - Absorption of irradiation
    - E.g. OH•, and H•
  - Endogenous normal metabolic reactions
    - E.g. O_2^{-}•, and H_2O_2
  - Transition metals
    - E.g. Fe^{+++}
  - nitrous oxide
    - an important paracrine-type mediator that helps regulate vascular pressure
  - Toxins
    - e.g. carbon tetrachloride

Free radicals

- Free radicals are removed by….
  - Spontaneous decay
  - Anti-oxidants
    - E.g. Vitamin E, vitamin A, ascorbic acid, glutathione
  - Storage proteins
    - E.g. transferrin, ferritin, ceruloplasmin
  - Enzymes
    - Catalase, SOD, glutathione peroxidase

Free radicals

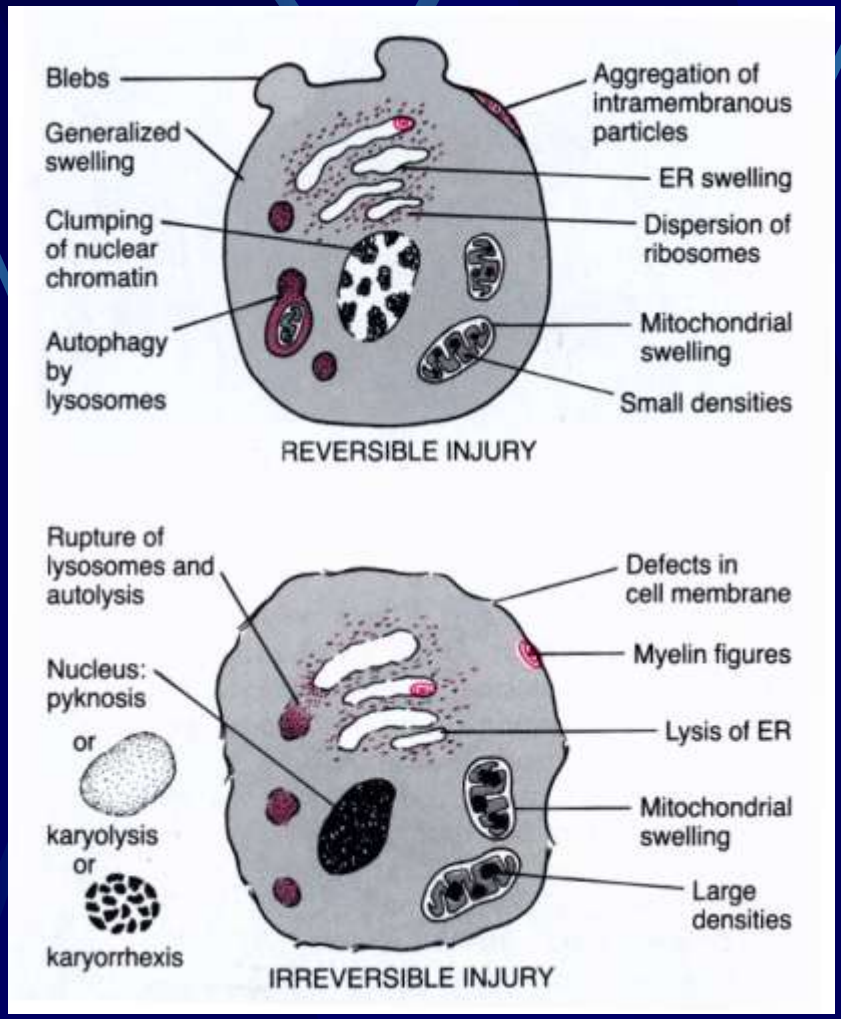
- Injure cells by…..
  - Membrane lipid peroxidation
    - Autocatalytic chain reaction
  - Interaction with proteins
    - Protein fragmentation and protein-protein cross-linkage
  - DNA damage
    - Single strand breaks (genomic and mitochondrial)

General protective mechanisms

- *Heat shock response genes*
  - comprise a large group of genes
  - expression is up-regulated in the face of cell stressors and
  - serve to protect proteins from stress-related damage
  - "clean up" damaged proteins from the cell.
- Many tissues and organs can survive significant injury if they are "pre-stressed"
  - Ways to exploit this phenomenon to improve organ transplantation and tissue repairs are being tested in clinical trials.

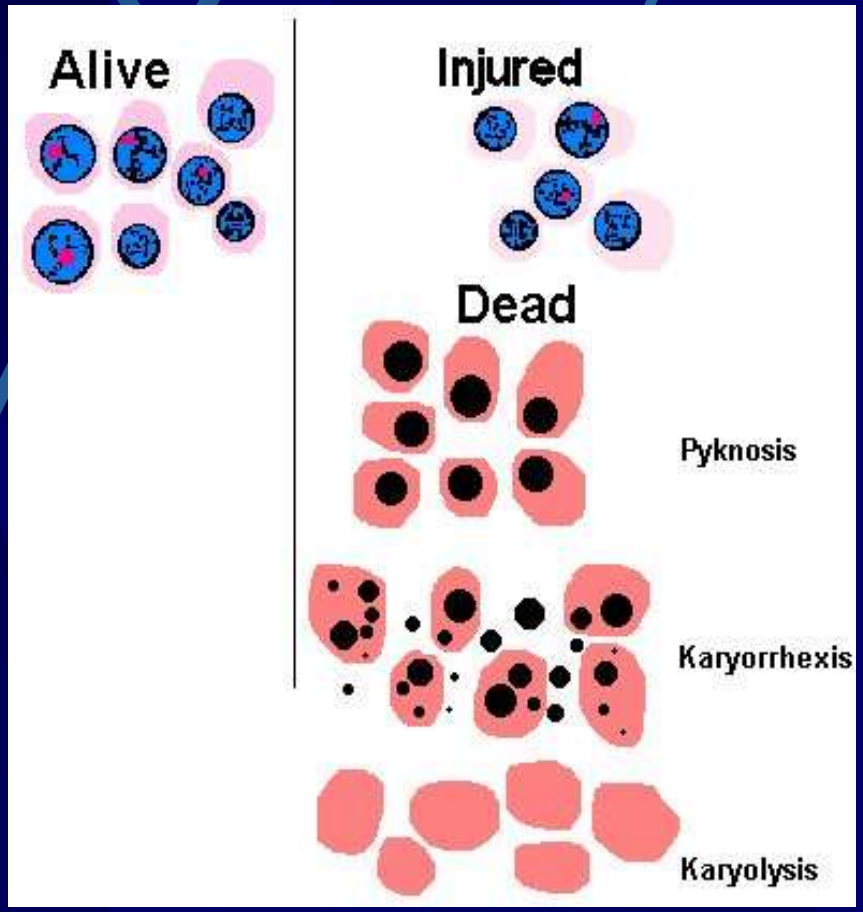
Cell injury - morphology

- Reversible
- Irreversible



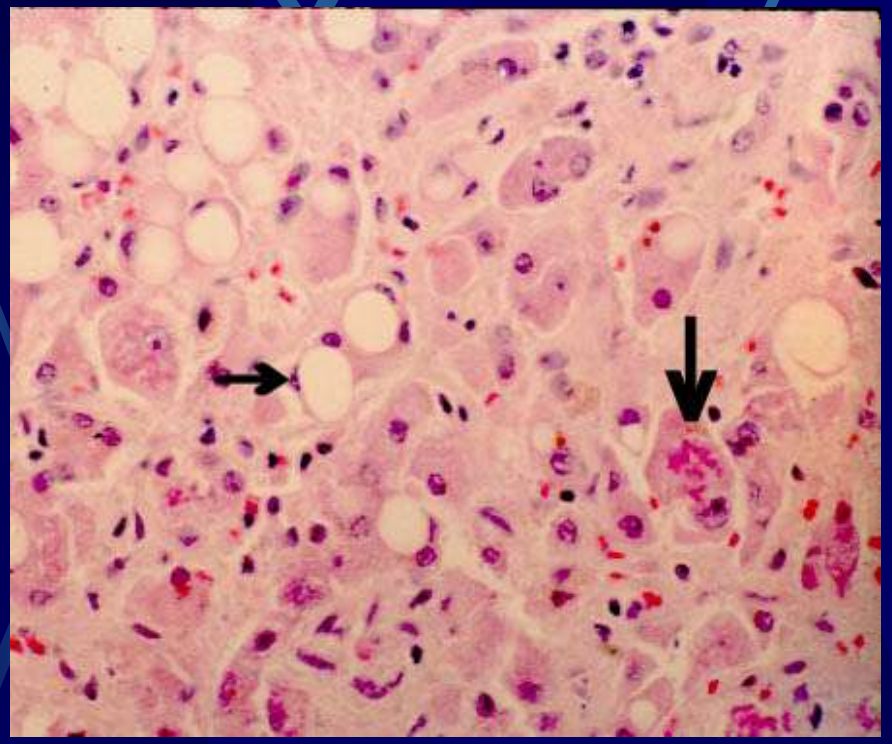
Cell injury - morphology

- Light microscopy
  - Cytoplasmic changes
  - Nuclear changes



Cell injury - morphology

- Abnormal accumulations
  - Lipid
  - Protein

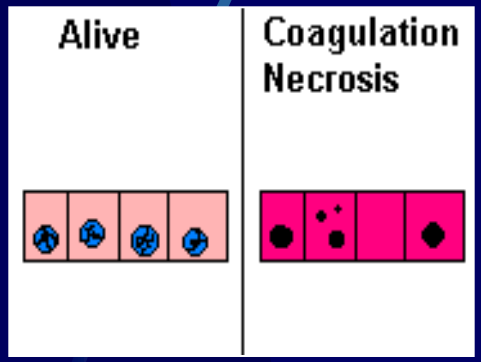


Necrosis

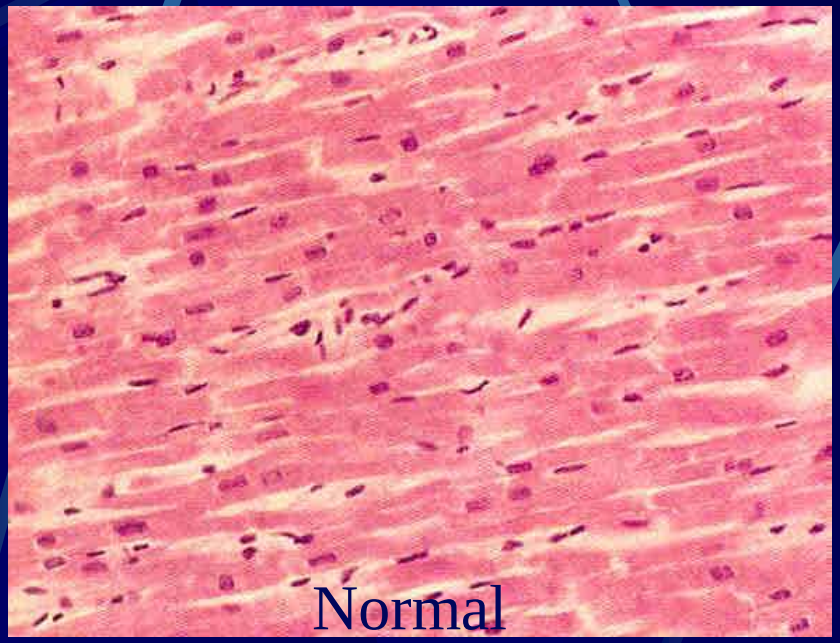
- Definition
  - Death of groups of contiguous cells in tissue or organ
- Patterns
  - Coagulative
  - Liquefactive
  - Caseous
  - Fat necrosis
  - (gangrene)
  - (Infarct)
    - Red/haemorrhagic
    - White

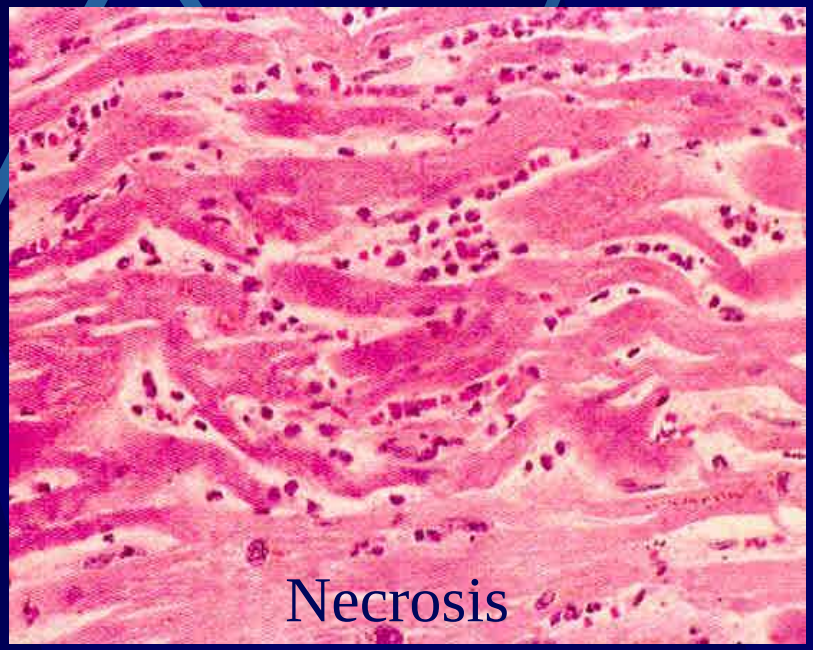
Coagulative necrosis

- Cells have died but the basic shape and architecture of the tissue endures
- Most common manifestation of ischaemic necrosis in tissues.
- Affected tissue maintains solid consistency.
- In most cases the necrotic cells are ultimately removed by inflammatory cells.
- The dead cells may be replaced by regeneration from neighboring cells, or by scar (fibrosis).

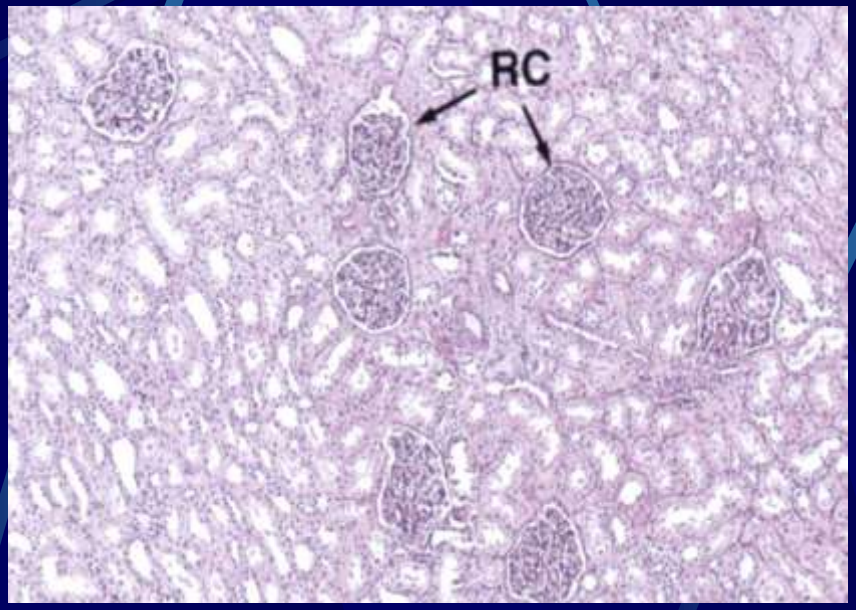


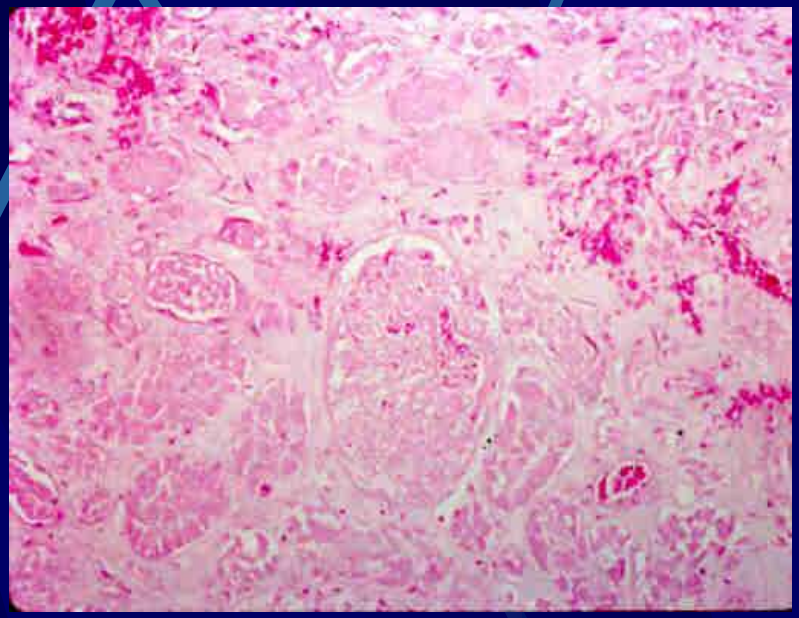
Coagulative necrosis


Normal


Necrosis

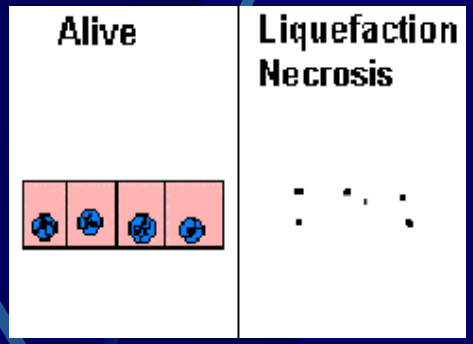
Coagulative necrosis



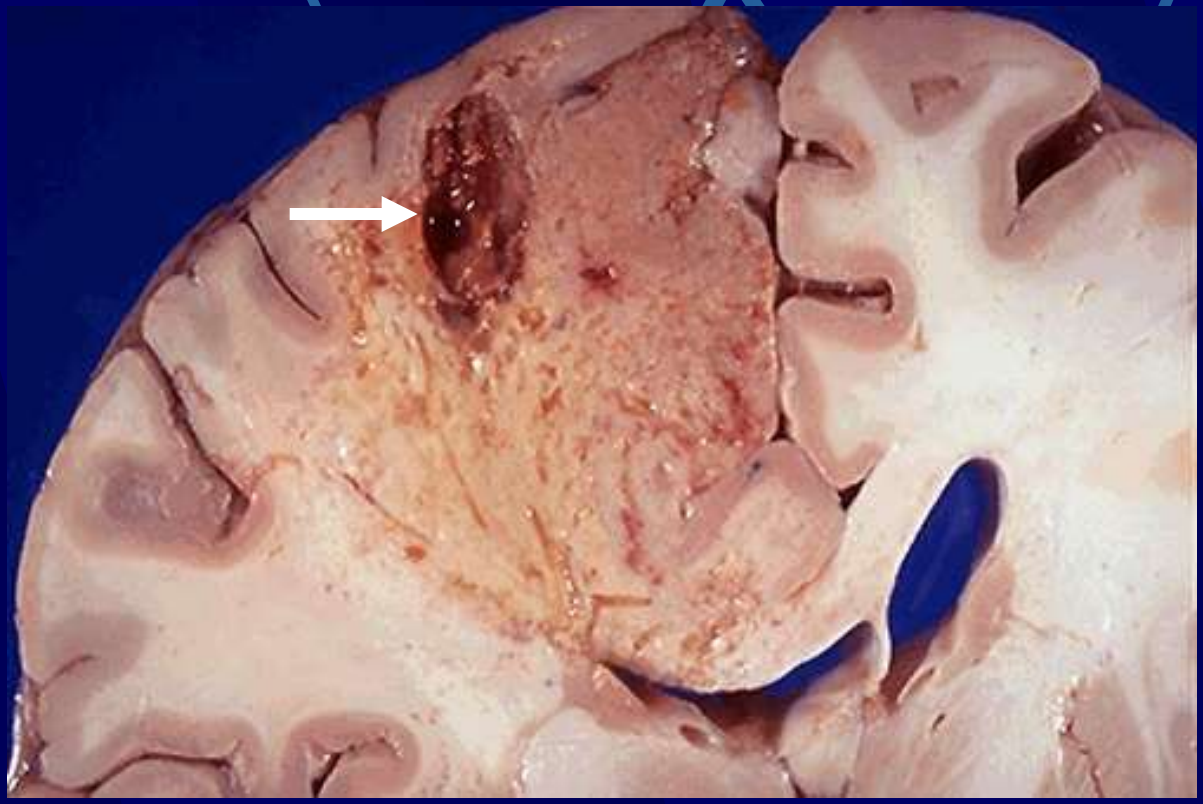


Liquefactive necrosis

- Complete dissolution of necrotic tissue.
- Most commonly due to massive infiltration by neutrophils (abscess formation).
  - Release of reactive oxygen species and proteases
- Liquefaction is also characteristic of ischaemic necrosis in the brain.

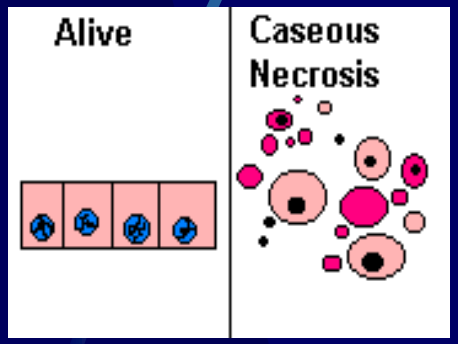


Liquefactive necrosis



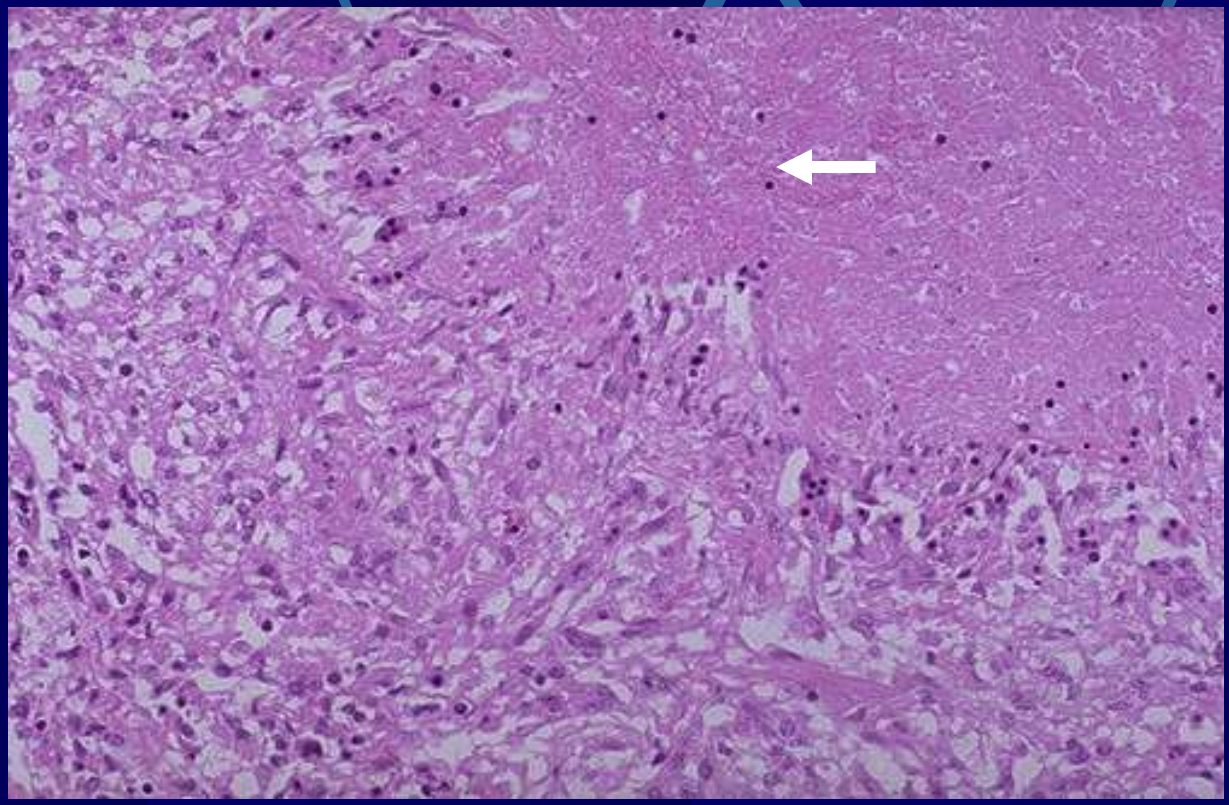
Caseous necrosis

- Accumulation of amorphous (no structure) debris within an area of necrosis.
- Tissue architecture is abolished and viable cells are no longer recognizable.
- Characteristically associated with the granulomatous inflammation of tuberculosis. Also seen in some fungal infections.



Caseous necrosis

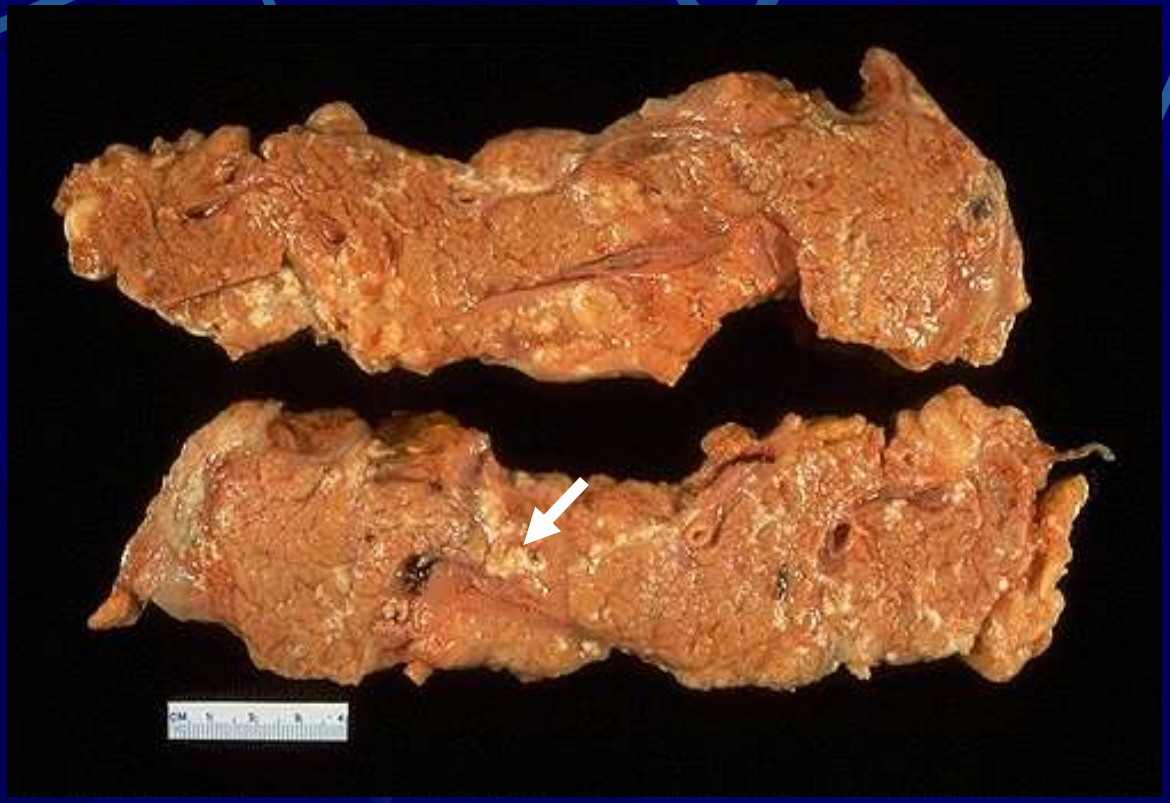
Caseous necrosis



Fat necrosis

- Results from the action of lipases released into adipose tissue.
  - pancreatitis, trauma.
- Free fatty acids accumulate and precipitate as calcium soaps (saponification).
  - These precipitates are grossly visible as pale yellow/white nodules
- Microscopically, the digested fat loses its cellular outlines. There is often local inflammation

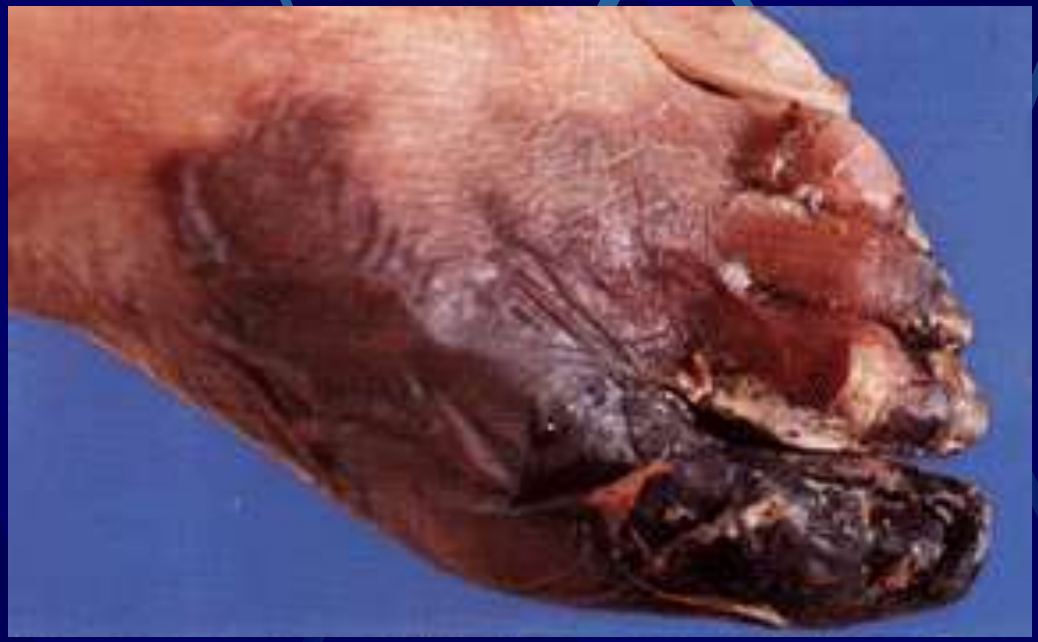
Fat necrosis



Gangrene ("gangrenous necrosis")

- Not a separate kind of necrosis at all, but a term for necrosis that is advanced and visible grossly.
  - If there's mostly coagulation necrosis, (i.e., the typical blackening, desiccating foot which dried up before the bacteria could overgrow), we call it dry gangrene.
  - If there's mostly liquefactive necrosis (i.e., the typical foul-smelling, oozing foot infected with several different kinds of bacteria), or if it's in a wet body cavity, we call it wet gangrene.

Gangrenous necrosis

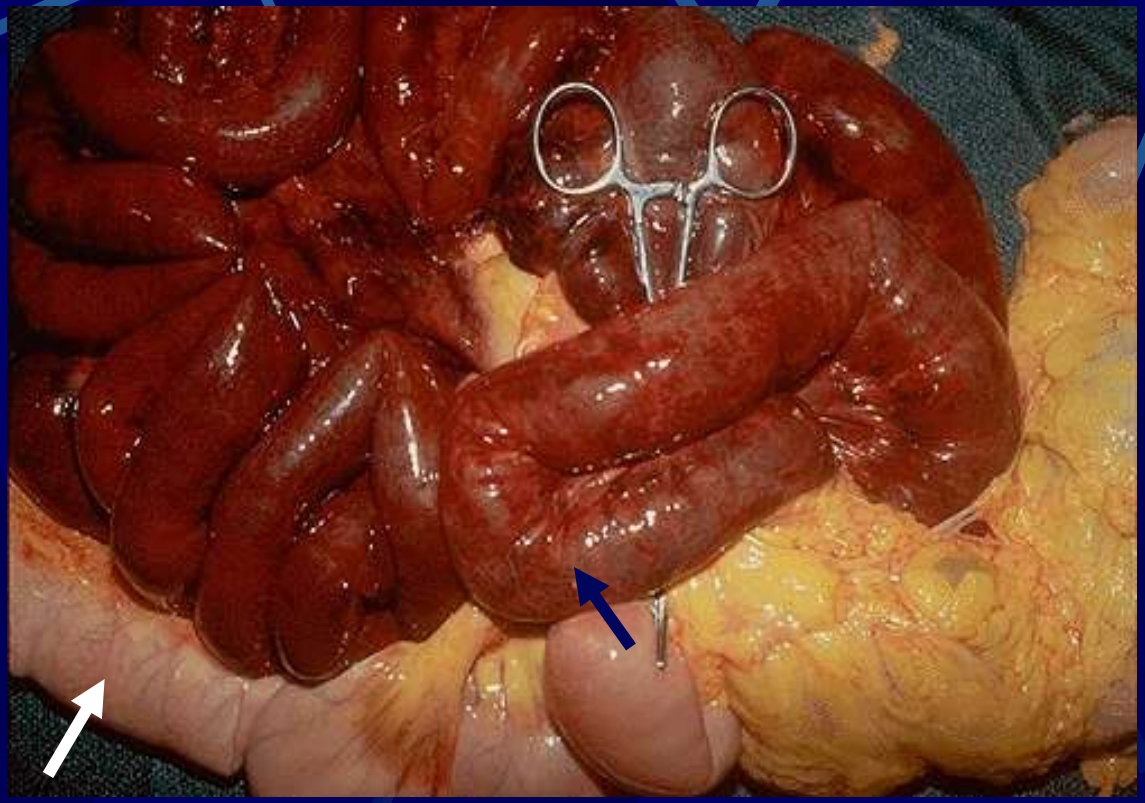


Infarction

- An area of ischaemic necrosis in a tissue or organ
  - White
    - Arterial occlusion in most solid tissues
  - Red/haemorrhagic
    - Venous occlusion
    - Loose tissues
    - Dual blood supply
    - Previously congested

White infarct

Red infarct

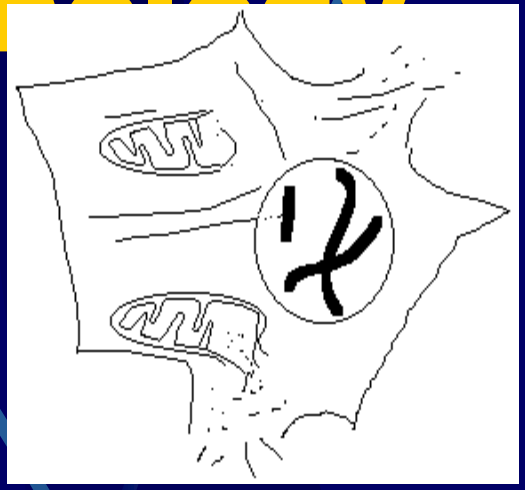


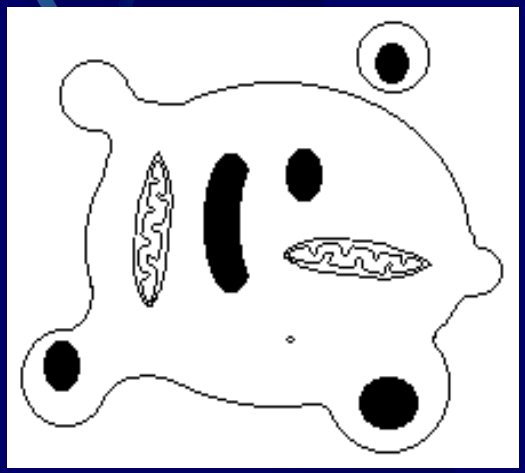
Apoptosis - basics

- is a distinct reaction pattern which represents programmed single-cell suicide.
- Cells actually expend energy in order to die.
- Derived from Greek "falling off" (as for autumn leaves)
- Apoptosis is "the physiological way for a cell to die", seen in a variety of normal situations.

Apoptosis - morphology

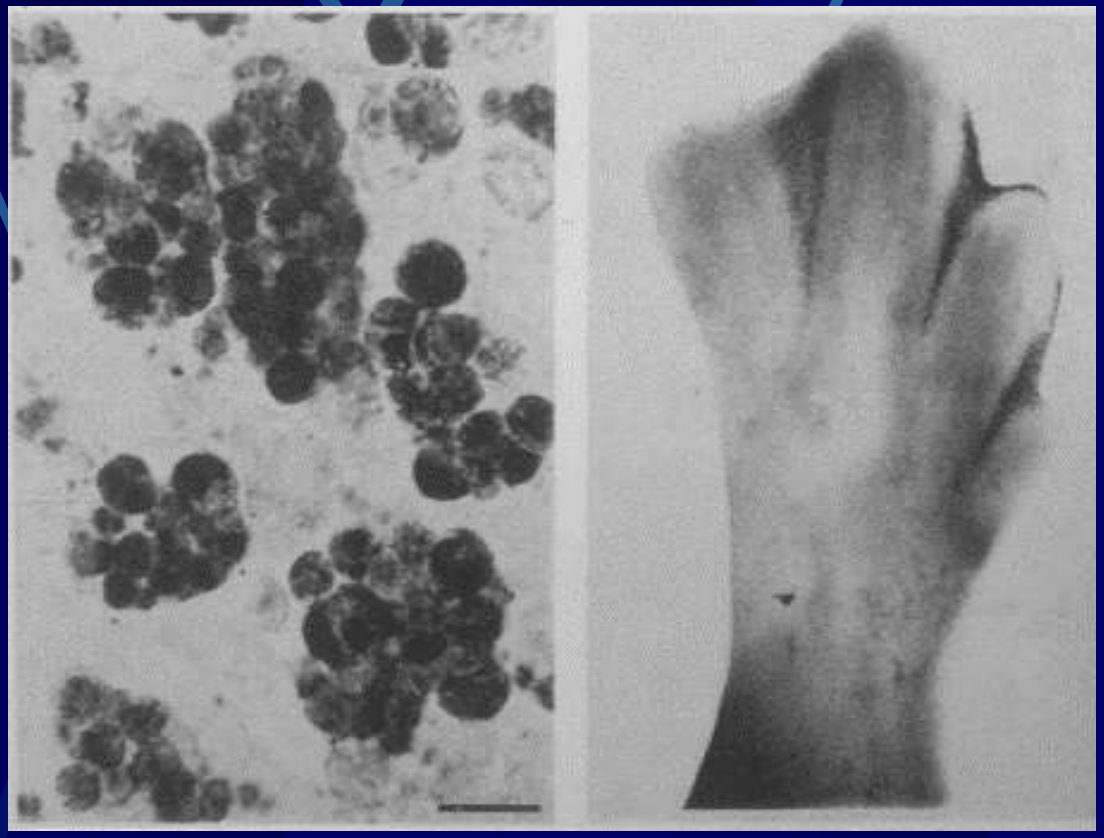
- Necrosis:
  - pathological response to cellular injury.
  - Chromatin clumps, mitochondria swell and rupture, membrane lyses, cell contents spill, inflammatory response triggered
- Apoptosis
  - DNA cleaved at specific sites - 200 bp fragments.
  - Cytoplasm shrinks without membrane rupture
  - Blebbing of plasma and nuclear membranes
  - Cell contents in membrane bounded bodies, no inflammation





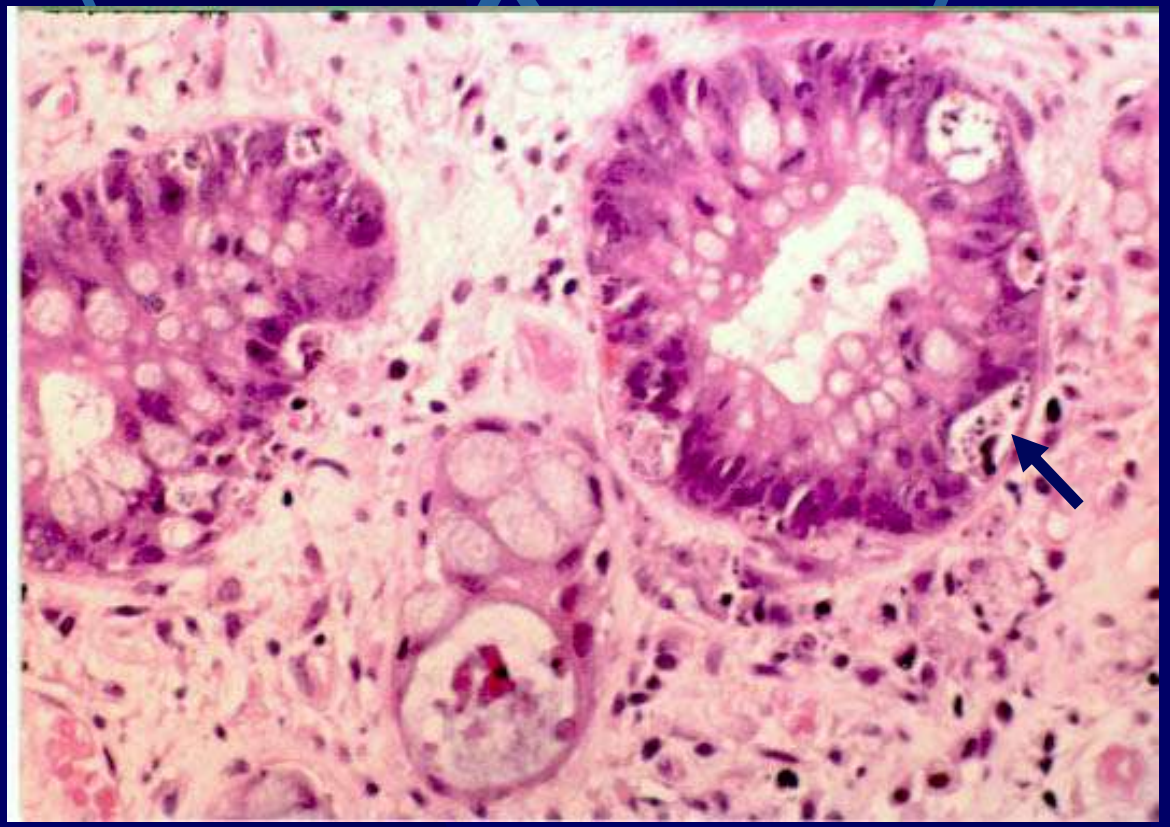
Apoptosis - normal

A stain for apoptotic cells in the developing paw of a foetal mouse.



Apoptosis -pathological

Graft-versus-host disease in colonic mucosa

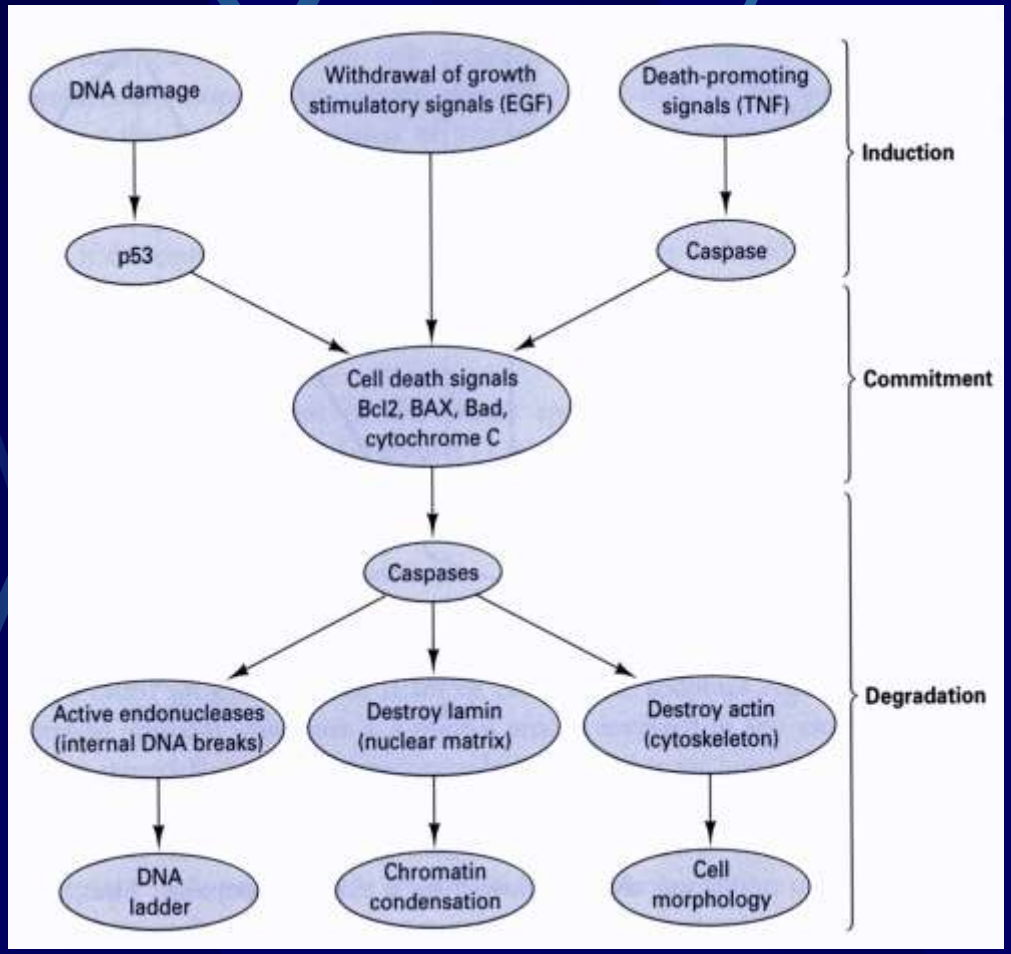


Apoptosis - triggers

- Withdrawal of growth stimuli
  - E.g. growth factors
- Death signals
  - E.g. TNF and Fas
- DNA damage
  - p53 plays an important role

Apoptosis - mechanisms

- Extrinsic factors
  - E.g. by members of the TNF family
- Intrinsic mechanisms
  - E.g. hormone withdrawal



Summary

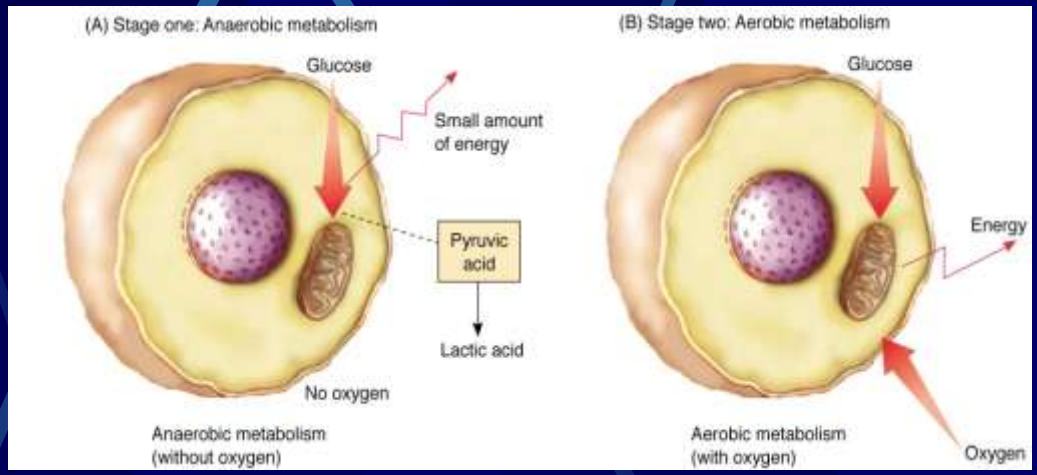
- This talk has covered….
  - Causes of cell injury
  - Cellular targets
  - Pathogenesis
  - Morphology of cell injury
  - Patterns of necrosis
  - Apoptosis

Final thought…

Our lives are filled with joys and strife,
And what is death but part of life?
Will come the day that we must die,
And leave behind those learning why.

Cellular Injury

- Hypoxic injury
  - Most common cause of cellular injury
  - May result from:
    - Decreased amounts of oxygen in the air
    - Loss of hemoglobin or hemoglobin function
    - Decreased number of red blood cells
    - Disease of respiratory or cardiovascular system
    - Loss of cytochromes
      - Iron containing protein in the mitochondra (electron transport system)



Cellular Injury

- Chemical agents causing cellular injury
  - Poisons
  - Lead
  - Carbon monoxide
  - Ethanol
  - Pharmacological

Cellular Injury

- Infectious injury
  - Disease causing agents (Pathogens)
  - Virulence or pathogenicity of microorganisms depends on their ability to survive and reproduce in the human body, where they injure cells and tissues
  - Disease producing potential depends upon its ability to
    - Invade and destroy cells
    - Produce toxins
    - Produce hypersensitivity reactions

Infectious Injury

- Possible outcomes
  - Pathogen wins
  - Pathogen and body battle to a draw
  - Body defeats pathogen

Bacteria

- Survival and growth depend upon the effectiveness of the body's defense mechanisms and the bacteria's ability to resist the mechanisms
  - Coating protects the bacterium from ingestion and destruction by phagocytes and capsules may also function as exotoxins (outside poisonous substance)
  - Not all virulent extracellular pathogens are encapsulated mycobacterium tuberculosis can survive and be transported by phagocytes

Bacteria

- Bacteria also produce substances such as enzymes or toxins which can injure or destroy cells
  - Toxins are produced by many microorganisms
    - Exotoxins (staph, strep, psuedomonas)
    - Endotoxins (lipopolysaccharide that is part of the cell wall of gram-negative bacteria)
  - Fever is caused by the release of endogenous pyrogens from macrophages or circulating WBC's
  - Inflammation is one of the body's responses
  - Hypersensitivity reactions is an important pathogenic mechanism
  - Bacteremia or septicemia is proliferation of microorganisms in the blood

Viruses

- Viral diseases are among the most common afflictions seen in humans
- Intracellular parasites take over the control of metabolic machinery of host cells for use to replicate the virus
- Protein coat (capsid) encapsulating most viruses allows them to resist phagocytosis
- Viral replication occurs within host cell
- Having no organelles, viruses are incapable of metabolism
- Viruses do not produce exotoxins or endotoxins
- Viruses can evoke a strong immune response but can rapidly produce irreversible and lethal injury in highly susceptible cells (as in AIDS)

Immunologic and Inflammatory Injury

- Cellular membranes are injured by direct contact with cellular and chemical components of the immune or inflammatory process as in phagocytes and others such as histamine, antibodies, lymphokines
- Membrane alterations are associated with rapid leakage of potassium out of the cell and an influx of water
- Can result in
  - Hypersensitivity: exaggerated immune response
  - Anaphylactic: life threatening

Injurious Physical Agents

- Cellular damage can be caused by physical agents
- Physical agents causing injury
  - Temperature extremes
  - Burns
  - Atmospheric pressure changes (blast injury, deep sea diving accident)
  - Ionizing radiation
  - Illumination (eye strain from lighting)
  - Skin cancer
  - Noise
  - Mechanical stressors (trauma)

Injurious Nutritional Imbalances

- Improper nutrition contributes to one of the most widely publicized forms of cellular injury
- Examples
  - Atherosclerosis
  - Vitamin deficiency
  - Malnutrition
  - Starvation

Injurious Genetic Factors

- Some cellular dysfunctions are caused by genetic predispostion, either defective genes or altered chromosomes that a person is born with
- Genetic injuries involve
  - Alterations to the nucleus or cell membrane
  - Alterations to the shape of cell or receptors of cell membrane
  - Alteration to transport mechanism that carries substances across cell membrane

Manifestation of Cellular Injury

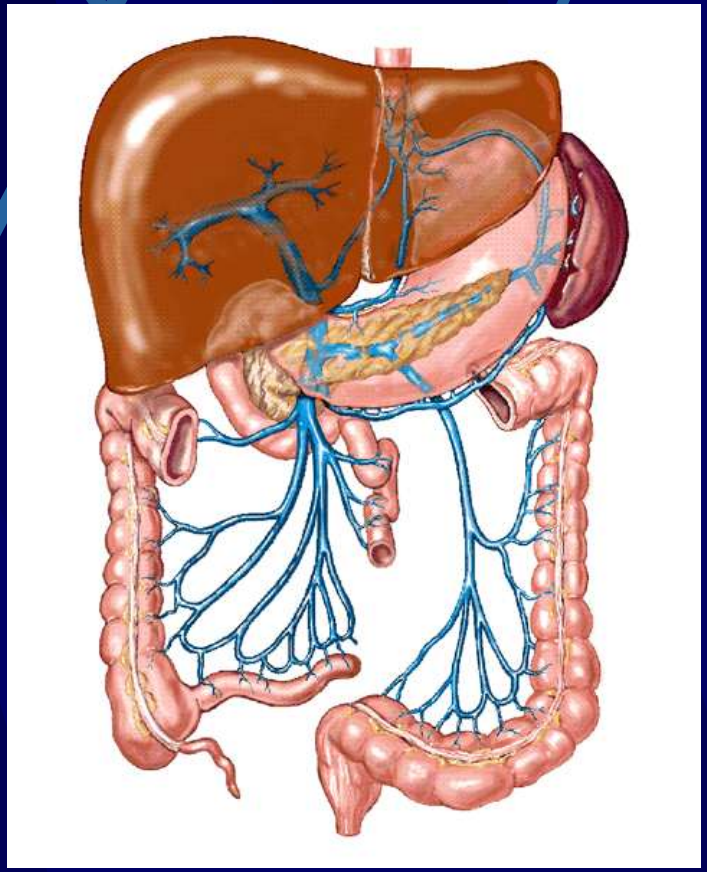
- When cells are injured metabolism is changed, causing substances to infiltrate or accumulate to an abnormal degree in cells.

Cellular Swelling

- Results from a permeable or damaged cellular membrane.
- Caused by an inability to maintain stable intra-and extracellular fluid and electrolyte levels.

Fatty Change

- Lipids invade the area of injury.
- Occurs most commonly in vascular organs, most frequently the liver.
- Causes a disruption of the cellular membrane and metabolism and interferes with the vital functions of the organ.



Signs and Symptoms of Cellular Change

- Fatigue and malaise
- Altered appetite
- Fever
- Increased heart rate associated with fever
- Pain

Cell Death

- Apoptosis
  - Injured cell releases enzymes that engulf and destroy the cell.
  - Cells shrink.
  - Eliminating damaged and dead cells allows tissues to repair and possibly regenerate.

Cellular Necrosis

- Cell death; a pathological cell change
- Four forms of necrotic cell change
  - Coagulative
  - Liquefactive
  - Caseous
  - Fatty

Cellular Necrosis

- Coagulative necrosis
  - Generally results from hypoxia and commonly occurs in kidneys, heart, and adrenal glands
  - Transparent viscous albumin of the cell becomes firm
- Liquefactive necrosis
  - Cells become liquid and contained in walled cysts
  - Common in ischemic death of neurons and brain cells
- Caseous necrosis
  - Common in TB
  - Cells become infected and look like fried cheese
- Fatty necrosis
  - Fatty acids combine with calcium, sodium, and magnesium ions

Gangrenous Necrosis

- Tissue death over a wide area
- Types
  - Dry gangrene: results from coagulative necrosis
  - Wet gangrene: results from liquefactive necrosis
  - Gas gangrene: results from bacterial infection in tissue generating gas bubbles in cells

The Inflammatory Response

- Key purposes = DEFENSE
  1. To hunt & kill invaders
  2. To limit their spread
  3. To prepare tissue for repair
- Key events
  1. Increase of vascular permeability
  2. Recruitment (margination) & emigration (diapedesis) of WBC's
  3. Phagocytosis

The Inflammatory Response

- Inflammatory response = normal body defense mechanism to tissue injury
  - Note: Inflammation is NOT infection

- Cells of the inflammatory response when get tissue injury
  - Main groups;
    - Phagocytes --- "the eaters"
      - Macrophages --- become active as APC's (antigen presenting cell)
      - Neutrophils --- "little eaters"
      - Monocytes --- become tissue macrophages
    - T- lymphocytes (helper-T) ---- produce cytokines which " call all to action"
    - Platelets ---- release PAF (platelet activating factor) which in turn begins call to action and release of chemical mediators
    - Mast cells --- release chemical mediators that begin inflammation

Chemical Mediators

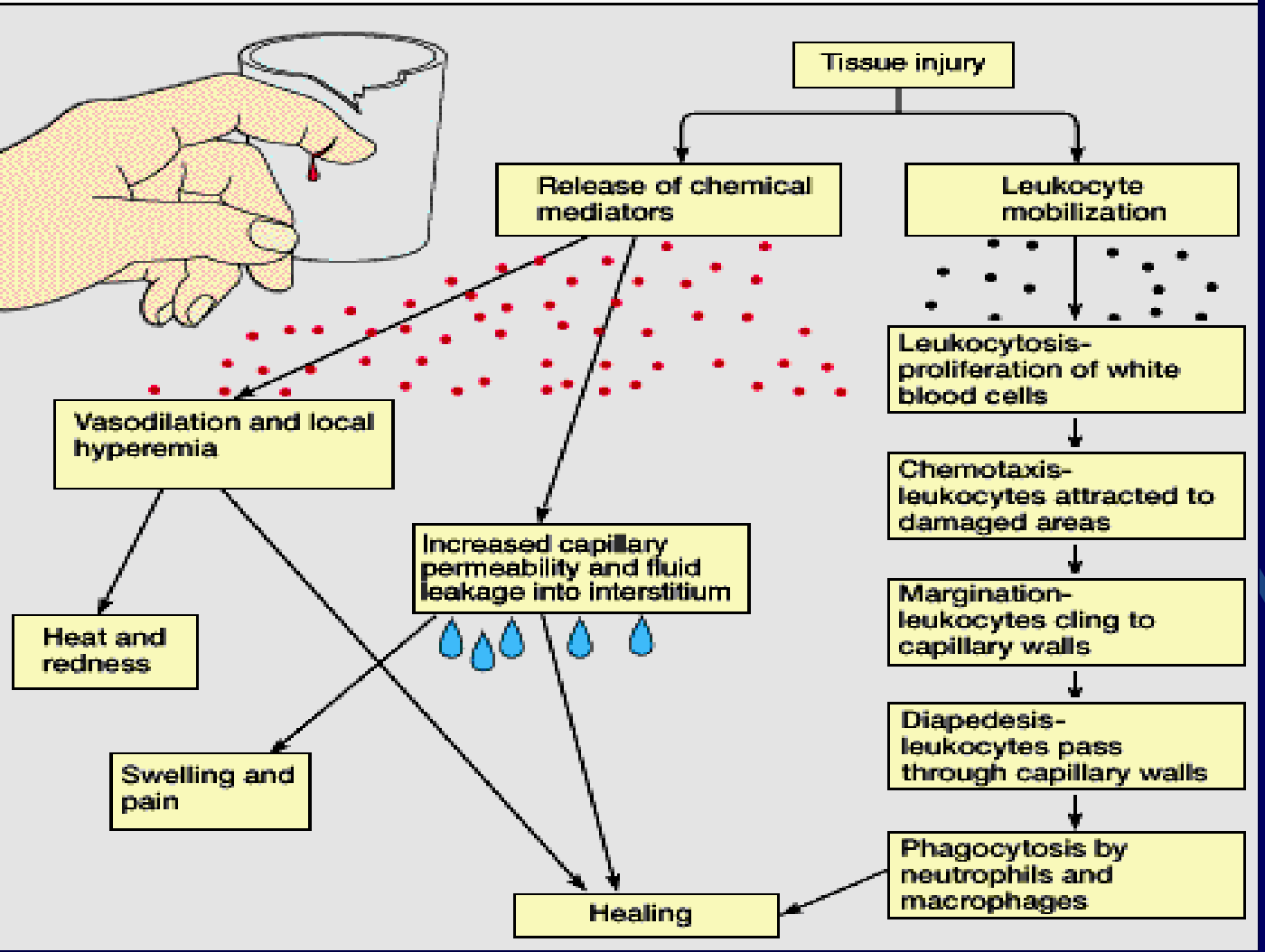
- The initial "macrophage (APC cell) – antigen complex" causes chemical mediators to be released:
  - Histamine
    - From basophils & mast cells
    - Cause vasodilation & increased permeability of vessels via release of nitric oxide
  - Prostaglandins
    - Made in mast cell membrane from fatty acid (arachidonic)
    - Cause pain & vasodilation
  - Leukotrienes
    - "bad" prostaglandins since cause symptoms of inflammation (pain & swelling)
    - Cause chemotaxis
    - Very important for causing allergies, asthma, & anaphylaxis

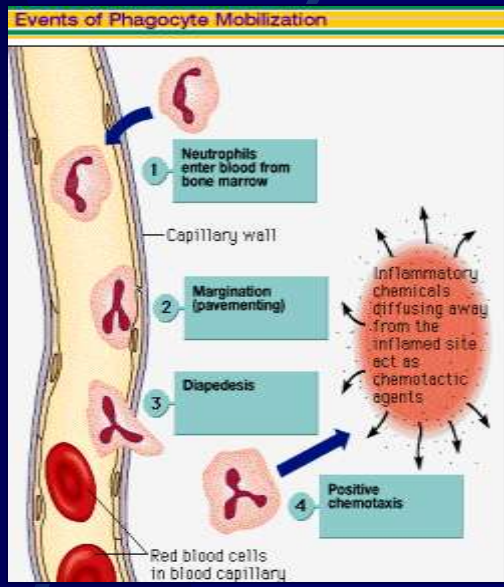
Chemical Mediators

- **Complement**
  - Coats bacterial surface; enhances phagocytosis & lyses bacteria
  - Inactive plasma proteins become activated by initial An-Ab complex
- **Interferon**
  - Proteins that are released by helper T's & kill viruses
- **Bradykinins**
  - From inactivated plasma protein
  - Cause similar effects like histamine
  - Cause pain
  - Induce WBC's into area (chemotaxis

- **Local effects of inflammation**
  - 4 cardinal signs of inflammation
    - Redness (rubor) – from increased blood supply
    - Heat (calor) – from increased blood supply
    - Swelling (tumor) – from increased permeability & increased proteins in interstitial fluid
    - Pain (dolar) – from chemical mediators
  - Also get inflammatory exudate
    - Serous – from allergic reactions & burns
    - Purulent – from infections
      - May lead to abscess
- **Systemic effects of inflammation**
  - General malaise
  - Fatigue
  - Headache
  - Fever
    - Caused by pyrogens (chemicals released from phagocytes)
    - Beneficial
      - Inhibits growth of pathogens
      - Enhances repair process via increased metabolic rate

Events of Inflammation





- Leukocytosis
- Chemotaxis
- Margination
- Diapedesis

- **Potential complications of inflammation**
  - Infection
  - Ulceration – from chronic inflammation
    - May lead to:
      - perforation of viscera
      - excess scar formation
  - Skeletal muscle spasm
  - Local tissue reactive changes
    - Joints from decreased ROM become stiff
    - Lungs cannot exchange gases

- **Diagnostic tests for inflammation**
  - Leukocytosis
  - Differential WBC count
  - ESR
  - Cell enzymes – may or may not be tissue specific
    - C-reactive protein

- **Chronic Inflammation**
  - The acute inflammatory reaction usually subsides within 48 –72 hours as long as the cause is removed (e.g. touching a hot stove)
  - If the cause persists, you get chronic inflammation
  - Clinically:
    - Increase in connective tissue reaction to the chronicity
      - Get more fibroblasts & more collagen
        - Thus get more scar tissue
        - Can get granulomas (collection of chronically inflamed tissue)

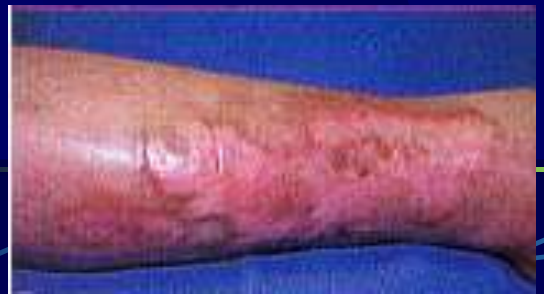
- **Treatment of inflammation**
  - Aspirin
  - NSAID's
  - Glucocorticoids
  - Heat & cold
  - Physiotherapy if chronic
    - Prevents contractures

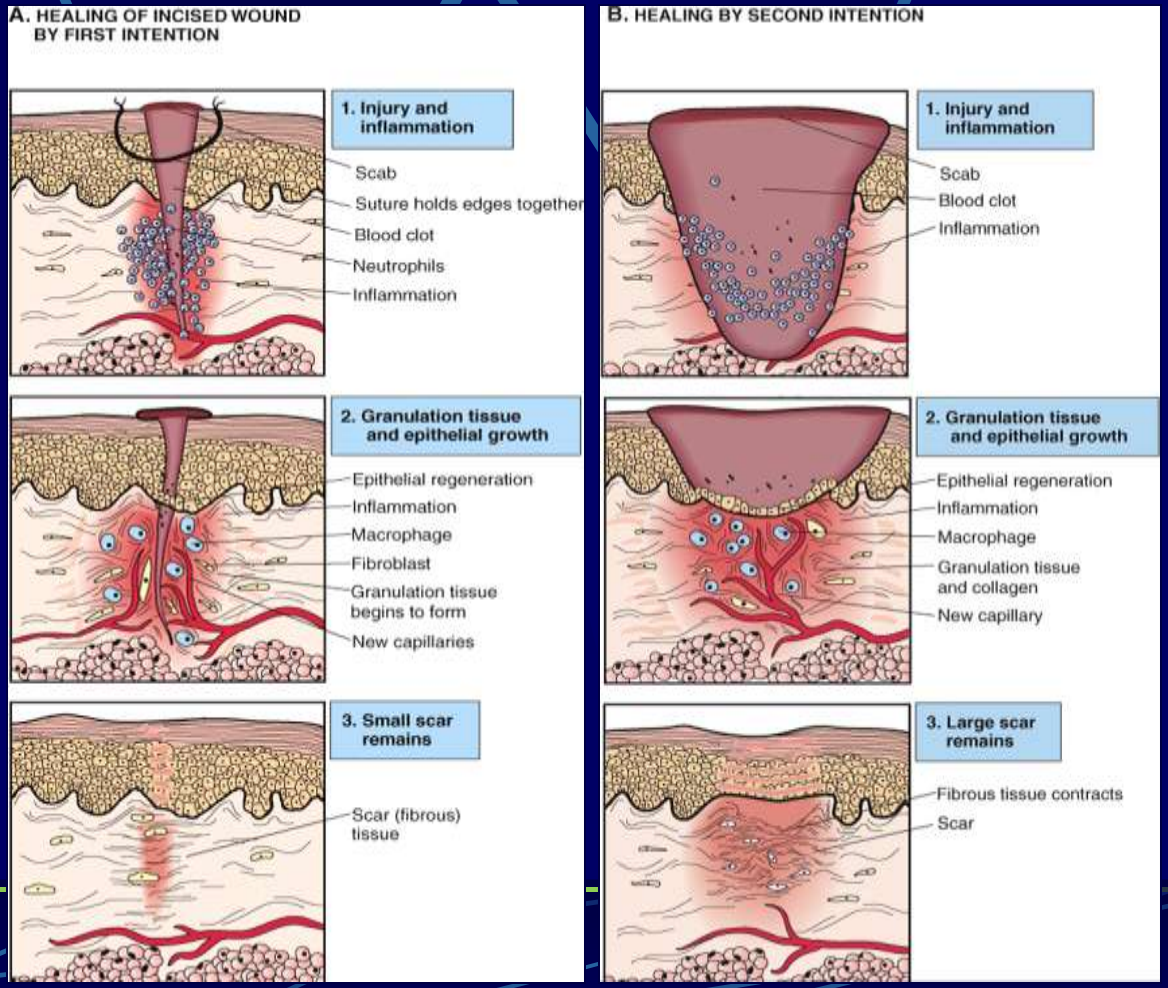
Healing

- 3 ways depending on the tissue involved & degree of injury
  - Resolution
    - Damaged cells recover in short time
    - Exp = mild sunburn
  - Regeneration
    - Damaged cells replaced by identical cells via mitosis
    - Only occurs in epithelia & connective tissue
    - If complex organ, some damaged tissue replaced by regeneration & some by scar
  - Scar formation
    - Key tissue = granulation tissue(highly vascular connective tissue)
      - Collagen produced by fibroblasts makes granulation tissue into scar tissue
    - Scar tissue is non-functional

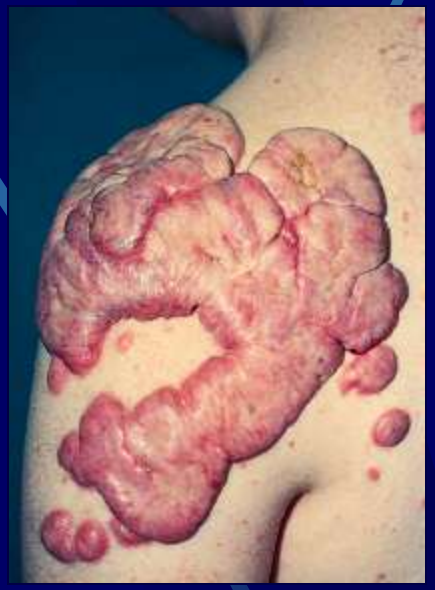
Healing by primary or secondary intention

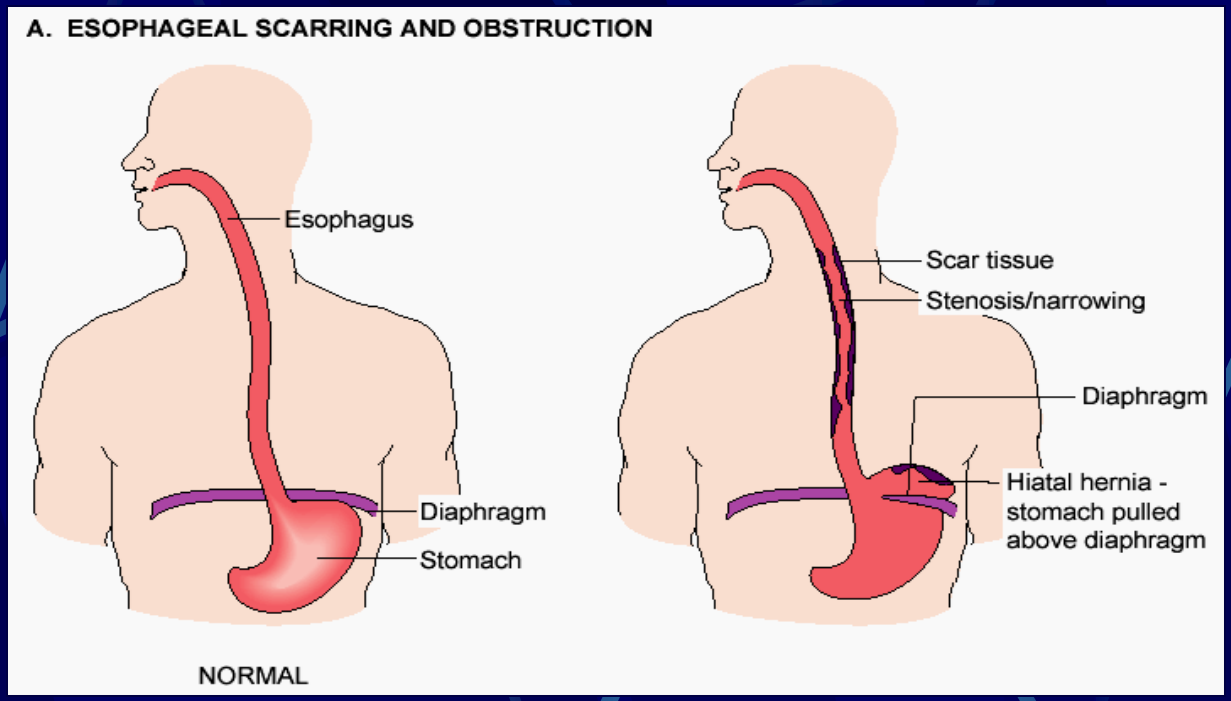
- Depend weather edges of lesion can be brought together
- Primary (first) intention gives small scar formation
- Secondary intention gives large scar formation
  - Heals via granulation tissue

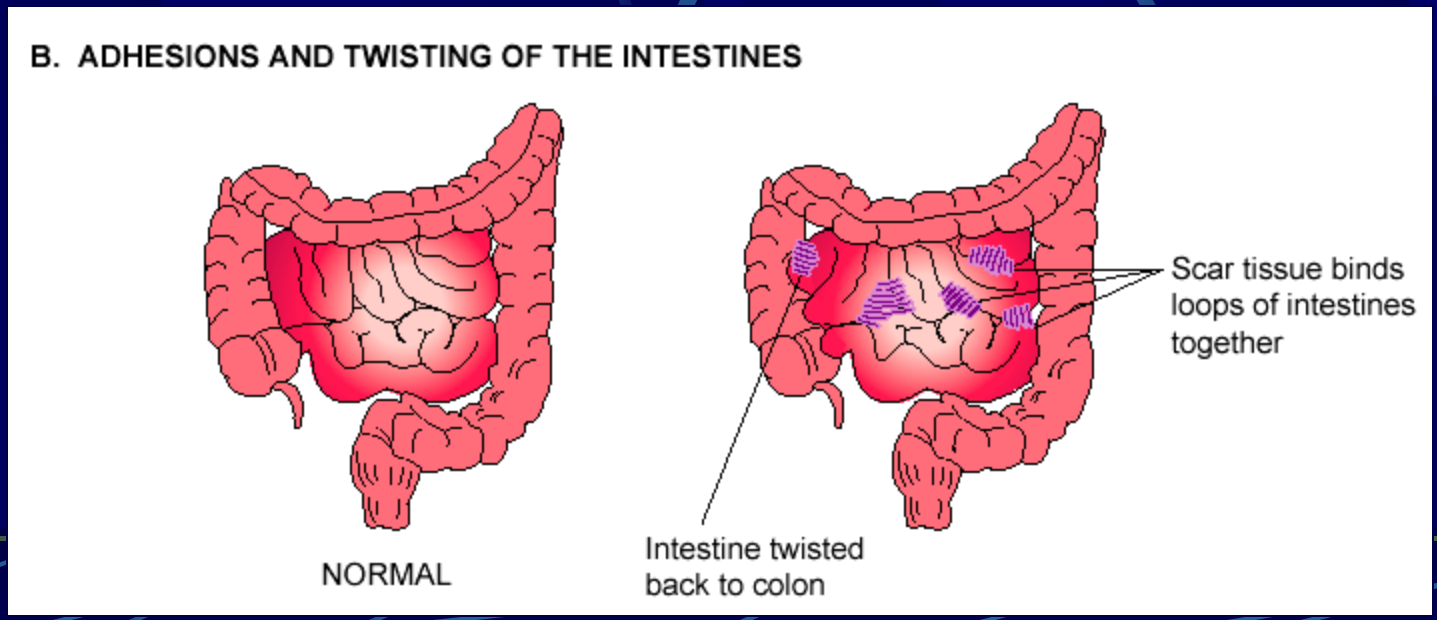




- **Complications from large scar formation**
  (see next slide)
  - Loss of function
  - Contractures & obstructions
    - Can lead to stenosis
  - Adhesions
  - Ulceration
- **Factors promoting healing**
  - Nutrition
  - Blood supply
  - Cleanness of area
  - Lack of complications
- **Factors delaying healing**
  - Old age
  - Presence of foreign material
  - Poor blood supply
  - Poor nutrition
  - Complications (bleeding, hematoma, excessive mobility)

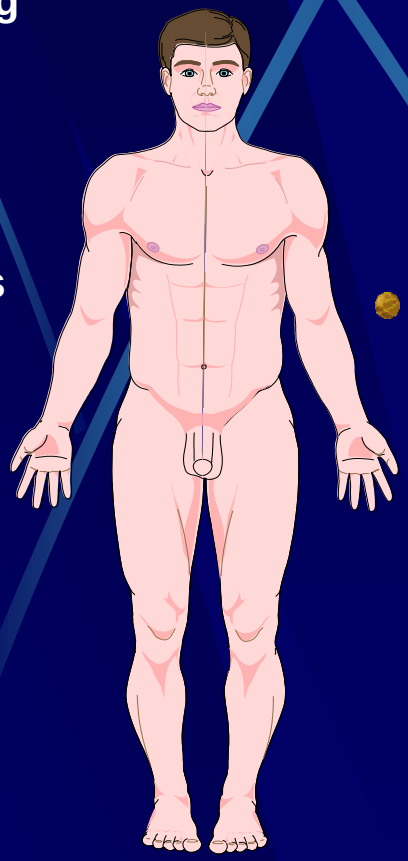



A. ESOPHAGEAL SCARRING AND OBSTRUCTION
Esophagus
Diaphragm
Stomach
NORMAL
Scar tissue
Stenosis/narrowing
Diaphragm
Hiatal hernia - stomach pulled above diaphragm

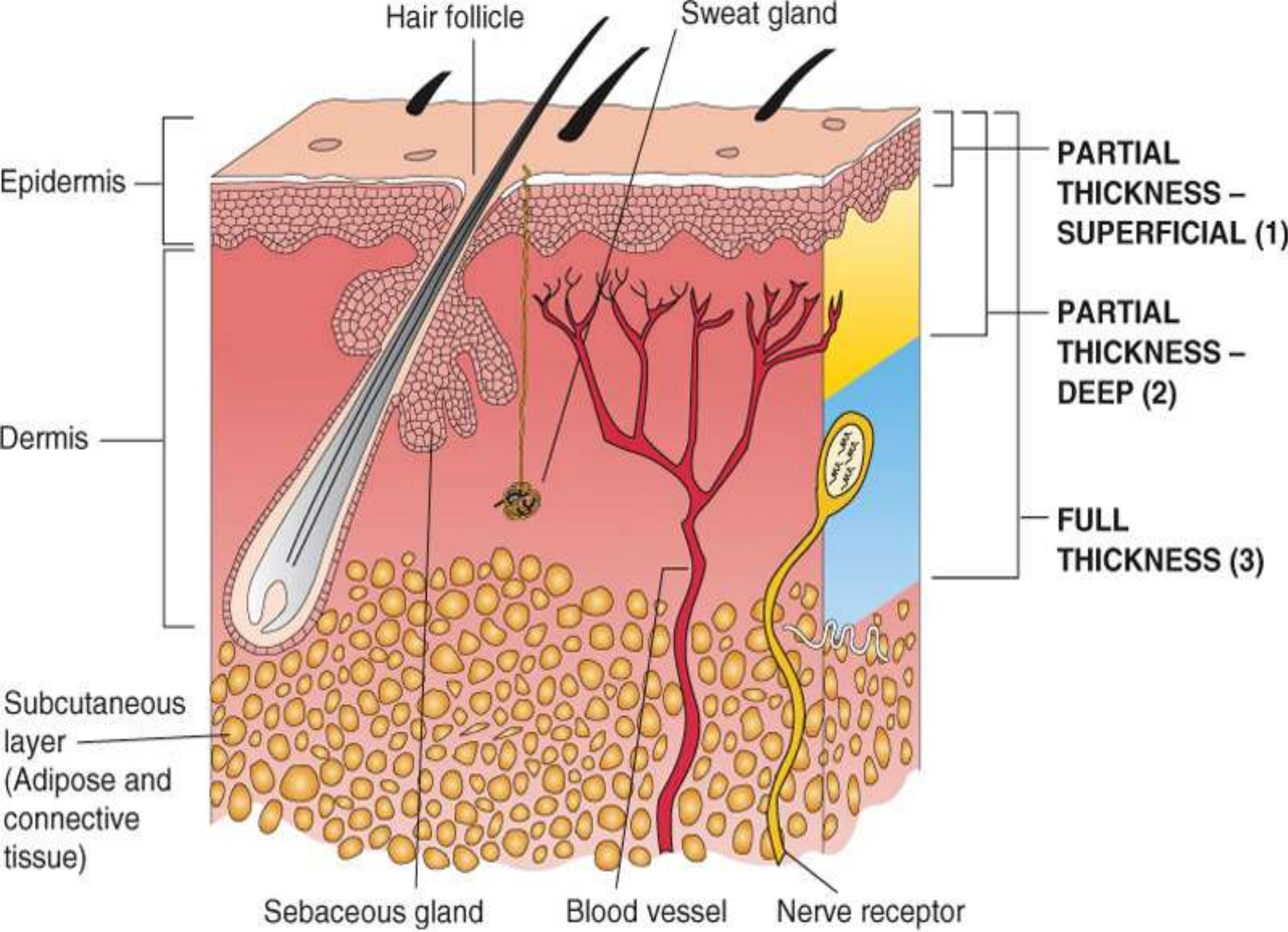

B. ADHESIONS AND TWISTING OF THE INTESTINES
NORMAL
Scar tissue binds loops of intestines together
Intestine twisted back to colon

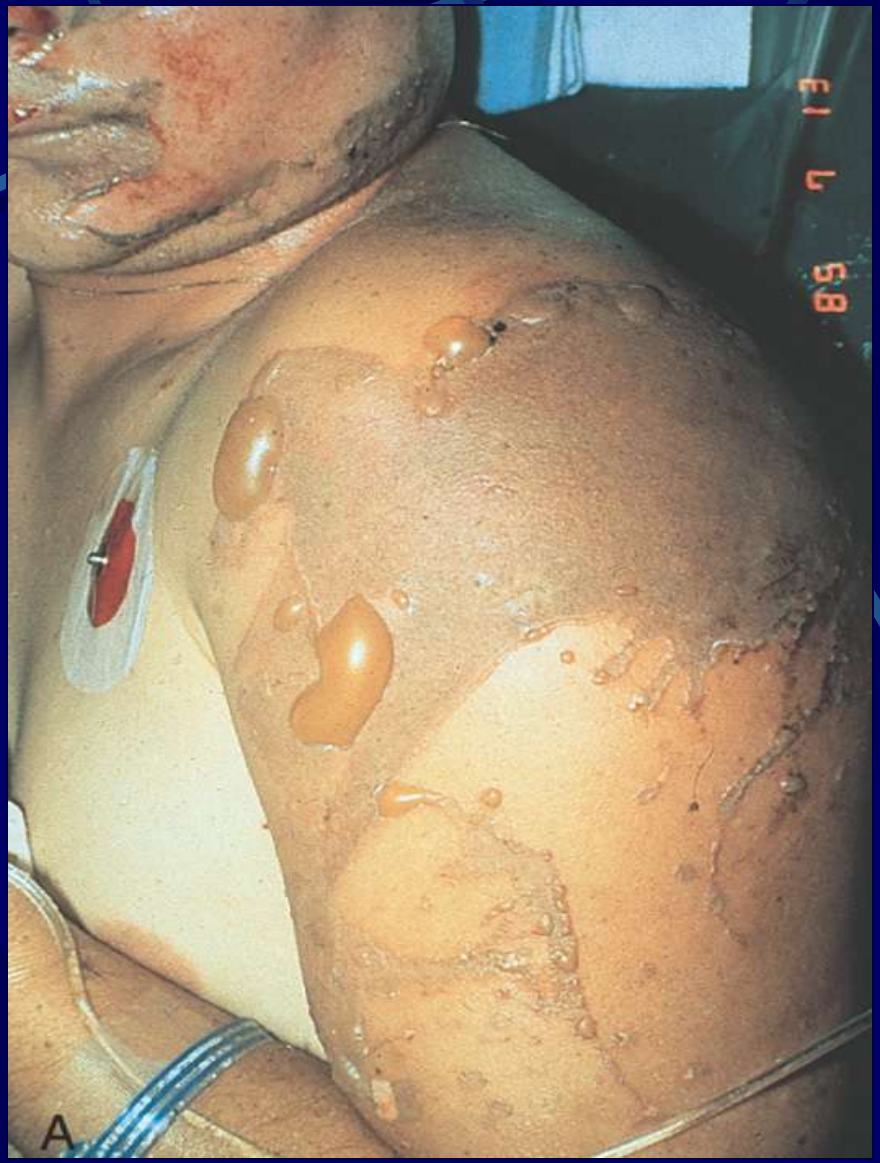
Burns

- First degree burns
  - Superficial partial-thickness
  - Involves just epidermis
  - Get redness but no blistering
  - May peel in 1-3 days
  - Get no scarring
- Second degree burns
  - Deep partial-thickness
  - Involves epidermis & dermis
  - Get redness & blistering
  - Can get scarring
  - Can get some fluid loss
  - Get significant pain
- Third degree burns
  - Full-thickness
  - Involves all 3 layers & may involve underlying tissue
  - Get no pain
  - Get serious fluid loss



- Rule of 9's
  - If burn 1st ,2nd , or 3rd & involves more than 20% ---- needs medical attention
  - If burn 2nd or 3rd & involves greater 20% = serious
  - If burn 2nd or 3rd & involves greater 40% = severe
- Complications
  - Fluid imbalance
  - Dehydration
  - Anemia
  - Infection
  - Excess scar formation




A

PATHOPHYSIOLOGY OF AUTOIMMUNITY

Dr. AJWADASSUMAIDAEE Ph. D

Exams syndrome

The day before : Hysteria

In morning : Anexiy & irritabilty

During written : Amensia

In clinical exam : Hallucination

In oral exam : Mental retardation

After Exam Results :

Severe depression
followed by
prolonged coma .

Self/Non-self Discrimination

Autoimmunity is a problem of self/non-self discrimination.

Autoimmune Diseases are defined as diseases in which immune responses to specific self-antigens contribute to the ongoing tissue damage that occurs in that disease. ADs may be either tissue-specific (e.g., thyroid, β-cells of the pancreas), where unique tissue-specific antigens are targeted, or may be more systemic, in which multiple tissues are affected

Autoimmunity

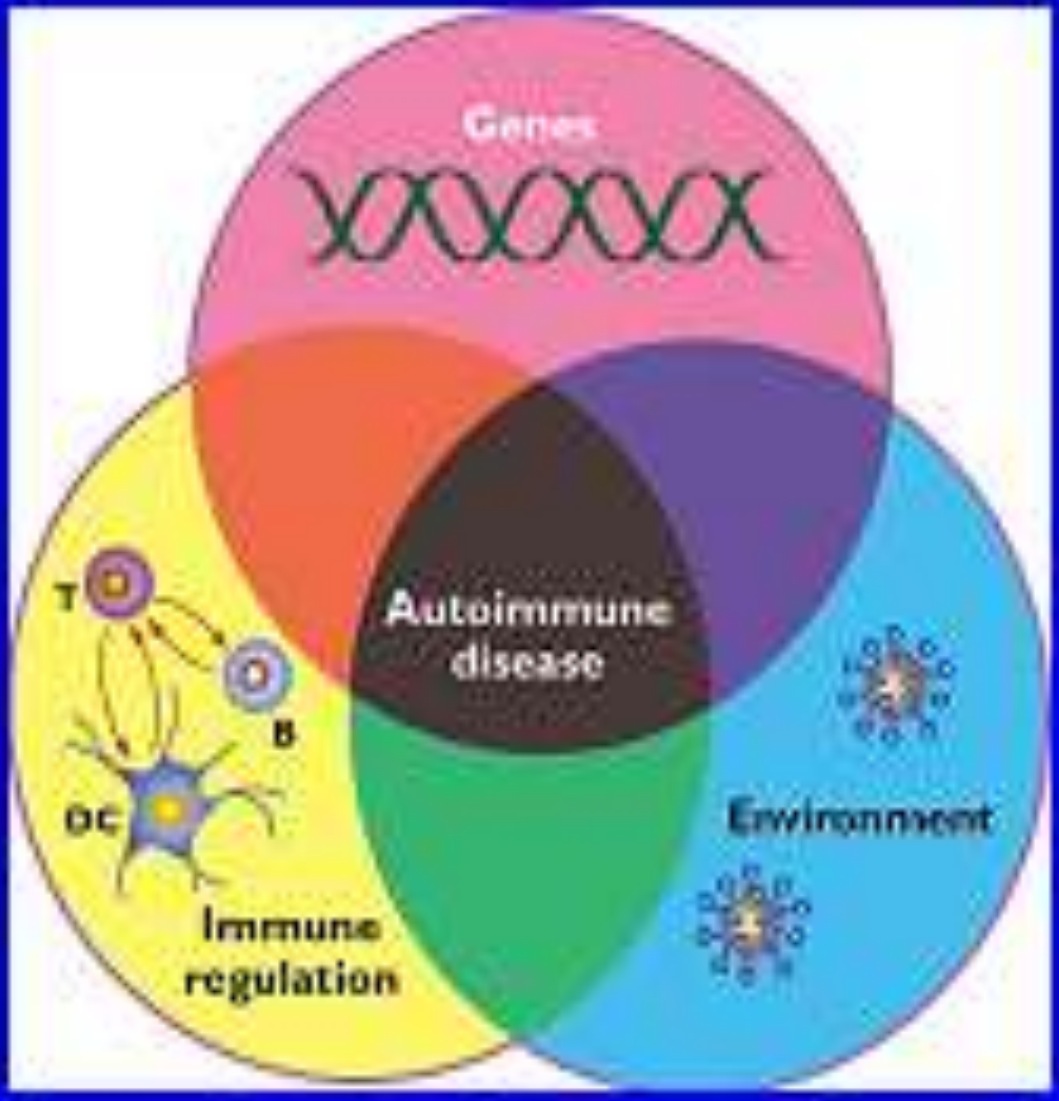
- 5 % to 7% adult affected.
- Two third women.
- More than 40 human diseases autoimmune in origin.

Autoimmunity

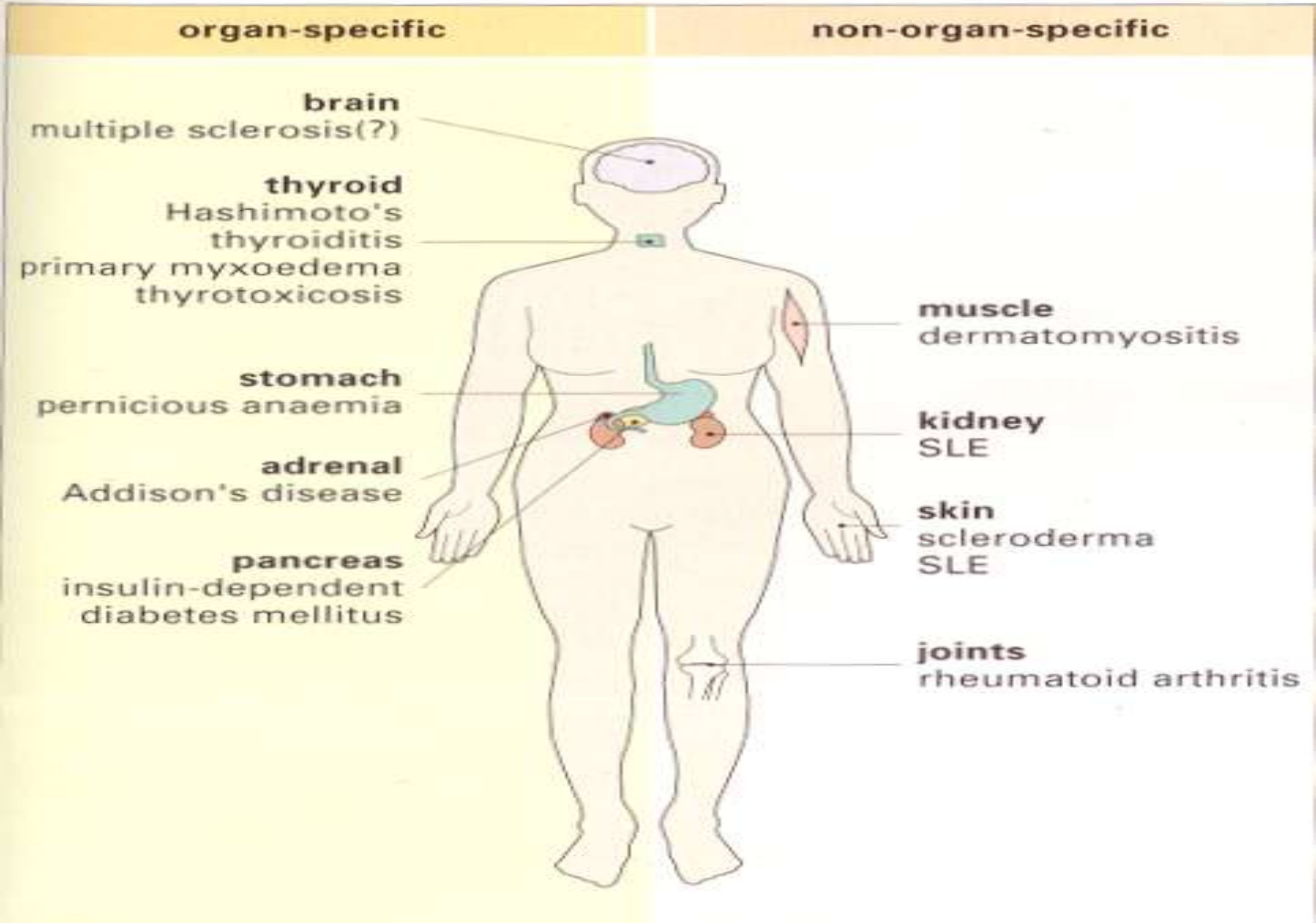
- **Definition: immune response against self (auto-) antigen, by implication pathologic**
  - **Disorders are often classified under "immune-mediated inflammatory diseases"**

- **General principles:**
  - **Pathogenesis: Susceptibility genes + environmental triggers**
  - **Systemic or organ-specific**

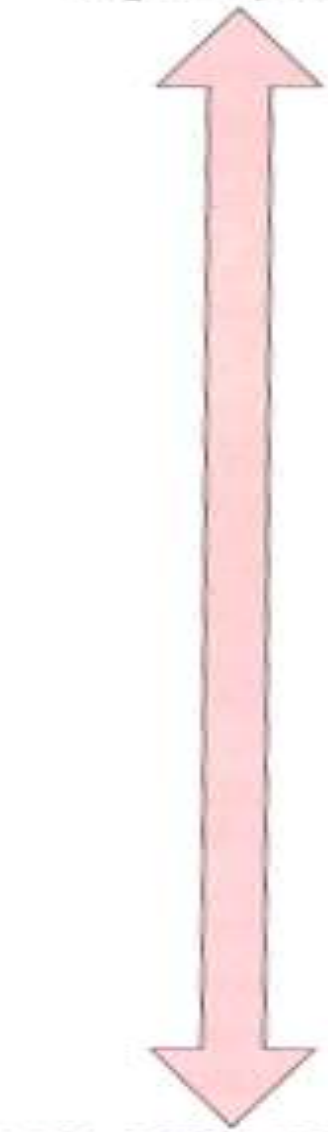
Autoimmunity



Two types of autoimmune disease



The spectrum of autoimmune diseases



Hashimoto's thyroiditis
primary myxoedema
thyrotoxicosis
pernicious anaemia
autoimmune atrophic gastritis
Addison's disease
premature menopause (few cases)
insulin-dependent diabetes mellitus
stiff-man syndrome
Goodpasture's syndrome
myasthenia gravis
male infertility (few cases)
pemphigus vulgaris
pemphigoid
sympathetic ophthalmia
phacogenic uveitis
multiple sclerosis (?)
autoimmune haemolytic anaemia
idiopathic thrombocytopenic purpura
idiopathic leucopenia
primary biliary cirrhosis
active chronic hepatitis (HBsAg negative)
cryptogenic cirrhosis (some cases)
ulcerative colitis
atherosclerosis(?)
Sjögren's syndrome
rheumatoid arthritis
dermatomyositis
scleroderma
mixed connective tissue disease
anti-phospholipid syndrome
discoid lupus erythematosus
systemic lupus erythematosus (SLE)

Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	**Autoantigen**	**Consequence**
Type II antibody to cell-surface or matrix antigens		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and FcR^+ phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Type III immune-complex disease		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
Type IV T cell-mediated disease		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-Cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

AUTOIMMUNITY & LEFT-HANDEDNESS

- LEFT handed individuals more affected.
- 11% of left handed & 4% of right handed.
- Reasons for this are obscure.
- left-handedness & immune malfunction may both result from abnormal endocrine function in fetal life.

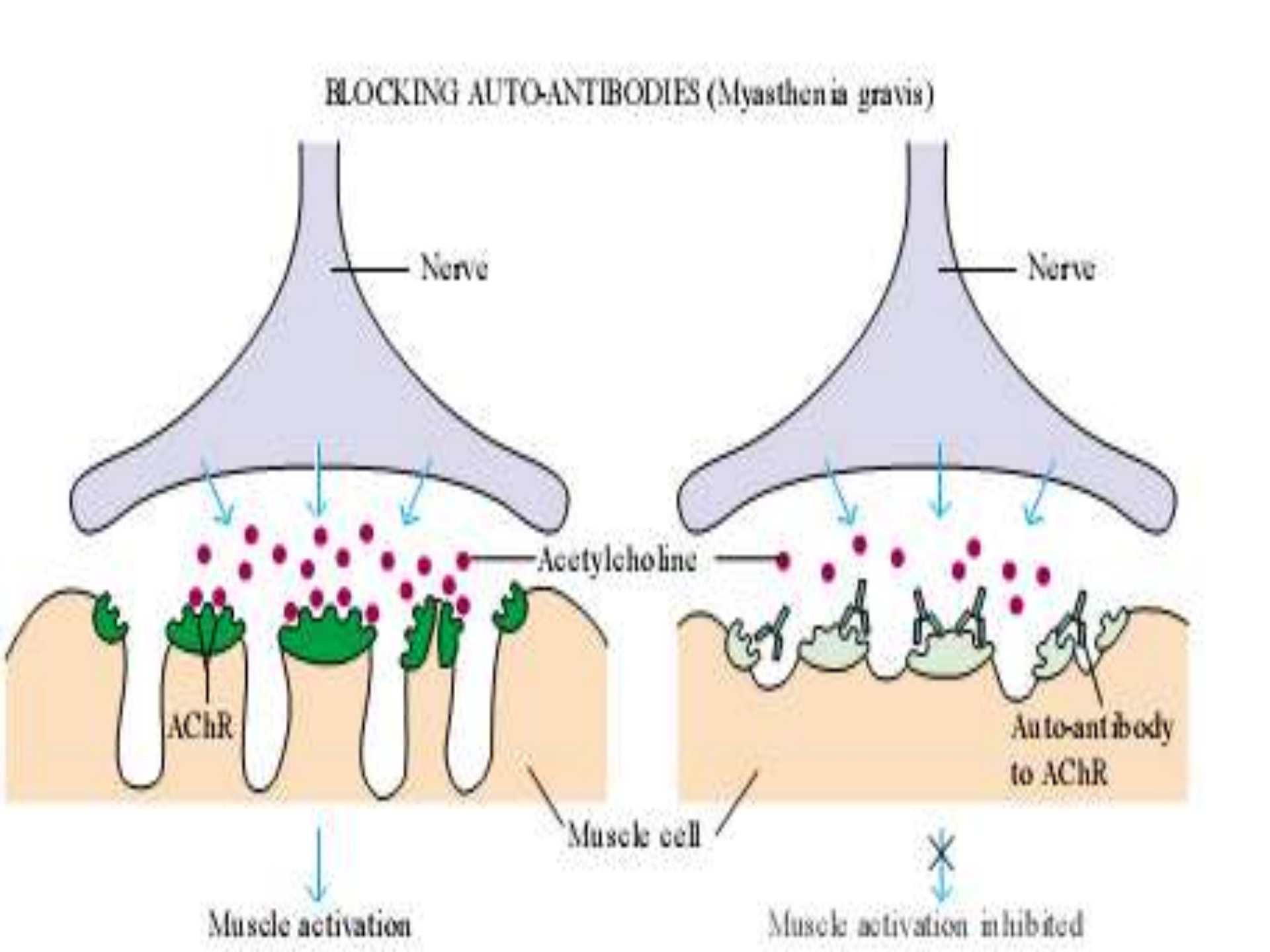
Epitope, also known as antigenic determinant, is the part of an antigen that is recognized by the immune system, specifically by antibodies, B cells, or T cells. For example, the epitope is the specific piece of the antigen that an antibody binds to. The part of an antibody that binds to the epitope is called a paratope

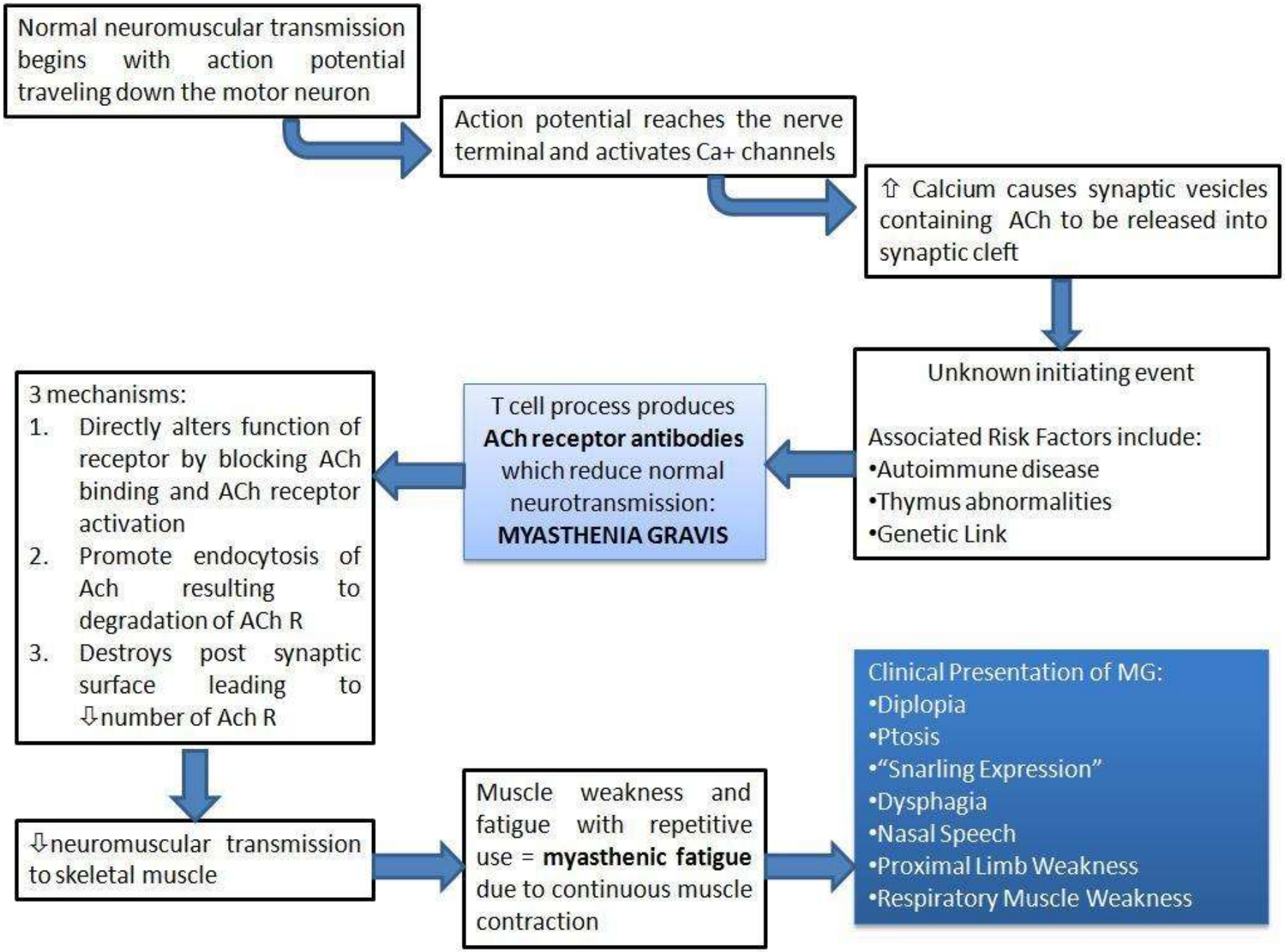
Effects of autoimmunity

1) Tissue destruction
Diabetes: CTLs (autoreactive cytotoxic T-Lymphocytes) CD8+ destroy insulin-producing b-cells in pancreas
2) Antibodies block normal function
Myasthenia gravis: Ab binds acetylcholine receptors
3) Antibodies stimulate inappropriate function
Graves' disease: Ab binds TSH receptor
Mimics thyroid-stimulating hormone
Activates unregulated thyroid hormone production
4) Antigen-antibody complexes affect function
Rheumatoid arthritis:
IgM specific for Fc portion of IgG
IgM-IgG complexes deposited in joints inflammation

Pathophysiology Myasthenia gravis

Myasthenia gravis (MG) is arguably the best understood autoimmune disease, and its study has also led to fundamental appreciation of mechanisms of neuromuscular transmission. MG is caused by antibodies against the acetylcholine receptor (AChR), which produce a compromise in the end-plate potential, reducing the safety factor for effective synaptic transmission. It is clear that AChR antibody destruction of the postsynaptic surface is dependent on complement activation. A muscle-specific kinase has been recently found to be an antigenic target in MG patients without antibodies against the AChR. Autoantibody production in MG is a T-cell-dependent process, but how a breakdown in tolerance occurs is not known.


BLOCKING AUTO-ANTIBODIES (Myasthenia gravis)
Nerve
Nerve
Acetylcholine
AChR
Auto-antibody to AChR
Muscle cell
Muscle activation
Muscle activation inhibited


Normal neuromuscular transmission begins with action potential traveling down the motor neuron
Action potential reaches the nerve terminal and activates Ca+ channels
⇧ Calcium causes synaptic vesicles containing ACh to be released into synaptic cleft
Unknown initiating event
Associated Risk Factors include:
•Autoimmune disease
•Thymus abnormalities
•Genetic Link
T cell process produces ACh receptor antibodies which reduce normal neurotransmission: MYASTHENIA GRAVIS
3 mechanisms:
1. Directly alters function of receptor by blocking ACh binding and ACh receptor activation
2. Promote endocytosis of Ach resulting to degradation of ACh R
3. Destroys post synaptic surface leading to ⇩number of Ach R
⇩neuromuscular transmission to skeletal muscle
Muscle weakness and fatigue with repetitive use = myasthenic fatigue due to continuous muscle contraction
Clinical Presentation of MG:
•Diplopia
•Ptosis
•"Snarling Expression"
•Dysphagia
•Nasal Speech
•Proximal Limb Weakness
•Respiratory Muscle Weakness

PATHOPHYSIOLOGY

- **Antibodies to AChR protein**:

  85 % of patients with generalized myasthenia and 60% of those with ocular myasthenia shows AChR Antibodies
- **Anti-MuSK Ab**(40% of seronegative cases)

  An immune response to muscle-specific kinase (MuSK) can also result in myasthenia gravis, possibly by interfering with **"AChR clustering"**

How do these antibodies act?

- **Blocks** the binding of ACh to the AChR.
- **INCREASES THE DEGRADATION** rate of AChR
  ANTIBODIES→ CROSS LINKING OF RECEPTORS →
  →CLUSTERING → ENDOCYTOEIS → DEGRADATION
- **A complement-mediated destruction** of the postsynaptic folds.

The latter two mechanisms would be expected to reduce the number of AChR at the synapse.

Multiple Sclerosis

Multiple Sclerosis

- Chronic, progressive, degenerative disorder of the CNS characterized by disseminated demyelination of nerve fibers of the brain and spinal cord

Multiple Sclerosis

Etiology

- Unknown cause
- Related to infectious, immunologic, and genetic factors

Multiple Sclerosis

Etiology

- Possible precipitating factors include
  - Infection
  - Physical injury
  - Emotional stress
  - Excessive fatigue
  - Pregnancy
  - Poor state of health

Multiple Sclerosis
Pathophysiology

- Mylelin sheath
  - Segmented lamination that wraps axons of many nerve cells
  - Increases velocity of nerve impulse conduction in the axons
  - Composed of myelin, a substance with high lipid content

Multiple Sclerosis
Pathophysiology

- Characterized by chronic inflammation, demyelination, and gliosis (scarring) in the CNS
- Initially triggered by a virus in genetically susceptible individuals
- Subsequent antigen-antibody reaction leads to demyelination of axons

Pathogenesis of MS

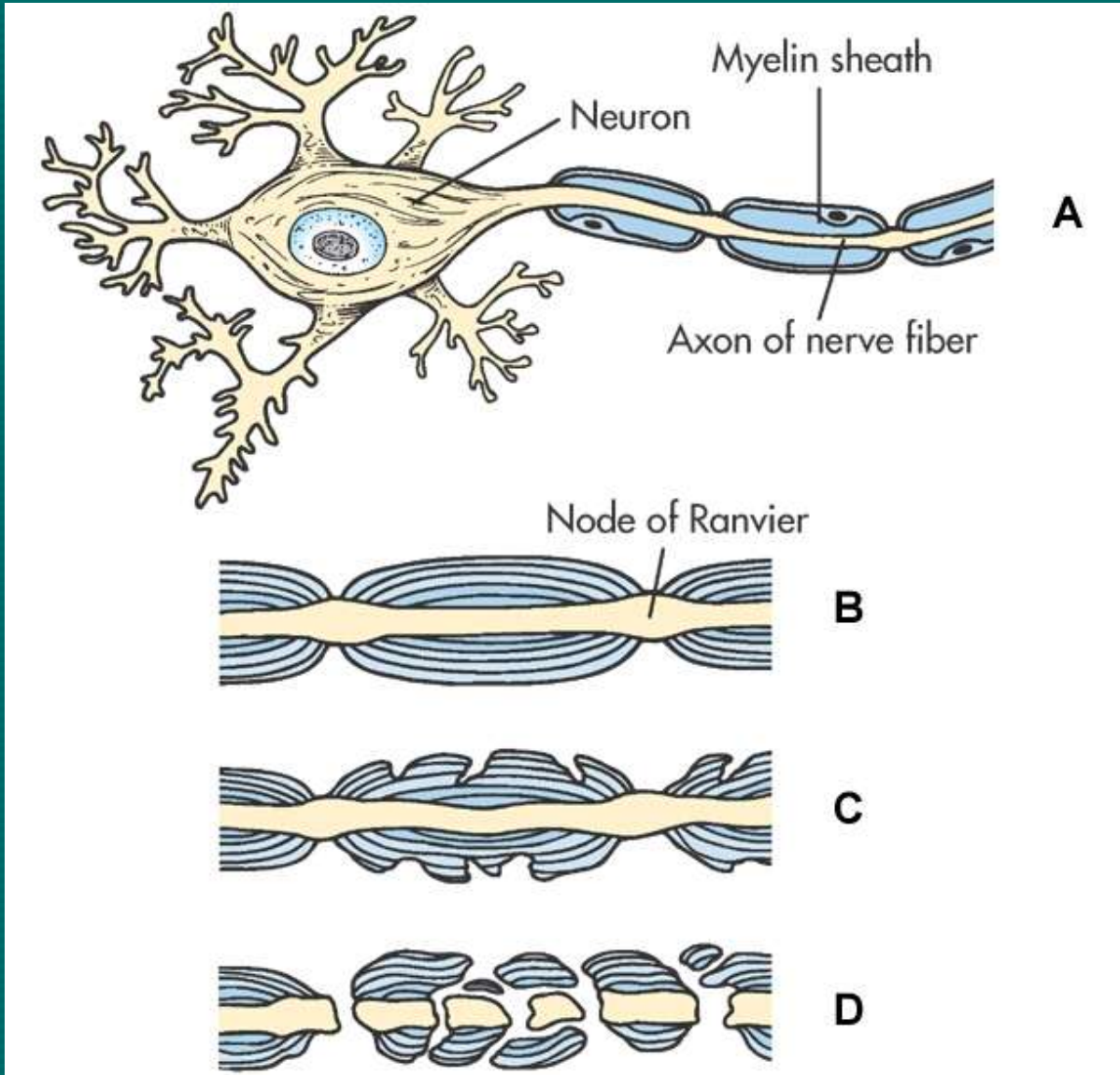


Fig. 57-1

Multiple Sclerosis

Pathophysiology

- Disease process consists of loss of myelin, disappearance of oligodendrocytes, and proliferation of astrocytes
- Changes result in plaque formation with plaques scattered throughout the CNS

Multiple Sclerosis

Pathophysiology

- Initially the myelin sheaths of the neurons in the brain and spinal cord are attacked, but the nerve fiber is not affected
- Patient may complain of noticeable impairment of function
- Myelin can regenerate, and symptoms disappear, resulting in a remission

Multiple Sclerosis
Clinical Manifestations

- Vague symptoms occur intermittently over months and years
- MS may not be diagnosed until long after the onset of the first symptom

Multiple Sclerosis
Clinical Manifestations

- Characterized by
  - Chronic, progressive deterioration in some
  - Remissions and exacerbations in others

Multiple Sclerosis
Clinical Manifestations

- Common signs and symptoms include motor, sensory, cerebellar, and emotional problems

Multiple Sclerosis
Clinical Manifestations

- Motor manifestations
  - Weakness or paralysis of limbs, trunk, and head
  - Diplopia (double vision)
  - Scanning speech
- Spasticity of musclesSensory manifestations
  - Numbness and tingling
  - Blurred vision
  - Vertigo and tinnitus
  - Decreased hearing
  - Chronic neuropathic pain

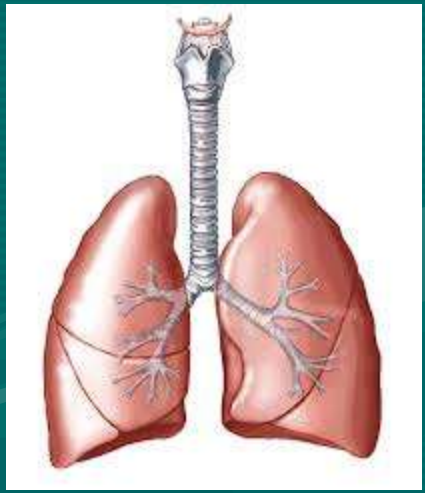
Multiple Sclerosis
Clinical Manifestations

- Cerebellar manifestations
  - Nystagmus
    - Involuntary eye movements
  - Ataxia
  - Dysarthria
    - Lack of coordination in articulating speech
  - Dysphagia
    - Difficulty swallowing

Causes of autoimmunity

- 1) Release of sequestered Ag
- Smoking can trigger Goodpasture's syndrome
- Alveolar basement membrane normally not exposed to
- immune system. Smoking damages alveoli, exposes collagen. Anti-collagen Ag damages lung and kidney
- Anti-sperm Ab produced in some men after vasectomy
- Injection of myelin basic protein (MBP) produces (multiple sclerosis MS-like Experimental autoimmune encephalomyelitis (EAE) in mice and this may be triggered by injury or infection

- Ernest Goodpasture first described the disorder in 1919. He reported a case of pulmonary hemorrhage and glomerulonephritis during an influenza epidemic.
- rare autoimmune disease
- antibodies attack the lungs and kidneys, leading to bleeding from the lungs and to kidney failure.
- It may quickly result in permanent lung and kidney damage, often leading to death.
- It is treated with immunosuppressant drugs such as corticosteroids and cyclophosphamide, and with plasmapheresis, in which the antibodies are removed from the blood.



Etiology

- **Causes**
- **Exposure to organic solvents (e.g. chloroform) or hydrocarbons.**
- **Exposure to tobacco smoke.**
- **Infection, such as influenza A.**
- **Bacteraemia.**
- **Sepsis.**
- **High-oxygen environments.**
- **Certain gene mutations (HLA-DR15).**
- **Cocaine inhalation.**
- **Metal dust inhalation.**
- **Treatment with anti-lymphocytic treatment (especially monoclonal antibodies)**

Some AD may initiate in response to drug treatment.

For example, 1- thiol-containing drugs and 2- sulfonamide derivatives, as well as 3- certain antibiotics and 4- non-steroidal anti-inflammatory drugs, appear to trigger the onset of pemphigus. 5- Drugs such as hydralazine and procainamide or similar aromatic amine drugs prescribed can induce SLE-like symptoms such as arthritis, pleuropericarditis, and myocarditis.

Immunopathology of Goodpasture's syndrome

- **GPS causes the abnormal production of anti-GBM antibodies, by the plasma cells of the blood. The anti-GBM antibodies attack the alveoli and glomeruli basement membranes. These antibodies, in turn, bind their reactive epitopes to the basement membranes and activate the compliment cascade, leading to the death of tagged cells. T cells are also implicated. It is generally considered a type II hypersensitivity reaction**

- IN MOST PATIENTS, THE AUTOANTIBODY IN GOODPASTURE SYNDROME IS DIRECTED AGAINST ALPHA3 CHAIN OF TYPE IV COLLAGEN
- ALTHOUGH BASEMENT MEMBRANES ARE UBIQUITOUS, ONLY THE ALVEOLAR AND GLOMERULAR BASEMENT MEMBRANES ARE AFFECTED CLINICALLY. THE PREFERENTIAL BINDING TO THE ALVEOLAR AND GLOMERULAR BASEMENT MEMBRANES APPEARS TO BE BECAUSE THEY ARE MORE ACCESSIBLE TO THE CIRCULATING ANTIBODIES.

When Someone says "Nothing can be More Complicated than Love", Just throw

PATHOPHYSIOLOGY TEXT BOOKS ON

their face...

Causes of autoimmunity

- 2) Immune stimulation

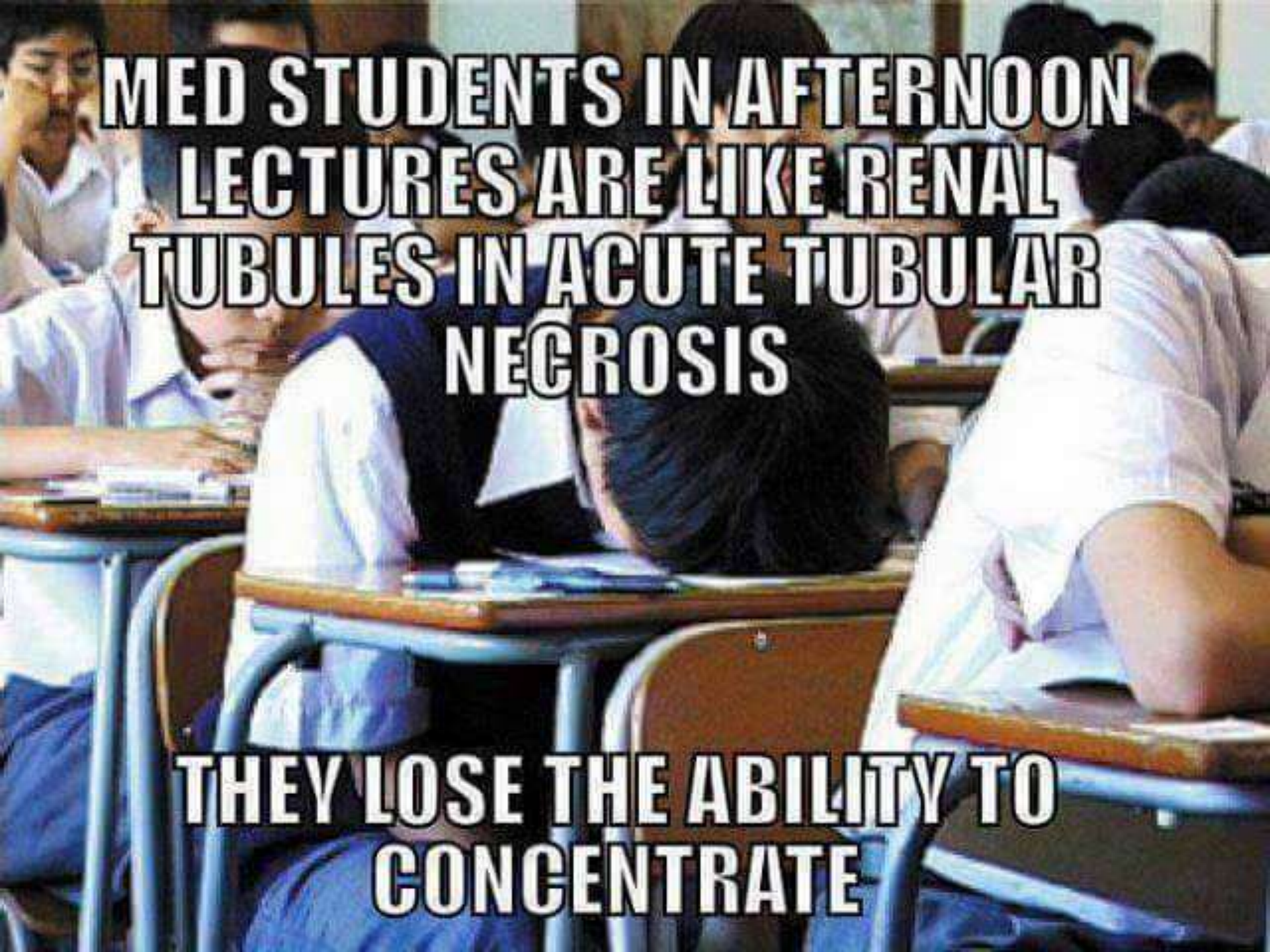
- Microbial infection stimulates APCs carrying self Ag

- High level of APCs with "second signal" breaks anergy (**immune unresponsiveness).**

Anergy:

A state of immune unresponsiveness. Induced when the T cell's antigen receptor is stimulated, effectively freezing T cell responses pending a "second signal" from the antigen-presenting cell. The delivery of the second signal by the antigen-presenting cell rescues the activated T cell from anergy, allowing it to produce the lymphokines necessary for the growth of additional T cells.

Lymphokines are a subset of cytokines that are produced by a type of immune cell known as a lymphocyte. They are protein mediators typically produced by T cells to direct the immune system response by signalling between its cells.


MED STUDENTS IN AFTERNOON LECTURES ARE LIKE RENAL TUBULES IN ACUTE TUBULAR NECROSIS
THEY LOSE THE ABILITY TO CONCENTRATE

Mechanisms of autoimmunity

- Ag released from hidden location.
- Antigen generated by molecular changes.
- Molecular mimicry.

  Molecular mimicry is defined as the theoretical possibility that sequence similarities between foreign and self-peptides are sufficient to result in the cross-activation of autoreactive T or B cells by pathogen-derived peptides.
- Alteration in Ag processing.
- Infection.
- Genetic factors.

Mechanisms of autoimmunity

- **Lymphocytes abnormalities.**

- **Failure of central tolerance.**

Central tolerance is the mechanism by which newly developing T cells and B cells are rendered non-reactive to self

- **Overcome of peripheral tolerance.**

immunological tolerance, is the ability of an individual to ignore "self", while reacting to "non-self". This breakage leads to the immune system's mounting an effective and specific immune response against self determinants.

Tolerance can also be differentiated into "Central" and "Peripheral" tolerance, on whether or not the above-stated checking mechanisms operate in the central lymphoid organs (Thymus and Bone Marrow) or the peripheral lymphoid organs (lymph node, spleen, etc., where self-reactive B-cells may be destroyed)

Failure of central tolerence

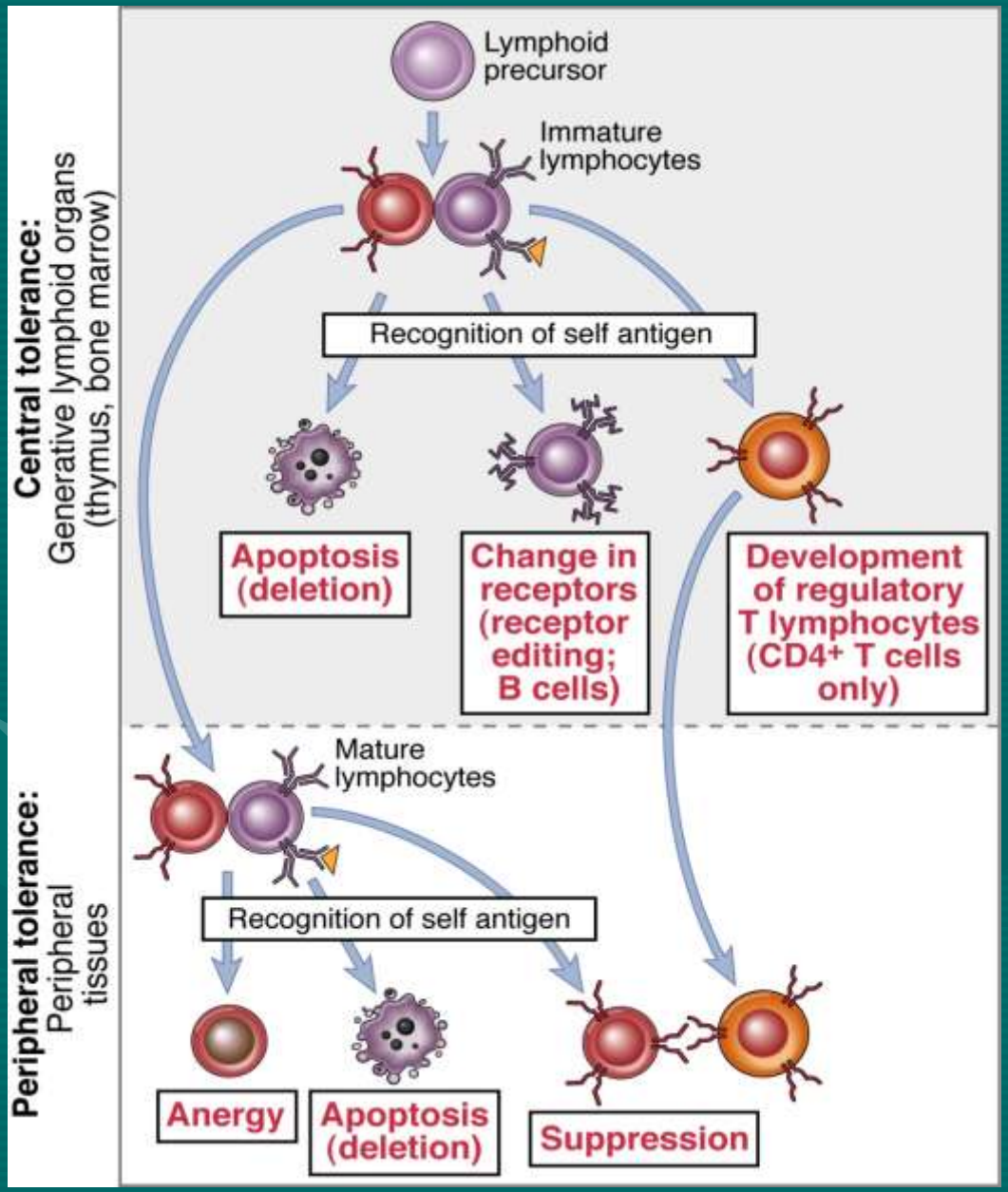
Inside primary lymphoid organ;

- positive selection

- negative selection (Deletion of self reacting T cells in thymus → apoptosis).

- Failure of central tolerance starts AU diseases.

Central and peripheral tolerance



The principal fate of lymphocytes that recognize self antigens in the generative organs is death (deletion), BUT:

Some B cells may change their specificity (called "receptor editing")

Some CD4 T cells may differentiate into regulatory (suppressive) T lymphocytes

POLYCLONAL LYMPHOCYTE ACTIVATION

- Stimulation of non deleted self reacting lymphocytes. These are activated by some activators-
- LPS- POLYCLONAL B CELL ACTIVATOR
- BACTERIAL SUPER ANTIGEN- POLYCLONAL T CELL ACTIVATOR

Ag related from hidden location

Many self Ag are found in hidden location eg. C N S ,TESTES ,EYE (CORNEA)

organ damage

↓

Hidden Ag released

↓

Reaches blood stream

↓

Encounter Ag sensitive cells

↓

Stimulate autoimmunity

Antigen generated by molecular changes

- Development of completely new epitopes on normal protein. eg RF immuno coaglutinine.

Mechanism of formation of RF :

Ab + Ag

↓

new epitopes exposed on Fc region of Ab

↓

Stimulate the formation of Rf

↓

Establishment of disease like rheumatiod artheritis and SLE

Molecular mimicry

- Sharing of epitopes between an infectious agent and its host.

- Antibodies directed against the infectious agents starts reacting with normal self Ag.

- Triggers autoimmunity.

Alteration in Ag processing

- A T cell may fail to develop tolerance to an self Ag simply because it is not efficiently procured.
- If something happens to improve the processing, an autoimmune disease may be triggered.
- This usually happens at the site of inflammation resulting in modified Ab.
- Eg. Thyrotoxicosis , diabetese.

Infection

- Here autoimmunity is not due to infectious agent itself ,but results from dis regulation of host immune response by the microbes.

This may be due to :

- Polyclonal lymphocyte activation.
- inhanced stimulation of co stimulator.
- Alteration of self Ag(cross reactive neo-Ag)

GENETIC FACTORS

The major histocompatibility complex (MHC), located on the short arm of Chromosome 6, is one of the most extensively studied regions in the human genome because of the contribution of multiple variants at this locus in autoimmune, infectious, and inflammatory diseases and in transplantation.

GENETIC FACTORS

- The important genes that regulate the development of autoimmunity are located within MHC.
- MHC have got critical role in maturation of T cell & induction of IR .
- MHC ll genes are directly responsible for auto antigen processing and presentation.

- Eg. Diabetes mellitus :

  DLA-A3, A7, A10 and DLA-B4

SLE: DLA- A7

POLYARTHRITIS: DLA- A7

Lymphocytes abnormalities

- Primary abnormalities either in B cell or T cell.
- Since these cells are critical regulators of all IR.

- MHC presentation of all antigenic peptide to these cells will be defective, in case the cells are abnormal.

- Abnormalities in lymphocytes could affect any one of the mechanism that normally maintains self tolerance.

Autoimmune Diseases

Disease	Organ(s) affected
Insulin dependent diabetes mellitus	Pancreas
Immune thrombocytopenic purpura	Platelets
Hemolytic anemia	Red blood cells
Systemic lupus erythematosus	Kidneys, skin, joints / tendons/ muscle, nerves, lungs, heart valves, GI tract
Grave's disease	Thyroid
Pemicious anemia	GI tract
Myasthenia gravis	Acetylcholine receptors on muscle cells
Ulcerative colitis	GI tract
Rheumatoid arthritis	Joints and other organs

Types of autoantigens	Examples of disease
Intracellular DNA, RNA	Systemic lupus erythematosus (SLE)
Cell receptors	
Thyrotropin receptor	Grave's disease
Acetyl choline receptor	Myasthenia gravis
Insulin receptor	Diabetes mellitus
Cell membranes	
Reb blood cells	Hemolytic anemia
Platelets	Immune thrombocytopenic purpura
Islet cells	Diabetes mellitus
Proteins	
Immunoglobulins	Rheumatoid arthritis, SLE
Complement	
Hormones	
Insulin	Diabetes mellitus
Thyroid hormones	Thyroiditis
Intrinsic factor	Pernicious anemia

Immunologically privileged sites
Brain
Eye
Testis
Uterus (fetus)
Hamster cheek pouch

Fig 13.35 © 2001 Garland Scie

Damage to **immunologically privileged sites** can lead to autoimmunity

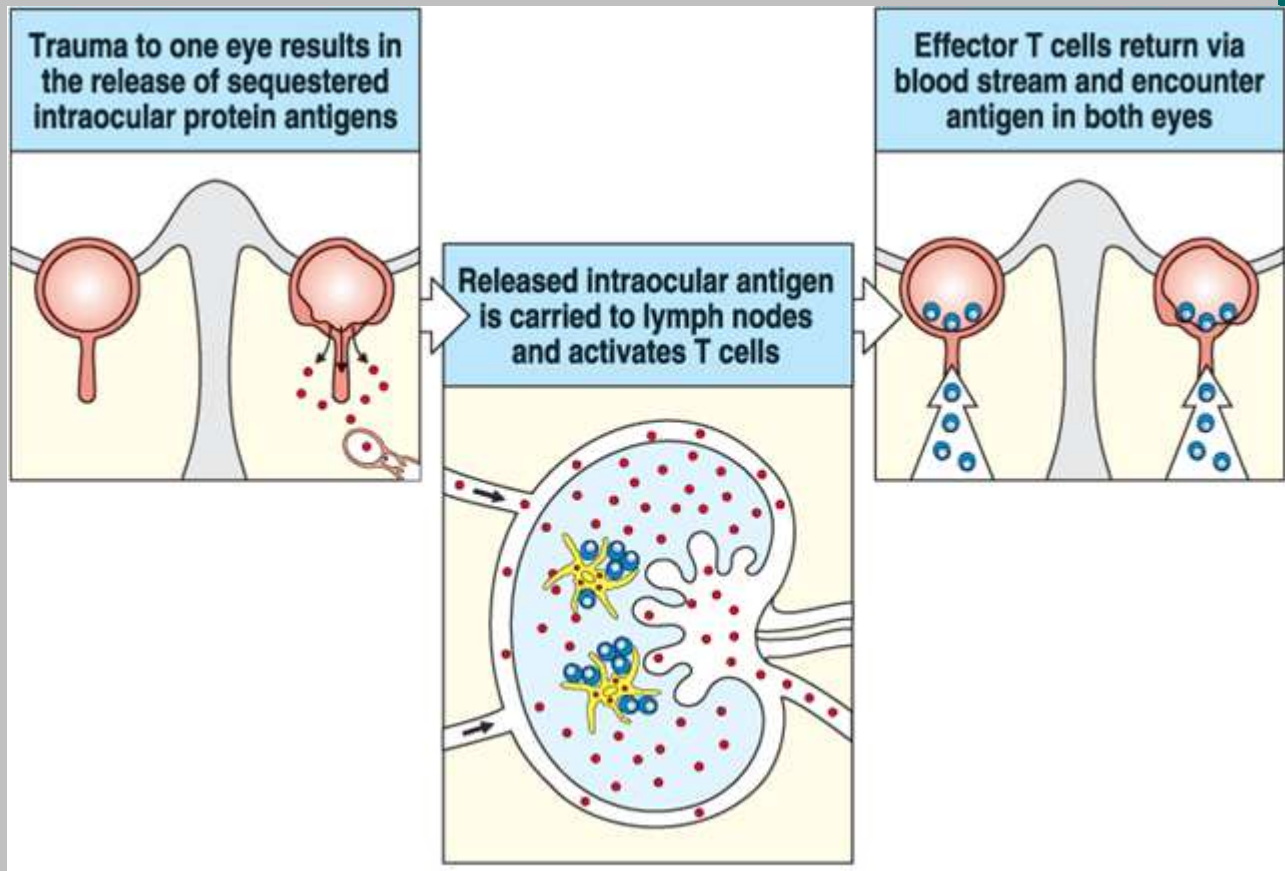


Fig 13.36 © 2001 Garland Science

Diabetes Mellitus

What is diabetes?

- Diabetes mellitus (DM) is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both.

- The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

- The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs.

Diabetes

- Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss.
- In its most severe forms, ketoacidosis or a non–ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death.
- Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made.

Diabetes Long-term Effects

- The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction.

- People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.

Types of Diabetes

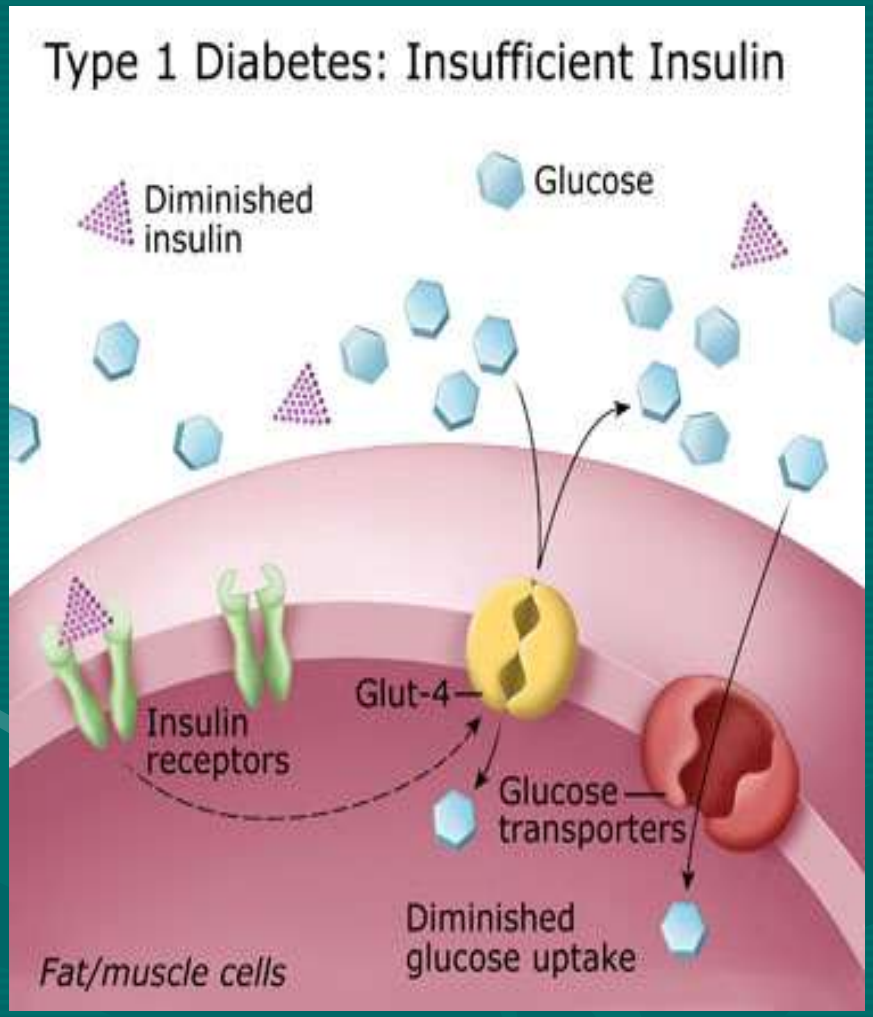
- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Gestational Diabetes
- Other types:
  - LADA ????
  - MODY (maturity-onset diabetes of youth)
  - Secondary Diabetes Mellitus

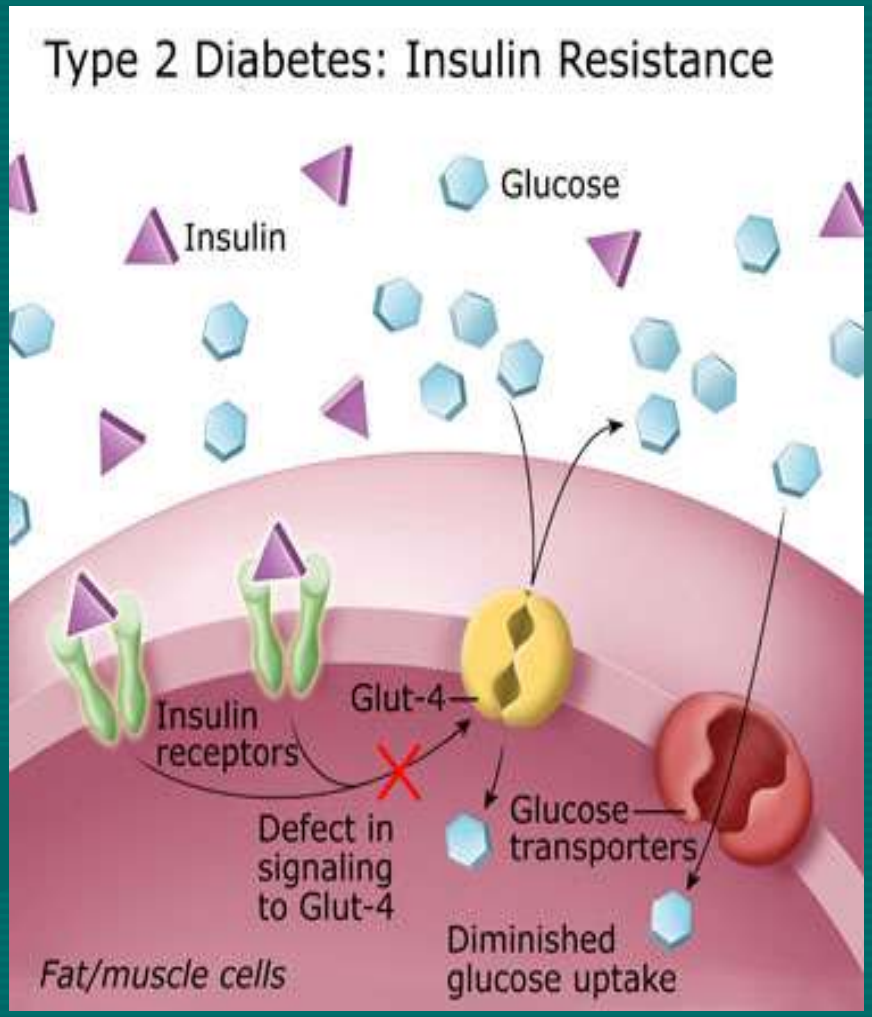
Type 1 diabetes

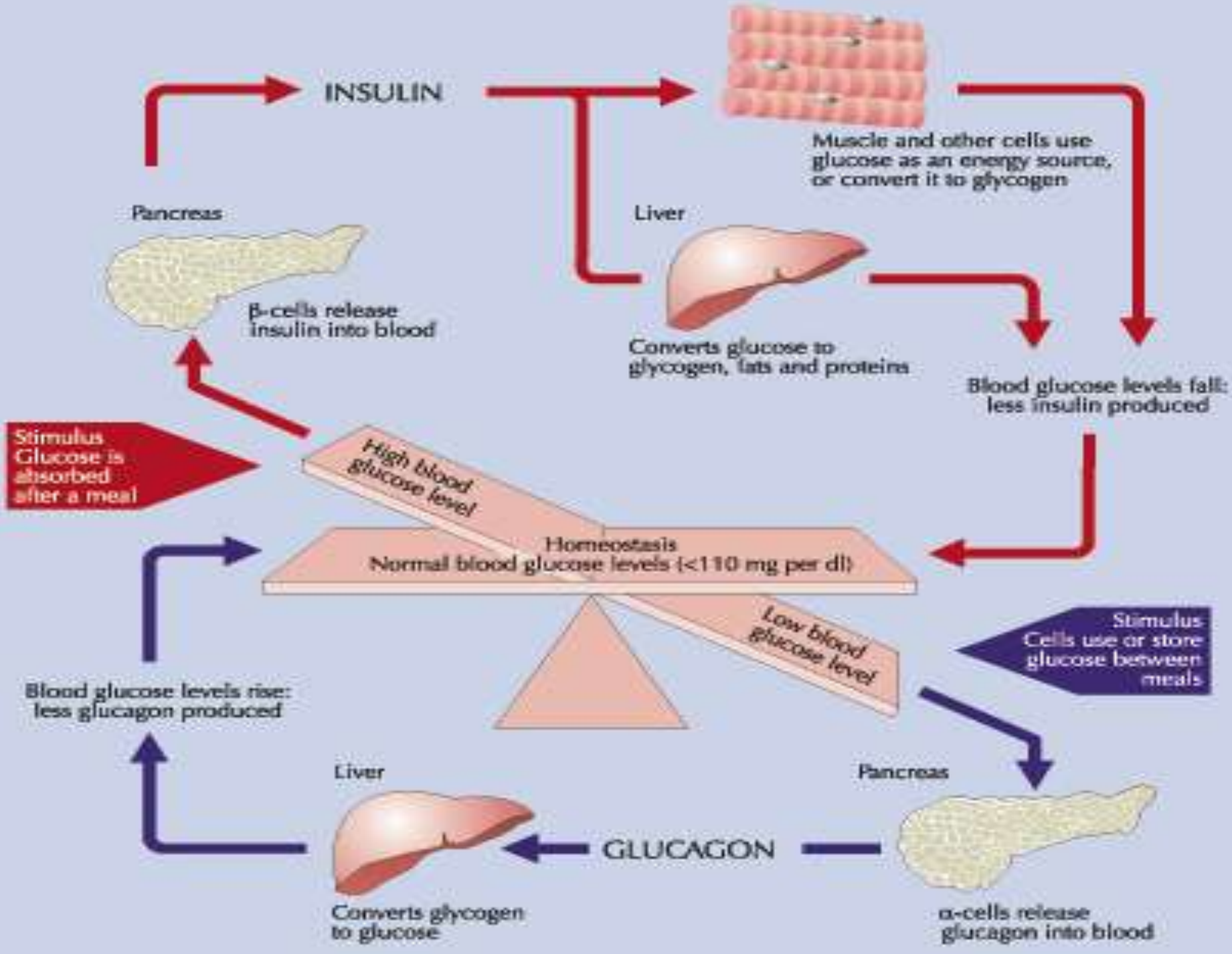
- Was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.
- Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose.
- This form of diabetes usually strikes children and young adults, although disease onset can occur at any age.
- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.
- Risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors.

Type 2 diabetes

- Was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes.
- Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.
- It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.
- Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.


Type 1 Diabetes: Insufficient Insulin
Diminished insulin
Glucose
Insulin receptors
Glut-4
Glucose transporters
Diminished glucose uptake
Fat/muscle cells


Type 2 Diabetes: Insulin Resistance
Insulin
Glucose
Insulin receptors
Glut-4
Defect in signaling to Glut-4
Glucose transporters
Diminished glucose uptake
Fat/muscle cells


INSULIN
Muscle and other cells use glucose as an energy source, or convert it to glycogen
Pancreas
β-cells release insulin into blood
Liver
Converts glucose to glycogen, fats and proteins
Blood glucose levels fall: less insulin produced
Stimulus Glucose is absorbed after a meal
High blood glucose level
Homeostasis
Normal blood glucose levels (<110 mg per dl)
Low blood glucose level
Stimulus Cells use or store glucose between meals
Blood glucose levels rise: less glucagon produced
Liver
GLUCAGON
Pancreas
Converts glycogen to glucose
α-cells release glucagon into blood

Gestational diabetes

- A form of glucose intolerance that is diagnosed in some women during pregnancy.
- Gestational diabetes occurs more frequently among African Americans, Hispanic/Latino Americans, and American Indians. It is also more common among obese women and women with a family history of diabetes.
- During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in the infant.
- After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes.
- Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in the next 5-10 years.

Other types of DM

- Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses.

- Such types of diabetes may account for 1% to 5% of all diagnosed cases of diabetes.

LADA

- Latent Autoimmune Diabetes in Adults (LADA) is a form of ***autoimmune*** (***type 1 diabetes***) which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes.
- Alternate terms that have been used for "LADA" include Late-onset Autoimmune Diabetes of Adulthood, "Slow Onset Type 1" diabetes, and sometimes also "Type 1.5
- Often, patients with LADA are mistakenly thought to have ***type 2 diabetes***, based on their age at the time of diagnosis.

LADA (cont.)

Features of LADA
Patients usually aged ≥ 25 years
Clinical presentation "masquerading" as non-obese type 2 diabetes
Initial control achieved with diet alone or diet and oral hypoglycaemic agents
Insulin dependency occurs within months but can take 10 years or more
Other features of type 1 diabetes
Low fasting and post-glucagon stimulated C-peptide
HLA susceptibility alleles
ICA+
GADA+

LADA (cont.)

- About 80% of adults apparently with recently diagnosed Type 2 diabetes but with GAD auto-antibodies (i.e. LADA) progress to insulin requirement within 6 years.

- The potential value of identifying this group at high risk of progression to insulin dependence includes:
  - the avoidance of using metformin treatment
  - the early introduction of insulin therapy

MODY

- MODY – Maturity Onset Diabetes of the Young
- MODY is a monogenic form of diabetes with an autosomal dominant mode of inheritance:
  - Mutations in any one of several transcription factors or in the enzyme glucokinase lead to insufficient insulin release from pancreatic ß-cells, causing MODY.
  - Different subtypes of MODY are identified based on the mutated gene.
- Originally, diagnosis of MODY was based on presence of non-ketotic hyperglycemia in adolescents or young adults in conjunction with a family history of diabetes.
- However, genetic testing has shown that MODY can occur at any age and that a family history of diabetes is not always obvious.

MODY (cont.)

Features suggestive of monogenic diabetes

MODY (majority have HNF-1alpha or HNF-4alpha mutations)

- Young onset of diabetes (generally <25 years of age)
- Strong family history of diabetes (typically 2–3 generations affected)
- Sulfonylurea sensitivity
- Absence of insulin resistance phenotype: normal BP, TG, HDL-C

PNDM (50% have Kir6.2 mutations)

- Diabetes onset <6 months of age
- DEND syndrome

MODY (cont.)

- Within MODY, the different subtypes can essentially be divided into 2 distinct groups: glucokinase MODY and transcription factor MODY, distinguished by characteristic phenotypic features and pattern on oral glucose tolerance testing.

- Glucokinase MODY requires no treatment, while transcription factor MODY (i.e. Hepatocyte nuclear factor -1alpha) requires low-dose sulfonylurea therapy and PNDM (caused by Kir6.2 mutation) requires high-dose sulfonylurea therapy.

Secondary DM

Secondary causes of Diabetes mellitus include:

- Acromegaly,
- Cushing syndrome,
- Thyrotoxicosis,
- Pheochromocytoma
- Chronic pancreatitis,
- Cancer
- Drug induced hyperglycemia:
  - Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
  - Beta-blockers - Inhibit insulin secretion.
  - Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
  - Corticosteroids - Cause peripheral insulin resistance and gluconeogensis.
  - Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
  - Naicin - They cause increased insulin resistance due to increased free fatty acid mobilization.
  - Phenothiazines - Inhibit insulin secretion.
  - Protease Inhibitors - Inhibit the conversion of proinsulin to insulin.
  - Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia. They also cause increased insulin resistance due to increased free fatty acid mobilization.

Prediabetes: Impaired glucose tolerance and impaired fasting glucose

- Prediabetes is a term used to distinguish people who are at increased risk of developing diabetes. People with prediabetes have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Some people may have both IFG and IGT.

- IFG is a condition in which the fasting blood sugar level is elevated (100 to 125 milligrams per decilitre or mg/dL) after an overnight fast but is not high enough to be classified as diabetes.

- IGT is a condition in which the blood sugar level is elevated (140 to 199 mg/dL after a 2-hour oral glucose tolerance test), but is not high enough to be classified as diabetes.

Prediabetes: Impaired glucose tolerance and impaired fasting glucose (cont.)

- Progression to diabetes among those with prediabetes is not inevitable. Studies suggest that weight loss and increased physical activity among people with prediabetes prevent or delay diabetes and may return blood glucose levels to normal.

- People with prediabetes are already at increased risk for other adverse health outcomes such as heart disease and stroke.

Diagnosis of Diabetes Mellitus

Values of Diagnosis of Diabetes Mellitus

Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

	Glucose concentration, mmol l^{-1} (mg dl^{-1})		
	Whole blood		Plasma[a]
	Venous	Capillary	Venous
Diabetes Mellitus:			
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
or			
2-h post glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)
or both			
Impaired Glucose Tolerance (IGT):			
Fasting (if measured)	< 6.1 (< 110)	< 6.1 (< 110)	< 7.0 (< 126)
and			
2-h post glucose load	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 7.8 (≥ 140) and < 11.1 (< 200)
Impaired Fasting Glycaemia (IFG):			
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
and (if measured)			
2-h post glucose load	< 6.7 (< 120)	< 7.8 (< 140)	< 7.8 (< 140)

Prevention or delay of diabetes: Life style modification

- Research studies have found that lifestyle changes can prevent or delay the onset of type 2 diabetes among high-risk adults.
- These studies included people with IGT and other high-risk characteristics for developing diabetes.
- Lifestyle interventions included diet and moderate-intensity physical activity (such as walking for 2 1/2 hours each week).
- In the Diabetes Prevention Program, a large prevention study of people at high risk for diabetes, the development of diabetes was reduced 58% over 3 years.

Prevention or delay of diabetes: Medications

- Studies have shown that medications have been successful in preventing diabetes in some population groups.
- In the Diabetes Prevention Program, people treated with the drug metformin reduced their risk of developing diabetes by 31% over 3 years.
- Treatment with metformin was most effective among younger, heavier people (those 25-40 years of age who were 50 to 80 pounds overweight) and less effective among older people and people who were not as overweight.
- Similarly, in the STOP-NIDDM Trial, treatment of people with IGT with the drug acarbose reduced the risk of developing diabetes by 25% over 3 years.
- Other medication studies are ongoing. In addition to preventing progression from IGT to diabetes, both lifestyle changes and medication have also been shown to increase the probability of reverting from IGT to normal glucose tolerance.


Management of
Diabetes Mellitus

Management of DM

- The major components of the treatment of diabetes are:

A	• Diet and Exercise
B	• Oral hypoglycaemic therapy
C	• Insulin Therapy

A. Diet (cont.)

The following principles are recommended as dietary guidelines for people with diabetes:

- Dietary fat should provide *25-35% of total intake of calories but saturated fat intake* should not exceed 10% of total energy. Cholesterol consumption should be restricted and limited to 300 mg or less daily.

- Protein intake can range between 10-15% total energy (0.8-1 g/kg of desirable body weight). Requirements increase for children and during pregnancy. Protein should be derived from both animal and vegetable sources.

- Carbohydrates provide *50-60% of total caloric content of the diet.* Carbohydrates should be complex and high in fibre.

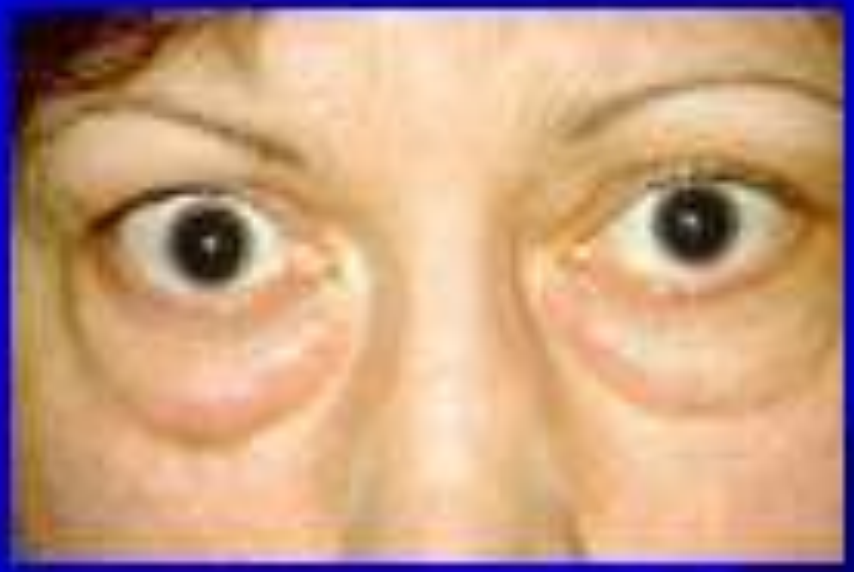
- Excessive salt intake is to be avoided. It should be particularly restricted in people with hypertension and those with nephropathy.

Oral Hypoglycaemic Medications

AGENTS & ACTIONS

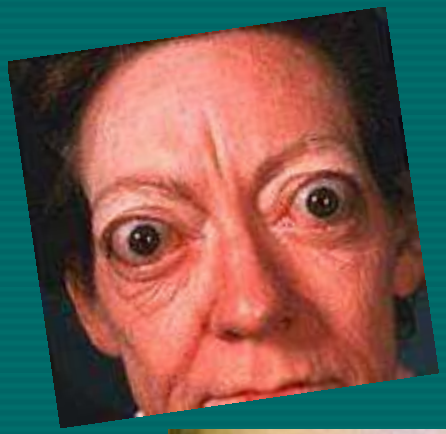
Drug Class	Drug Name	Brand Name	Mechanism of Action
Biguanides	Metformin	Glucophage®	Inhibit glucose production by the liver
Sulfonylureas (second-generation)	Glimepiride Glipizide Glyburide	Amaryl® Glucotrol® Diabeta®, Glynase PresTab®, Micronase®	Increase insulin secretion by pancreatic beta cells
Meglitinides	Repaglinide Nateglinide	Prandin® Starlix®	Increase insulin secretion by pancreatic beta cells
Thiazolidinediones (TZDs)	Pioglitazone Rosiglitazone	Actos® Avandia®	Increase glucose uptake by skeletal muscle
Alpha-glucosidase inhibitors	Acarbose Miglitol	Precose® Glyset®	Inhibit carbohydrate absorption in the small intestine

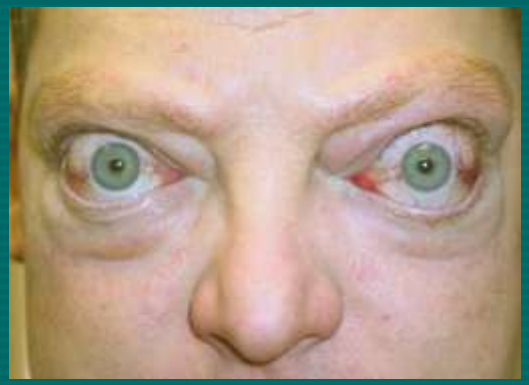
Autoimmune Thyroid diseasae

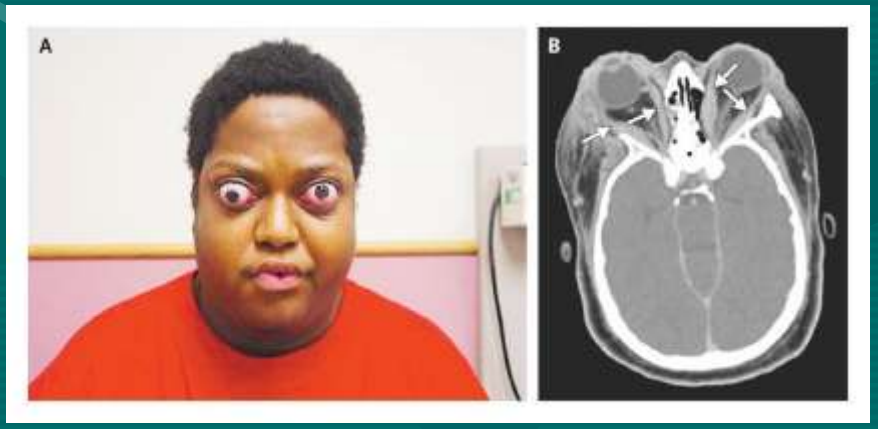


Graves' Disease

- Initiating mechanisms uncertain
- T and B cell infiltration into the thyroid
- Polyclonal autoreactive T cells, directed against wide variety of thryoid autoantigen epitopes
- Cytokine production
- HLA class I and II up-regulation
- Intrathyroidal lymphocytes major site of autoantibody synthesis
  - Antibody production
  - Anti-TSH receptor antibodies







Graves Disease

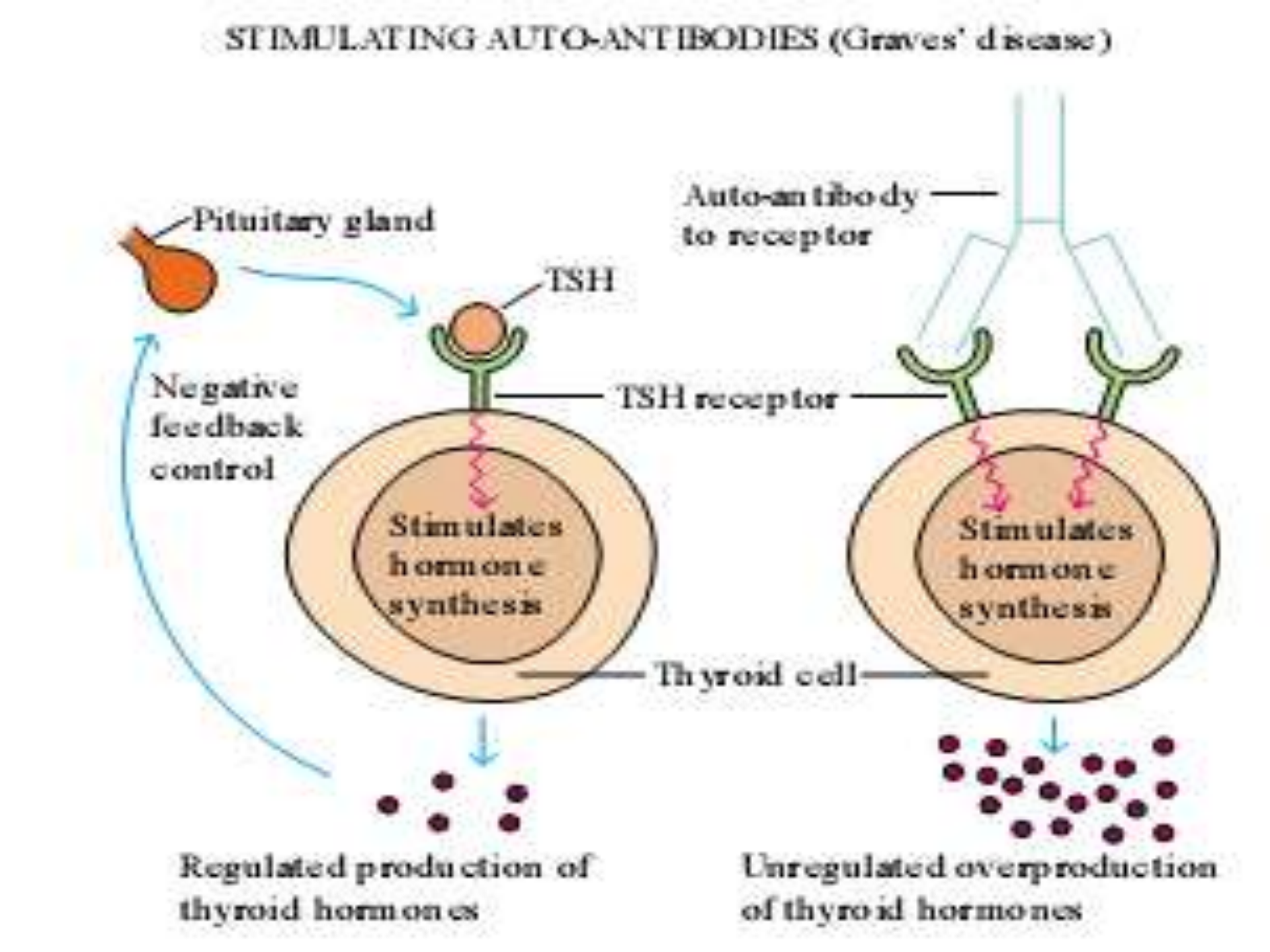
- Graves Disease is an autoimmune disorder that leads to over activity of the thyroid gland (hyperthyroidism)
- It is most common in women over age 20 but can effect either gender at any age

Symptoms

- **Anxiety**
- **Breast enlargement in men**
- **Difficulty concentrating**
- **Double vision**
- **Eyeballs that stick out (exophthalmos)**
- **Eye irritation and tearing**
- **Fatigue**
- **Frequent bowel movements**
- **Goiter**
- **Heart intolerance**
- **Increased appetite**
- **Increased sweating**
- Insomnia
- Irregular menstrual periods in women
- Muscle weakness
- Nervousness
- Rapid/irregular heartbeat (palpitations or arhythmia)
- Restlessness or difficulty sleeping
- Shortness of breath with activity
- Tremor
- Weight loss

Causes

- Abnormal immune system response that causes thyroid gland to produce too much thyroid hormone (hyperthyroidism)
- Normally, thyroid gets production orders through TSH (thyroid-stimulating chemical) released by the pituitary gland, but in Graves Disease, a malfunction in the body's immune system releases abnormal antibodies that mimic TSH


STIMULATING AUTO-ANTIBODIES (Graves' disease)
Pituitary gland
TSH
Auto-antibody to receptor
Negative feedback control
TSH receptor
Stimulates hormone synthesis
Stimulates hormone synthesis
Thyroid cell
Regulated production of thyroid hormones
Unregulated overproduction of thyroid hormones

Graves' Disease

TSH receptor antibodies
(usually stimulatory)

Initiation of
autoimmune response

TSH receptor

Thyroid gland

Goitre

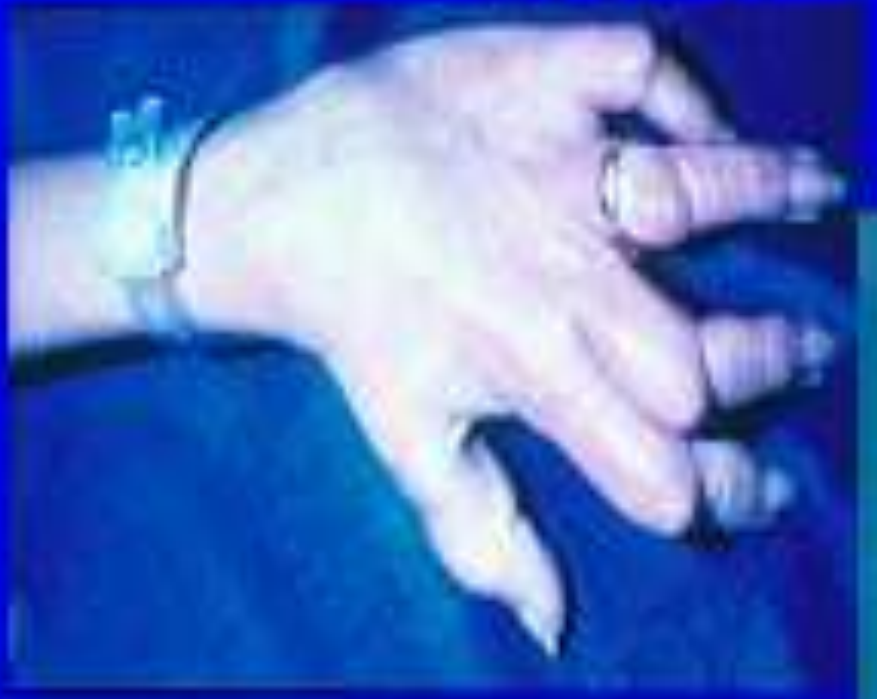
Excess
thyroid
hormone

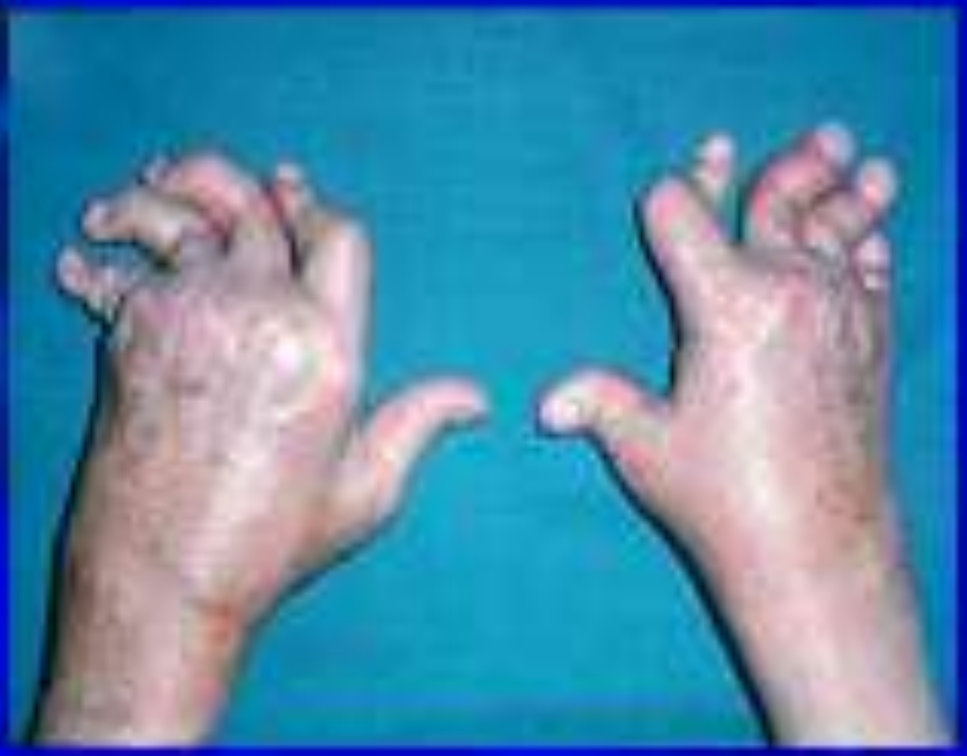
Graves' goitre

Rheumatiod Arthritis

- Auto-immune disorder which results in inflammation of the synovial lining of the joint and cartilage destruction.
- This result in loss of function.
- Affects 1% of adults.

Rheumatoid arthritis





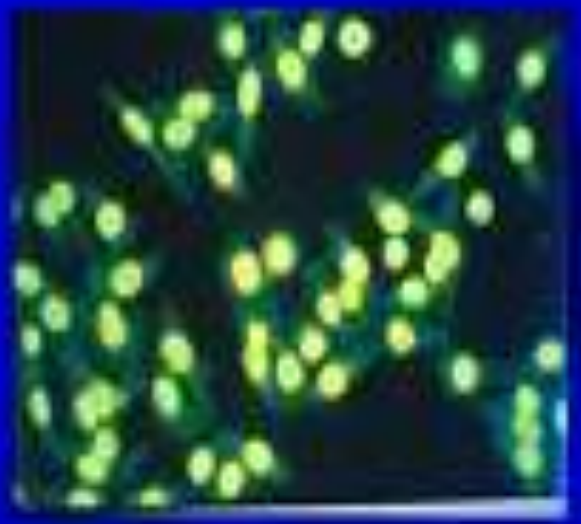
School of Pathology UNSW, Australia

Rheumatoid Factors

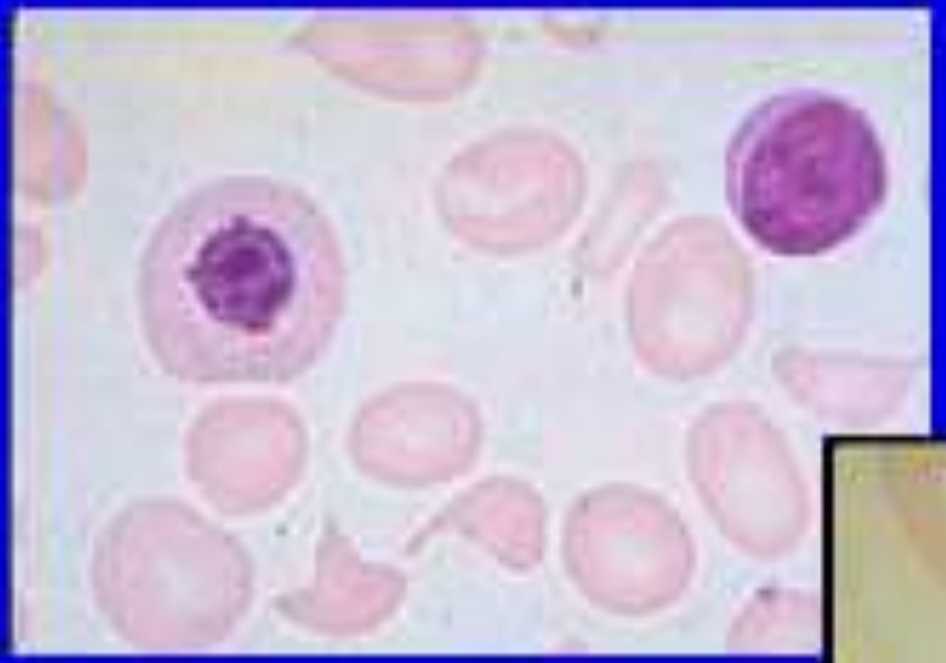
- These are auto-antibodies.
- IgM which binds to the patients own IgG.
- This can result in activation of the complement system (which can destroy cells, recruit neutrophils, etc).

Systemic Lupus Erythematosis

A 27 year old woman presented with a visual field defect in the L eye, head-aches and a facial rash. She had a positive ANA and proteinuria.



Pernicious anaemia



Macrocytic RBC

Hypersegmented PMN

Treatment for autoimmunity

- Immunosuppression (e.g., prednisone, cyclosporin A)
- Removal of thymus (some MG patients)
- Plasmapheresis (remove Ab-Ag complexes)
- T-cell vaccination (activate suppressing T cells??)
- Block MHC with similar peptide
- anti-CD4 monoclonal Ab
- anti-IL2R monoclonal Ab

PATHOPHYSIOLOGY OF CARDIOVASCULAR SYSTEM DISORDERS

Dr. AJWADASSUMAIDAEE PhD

Summary

- 1. Edema
- 2. Hyperemia and Congestion
- 3. Hemorrhage
- 4. Thrombosis
- 5. Embolism
- 6. Ischemia / Infarction
- 7- Shock
- 8- Coronary heart disease & Myocardial infarction
- 9- Rheumatic heart disease
- 10- Heart failure
- 11- Acute pulmonary edema
- 12- Essential hypertension
- 13- Secondary hypertension
- 14- Malignant hypertension
- 15- Hypotension
- 16- Aneurysm versus varicose veins

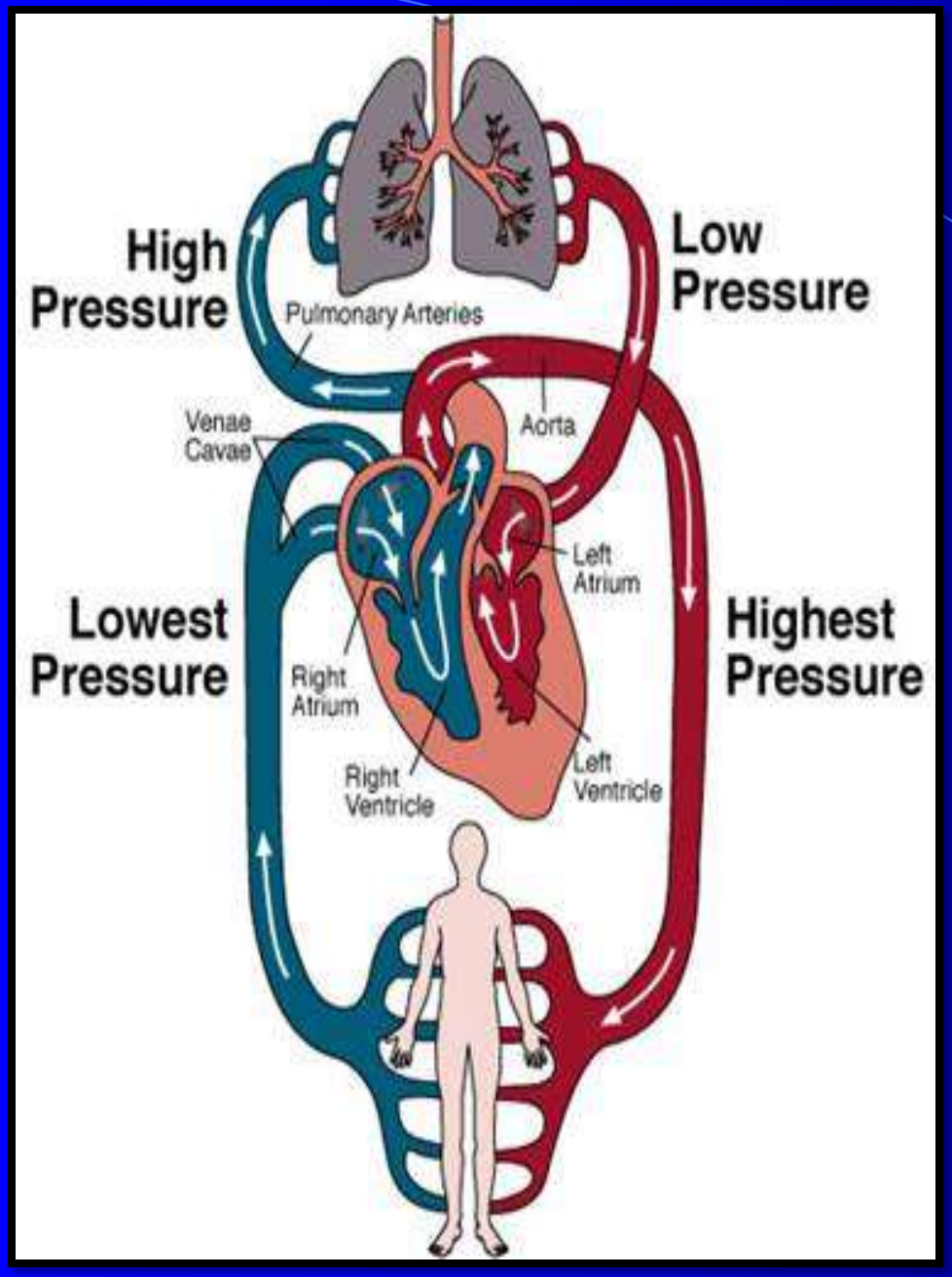
- Vascular disorders are responsible for more morbidity and mortality than any other category of human disease.

- Although the most clinically significant lesions typically involve arteries, venous diseases also occur.

- Vascular pathology results in disease via two principal mechanisms:

  (1) *Narrowing (stenosis)* or *complete obstruction* of vessel lumens, either progressively (e.g., by atherosclerosis) or precipitously (e.g., by thrombosis or embolism).

  (2) *weakening* of vessel walls, leading to dilation or rupture.



Containing

- Heart, artery, Vein
- General circulation
  Pulmonary circulation

Functions

- Deliver oxygen and nutrients
- Carry away metabolic wastes

A Healthy circulatory system

♠ *Normal blood volum*

♠ *Homeostasis*

Normal homeostasis

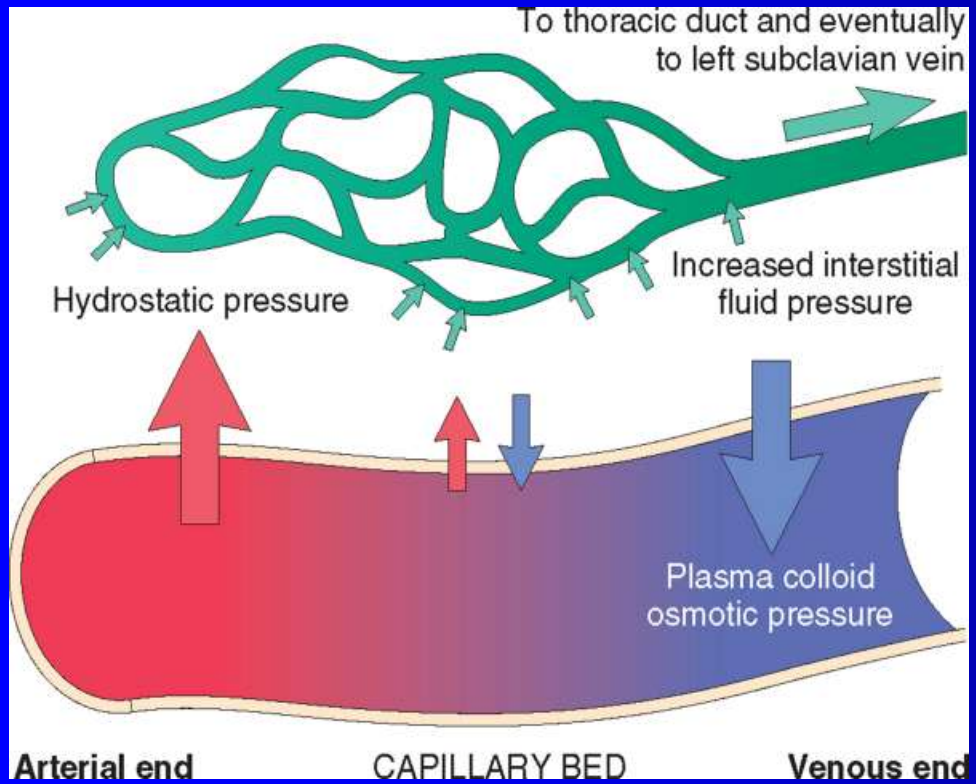
- ***vessel wall integrity***
- ***intravascular pressure***
- ***osmolarity***
- ***normal hemostasis***

- Edema
- Hyperemia & congestion
- Thrombosis & Embolism
- Infarction
- Hemorrhage
- Shock

Three Major Causes of morbidity and mortality

- ♦ Myocardial infarction
- ♦ Pulmonary embolism
- ♦ Cerebral vascular accident

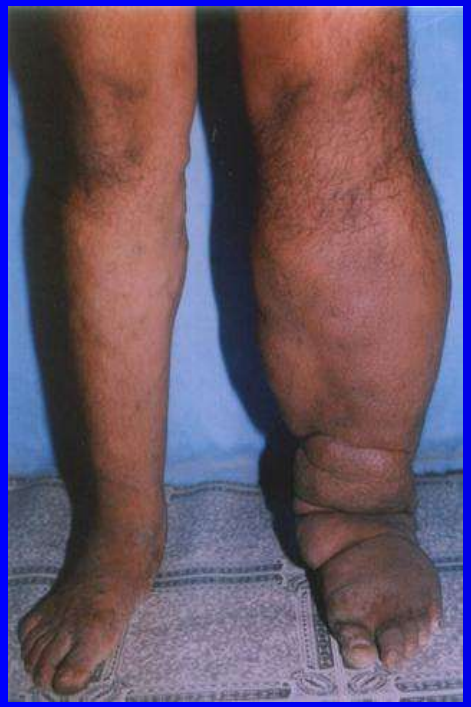
EDEMA



- Increased fluid in the interstitial tissue spaces
- General & local
- Pathogenesis
  - Vascular hydrostatic pressure
  - Plasma colloid osmotic pressure
  - Lymphatic drainage

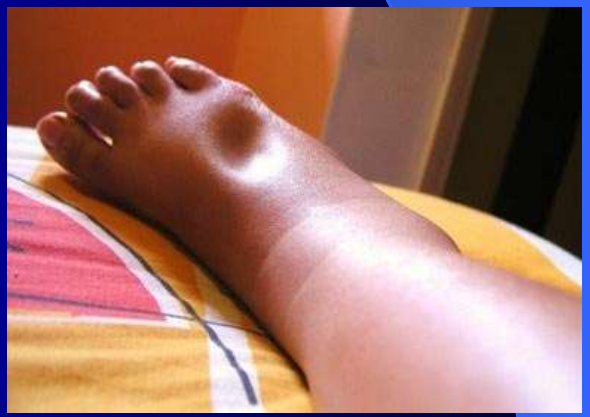
EDEMA

- Increased hydrostatic pressure *(cardiac edema, etc.)*
- Reduced plasma osmotic pressure *(nephrotic, hepatic, malnutrient edema, etc.)*
- Lymphatic obstruction *(filariasis infection — elephantiasis， breast surgery, etc)*
- Sodium and water retention *(ARF, etc)*



elephantiasis

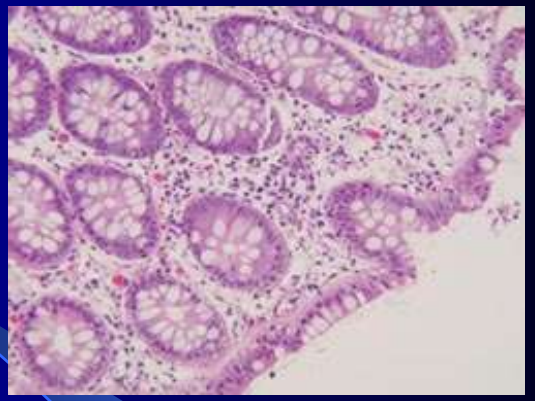
Minimal Change Disease

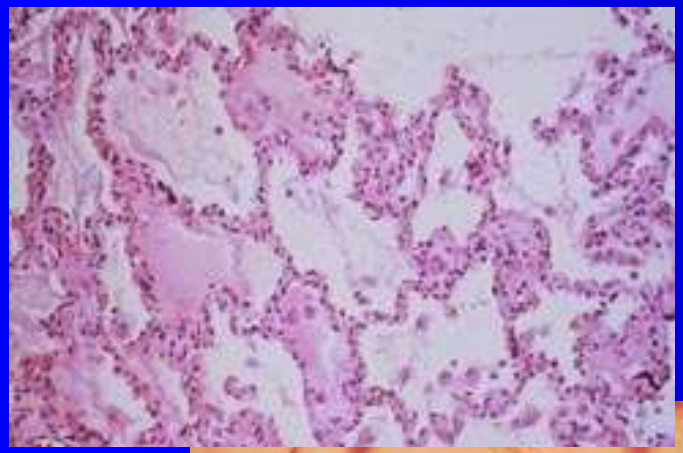


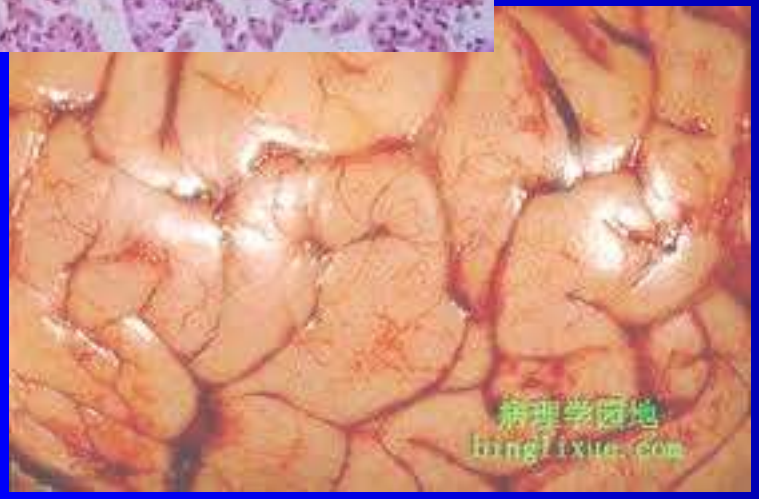
Pitting edema

EDEMA

- Morphology







LM:

Clearing and separation of the extracellular matrix elements

Cell swelling

Subcutaneous edema

Pulmonary edema

Edema of the brain

EDEMA

- Hydrothorax
- hydropericardium
- hydroperitoneum (ascites)
- anasarca

- ***Clinical correlation***

  from annoying to fatal

  indicate subtle disease

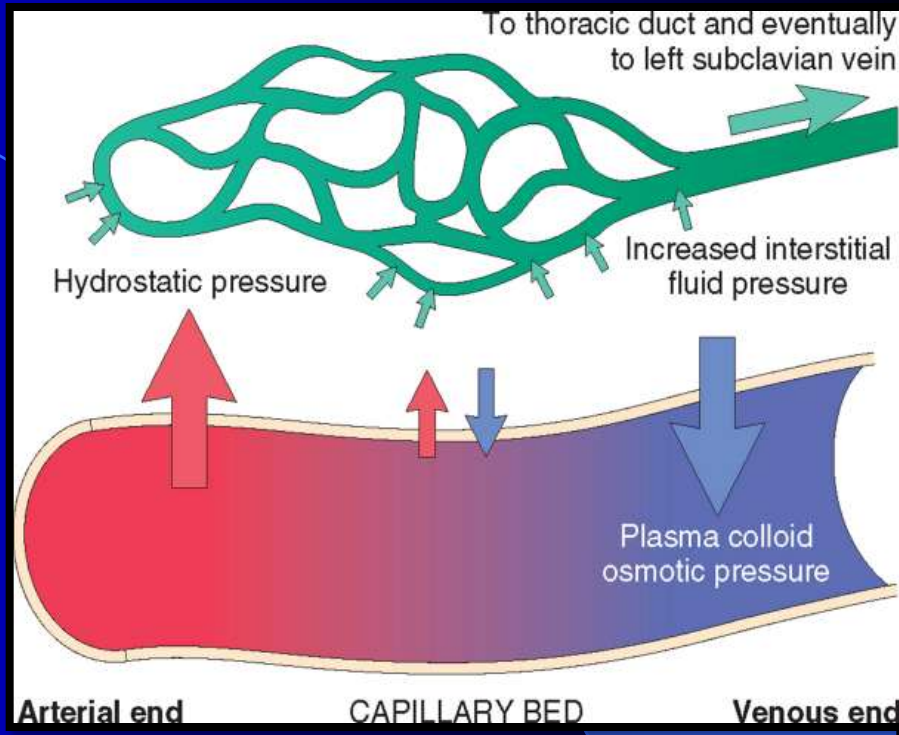
  benefit or harmful

1. Edema

= ↑ fluid in interstitium

- cavities – hydrothorax, hydropericardium, ascites
- anasarca = severe generalized edema
- 3 major factors:
  - hydrostatic pressure
  - plasma colloid osmotic pressure
  - lymphatic drainage
- inflammation

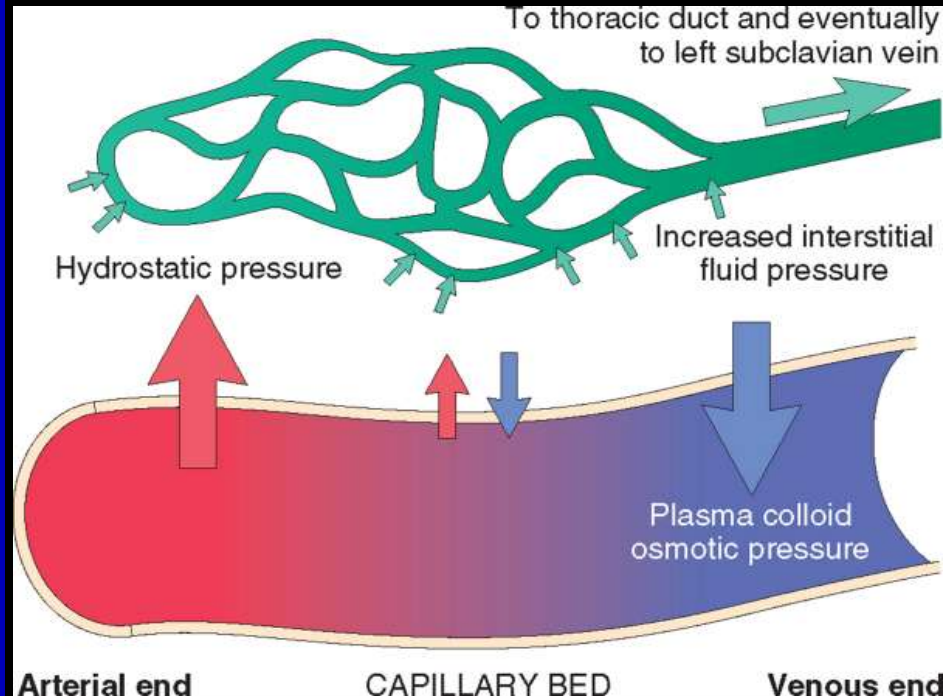
1. Edema



- **1. ↑ hydrostatic pressure**
  - impaired venous return
    - congestive heart failure
    - constrictive pericarditis
    - liver cirrhosis – ascites
  - venous obstruction or compression
    - thrombosis
    - external pressure

1. Edema

- **2. ↓ plasma colloid osmotic pressure**
- loss or reduced albumin synthesis
  - nephrotic syndrome
  - protein-losing gastroenteropathy
  - liver cirrhosis
  - malnutrition



1. Edema

- **3. lymphatic obstruction**
- **→ lymphedema**
  - **inflammatory → elephantiasis**
    - **Filariasis - *Wuchereria bancrofti***
    - ***Wuchereria bancrofti* is a human parasitic roundworm that is the major cause of lymphatic filariasis. It is one of the three parasitic worms, together with *Brugia malayi* and *B. timori*, that infect the lymphatic system to cause lymphatic filariasis**
    - **Lymphatic filariasis, also known as elephantiasis, is a human disease caused by parasitic worms known as filarial worms.[] Some people, however, develop a syndrome called elephantiasis, which is marked by severe swelling in the arms, legs, or genitals.**
    - **Erysipelas – *Streptococcus pyogenes***
  - **neoplastic – breast carcinoma**
  - **post-surgical (LN resection) + postirradiation**

1. Edema

- subcutaneous tissue (pitting edema) + cavities
- generalized x locally prominent

- right-sided heart failure – lower limbs
- left-sided heart failure - pulmonary edema
- nephrotic syndrome – periorbital edema (eyelids)
- brain edema – localized x generalized
  - gyri flattening + sulci narrowing → herniation

HYPEREMIA & CONGESTION

A local increased volume of blood in a particular tissue

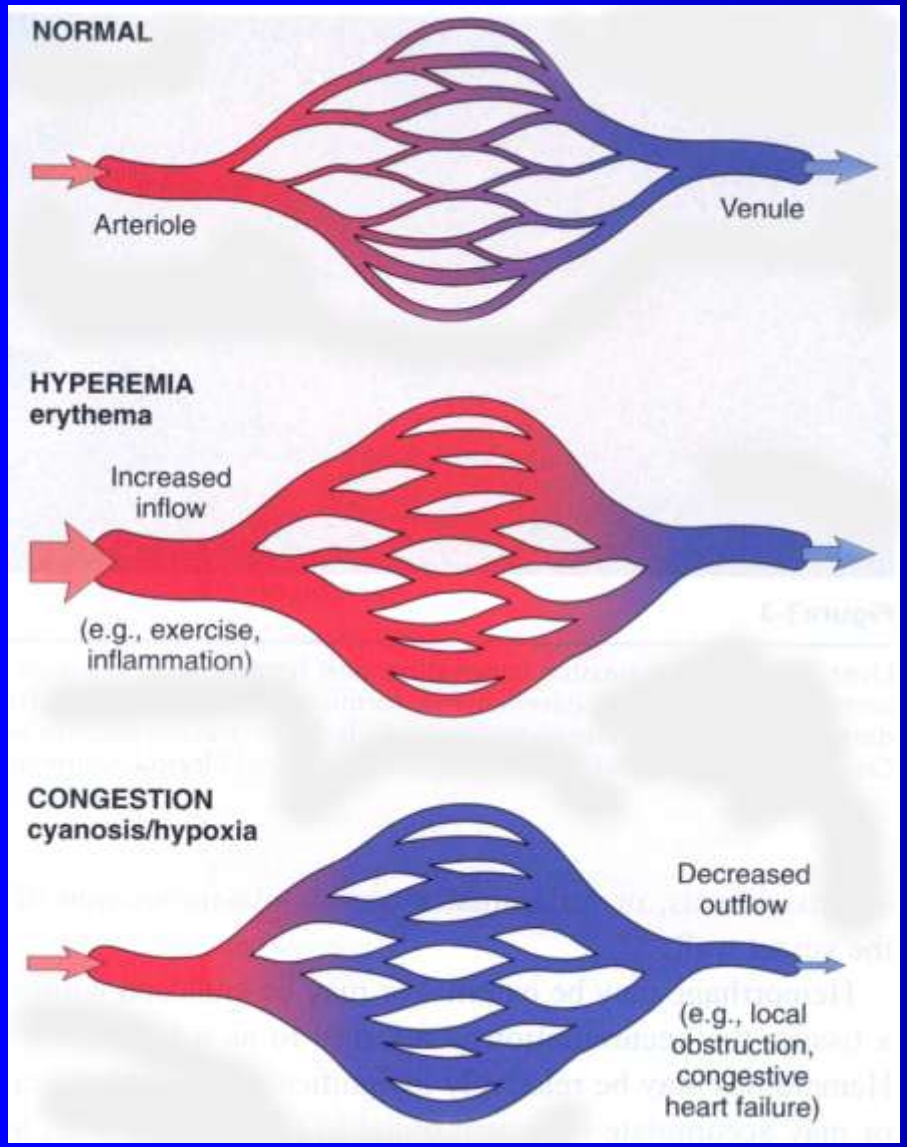
Arterial hyperemia (hyperemia)

An augmented blood flow inducing arteriolar and capillary dilation

Venous hyperemia (congestion)

Accumulation of Blood in Small Veins and capillaries result from drainage difficulty of veins

HYPEREMIA & CONGESTION



Hyperemia:

Active process;

Red, raised tempreture, increased volume ;

Enhanced function;

Congestion:

passive process;

general of local;

Reddish blue color (cyanosis), low temperature, increased volume, edema;

Decreased function

HYPEREMIA

- **Types**

  Physiological: Shy, exercise, taking Meal

  Pathological: Inflammatory, post-decompressed

- **Significance**
  - Benefits

    Plenty supply of O2, functional enhancement, nutrition substance
  - Hazards

    Headache , hemorrhage, stroke

CONGESTION

Causes:

Systemic: general or pulmonary

Cardiac dysfunction (right or left)

Local: local venous compression or obstruction

External Compression --- Tumor, Bandage

Occlusion of lumen --- Thrombosis, Embolism

Thickening of venous wall

Paralysis of neurogenic modulation --- Burn, frostbite

CONGESTION

Lung:

Acute pulmonary congestion

Gross: Plump swollen lung with shining pleura, edematous fluid flowing out while cutting the lung

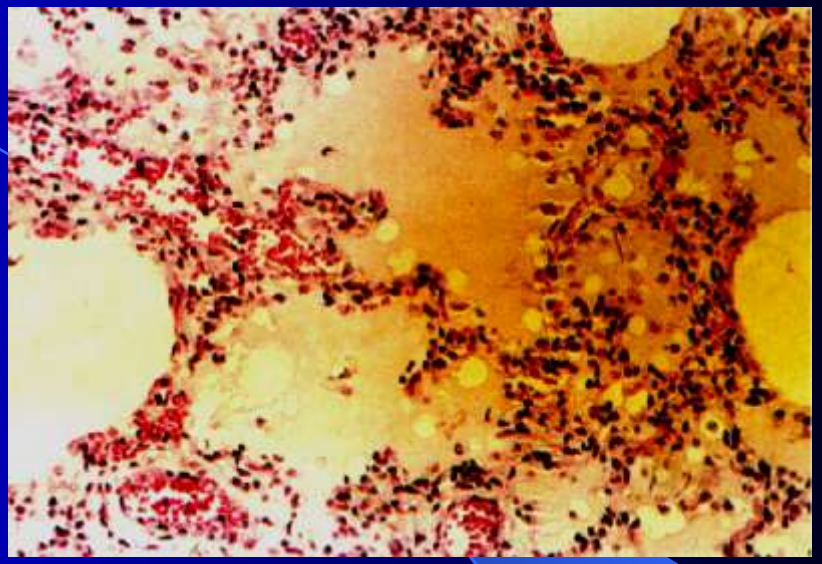
LM:

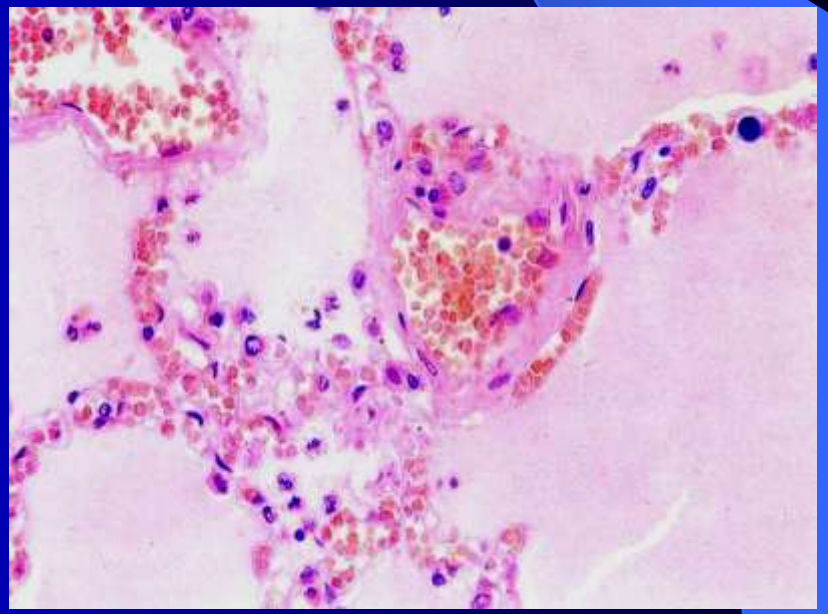
Alveolar capillaries highly dilated (rosary-like appearance) and engorged with blood

Alveolar cavity filled with eosinophilic edema fluid

Manifestation

Pink colored foamy sputum





CONGESTION

Lung:

Chronic pulmonary congestion

Gross: Hard, with brown spots scattered

—— Brown induration

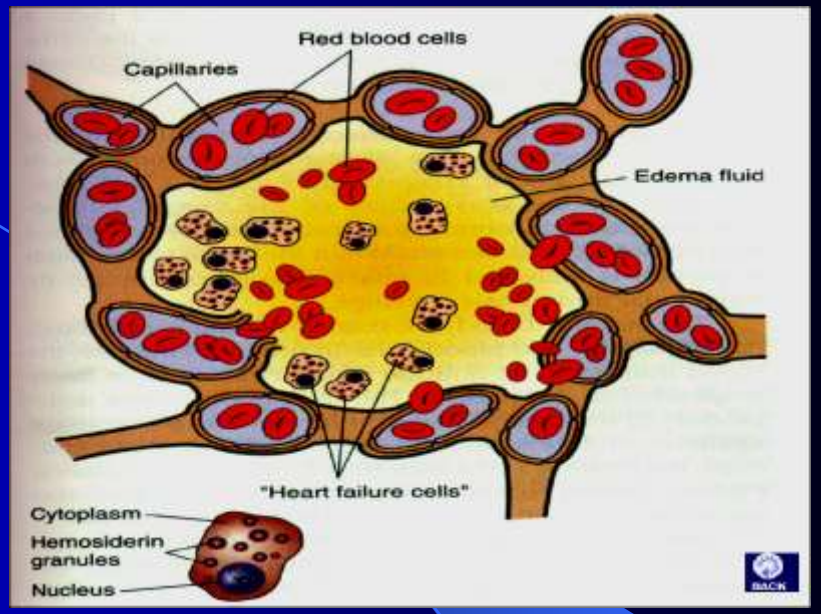
LM:

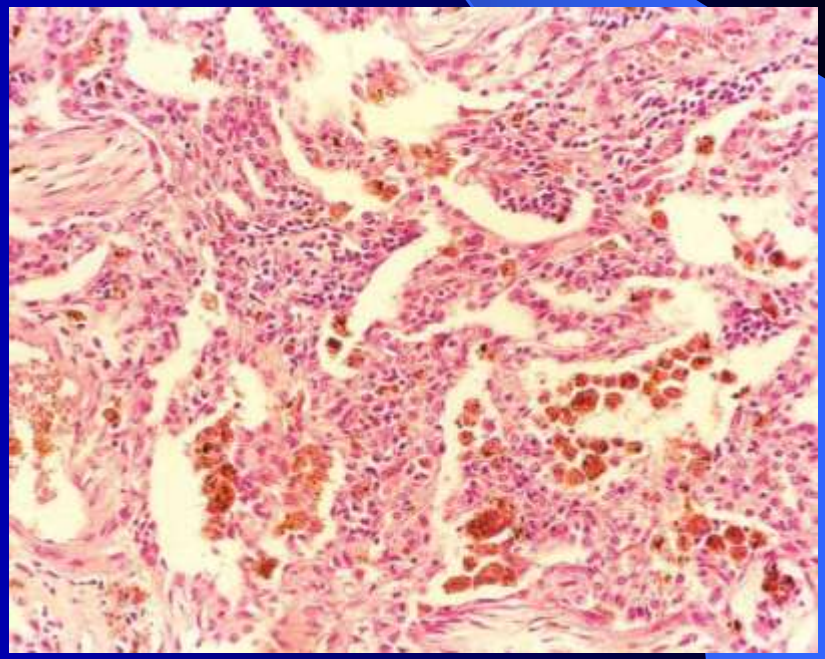
Septa thickened and fibrosis

Alveolar spaces containing 'heart failure cells'— hemosiderin-laden macrophages

Manifestation

Rusty sputum, dyspnea, etc.





CONGESTION

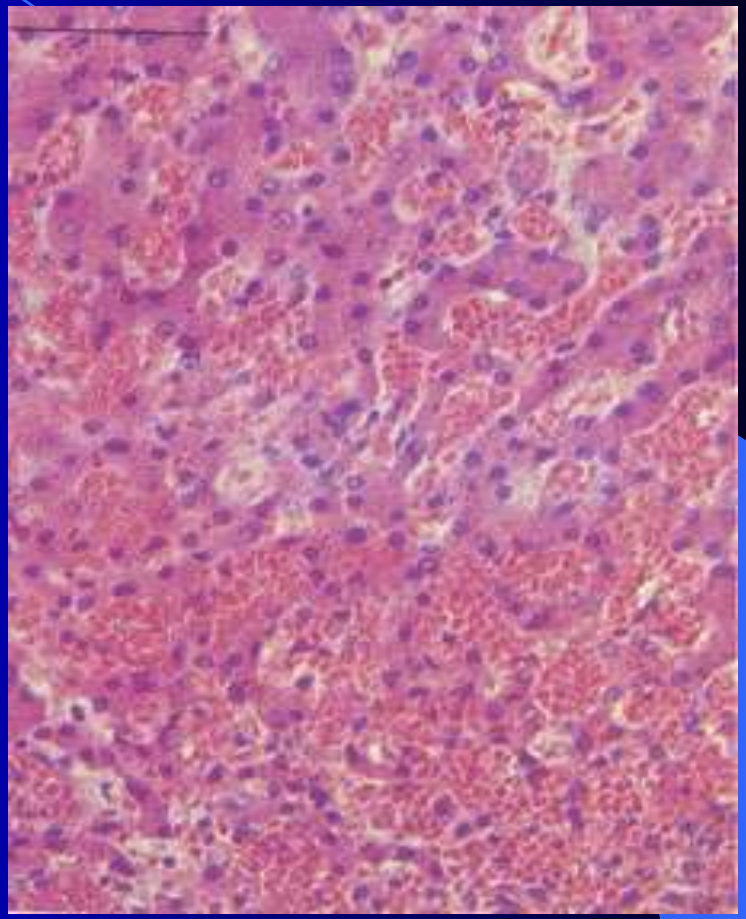
Liver:

Acute hepatic congestion

LM:

— Dilation of central vein and sinusoids with blood

— Atrophy, degeneration and necrosis of central hepatocytes



CONGESTION

Liver:

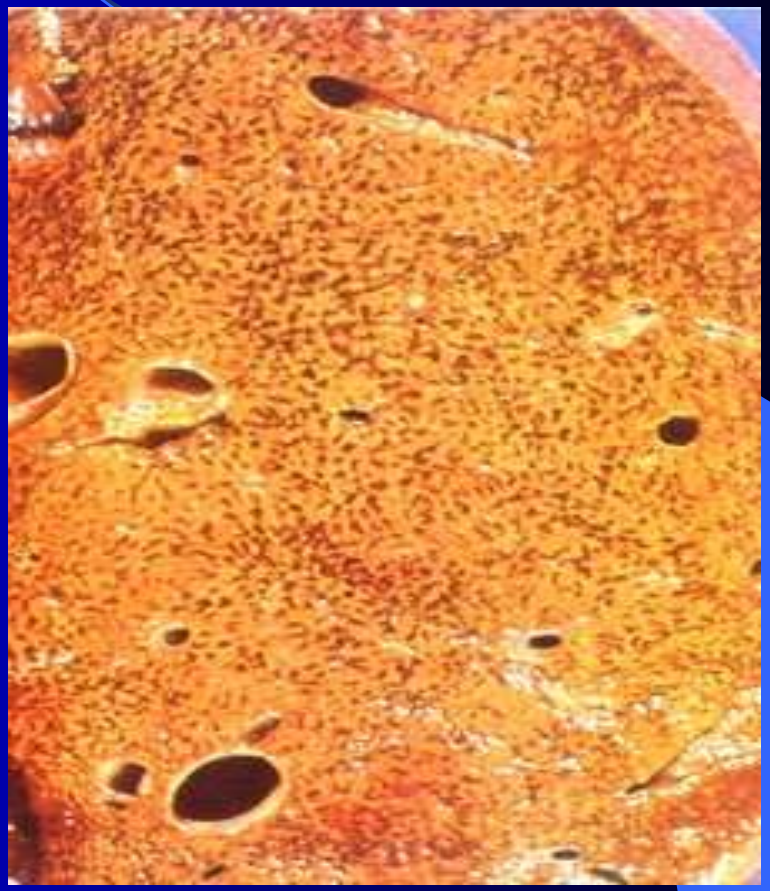
Chronic hepatic congestion

Nutmeg liver

Gross: red-brown zones accentuated against the yellow surrounding zones

LM: centrilobular necrosis and congestion, and perilobular fatty change; fibrosis

Long-standing, severe hepatic congestion: hepatic fibrosis (cardiac cirrhosis)



Hyperemia and Congestion

= ↑ blood volume in particular tissue

- a. hyperemia – active (arteriolar dilation)
  - red color
  - striated muscle exercise

- b. congestion – passive (impaired venous return)
  - systemic x local
  - blue-red color (cyanosis), edema
  - event. hypoxemic necrosis, e.g. bowel
  - accumulation of deoxygenated Hb
  - chronic → chronic hypoxia → regressive changes + small hemorrhages → siderophages=Heart failure cells are **siderophages** (hemosiderin-containing macrophages) generated in the alveoli of patients with left heart failure or chronic pulmonary edema, when the high pulmonary blood pressure causes red cells to pass through the vascular wall

2. Hyperemia and Congestion

- pulmonary congestion
- acute
  - by blood fulfilled septal capillaries
  - septal + alveolar edema + small hemorrhages
- chronic
  - septa thickening → fibrosis (induration)
  - alveoli - siderophages (heart failure cells)

2. Hyperemia and Congestion

- liver congestion
- acute
  - by blood fulfilled central veins + sinusoids
- chronic – “nutmeg liver“ – red-brown + fatty color
  - centrilobular necrosis + hemorrhage
  - periportal fatty change
  - in time - cardiac fibrosis

- bowel congestion
  - hemorrhagic necrosis

Hemorrhage

Causes

- Rupture of blood vessels
  Trauma
  Peptic ulcer, aneurism, atherosclerosis
- Diapedesis
  Enlarged interendothelial gap (basement membrane injury).
  The intergrity of the vessels remains intact
  Injury to vascular wall: sever infection, anoxia, toxins
  Change in number and quality of platelets
  uremia, leukemia, idiopathic
  Disturbance of coagulation mechanism
  congenital disease, DIC , deficiency of Vit. K

HEMORRHAGE

- *Petechiae*
- *Purpuras*
- *Ecchymoses*
- *Hematoma*
- *Hemothorax*
- *Hemopericardium*
- *Hemoperitoneum*
- *hemoarthrosis*

The clinical significance depends on the volume, the rate of loss and the site.

- Hemorrhagic shock
- Stroke

3. Hemorrhage

= extravasation of blood from blood vessels

- external (+ in hollow organs)
- internal: within tissue – hematoma

- hemorrhagic diatheses – insignificant injury
  - vasculopathies
  - thrombocytopenia
  - coagulopathy

3. Hemorrhage

- 1. Petechiae (1-2 mm) - skin + mucosa
  - ↑ intravascular pressure, ↓ platelets
- 2. Purpuras (3-5 mm)
  - trauma, vasculitis, vascular fragility
- 3. Ecchymosis (1-2 cm) = hematoma (bruise)
  - RBC phagocytosis by macrophages
  - Hb (red-blue) → bilirubin (blue-green) → hemosiderin (golden-brown)
- 4. Cavities
  - hemothorax, hemopericardium, hemoperitoneum
  - hemarthros

3. Hemorrhage - sequelae

- 1. loss volume
  - > 20% → hemorrhagic shock
- 2. loss rate
  - acute → hemorrhagic shock
  - chronic (peptic ulcer, metrorhagia, colonic adenoCa)
    - iron deficiency anemia
- 3. site
  - subcutaneous x brain

Disseminated Intravascular Coagulation (DIC)

- basis: widespread activation of thrombin
- fibrin thrombi in microcirculation
- 1. stage
  - multiple fibrin thrombi in microcirculation → consumption of PLT + coagulation proteins
- 2. stage
  - fibrinolytic system activation → serious bleeding (Consumption of coagulation substance and activation of fibrinolytic system)

HEMOSTASIS & THROMBOSIS

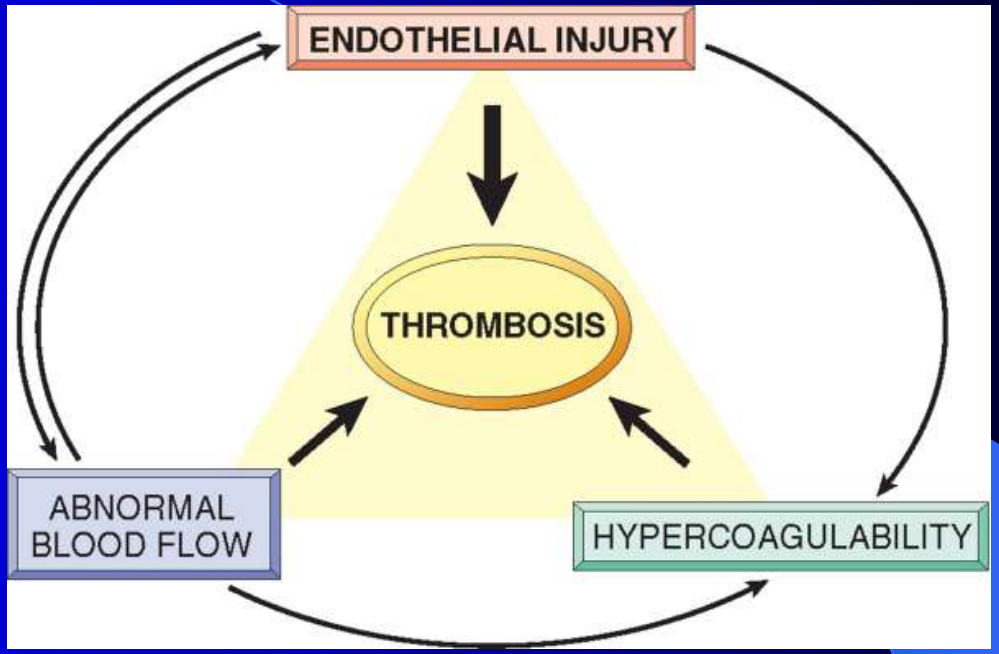
Normal hemostasis

- Maintain blood in a fluid, clot-free state
- Localized hemostatic plug

<>**Thrombosis**

Blood clot (thrombus) formation in cardiovascular system of a living body

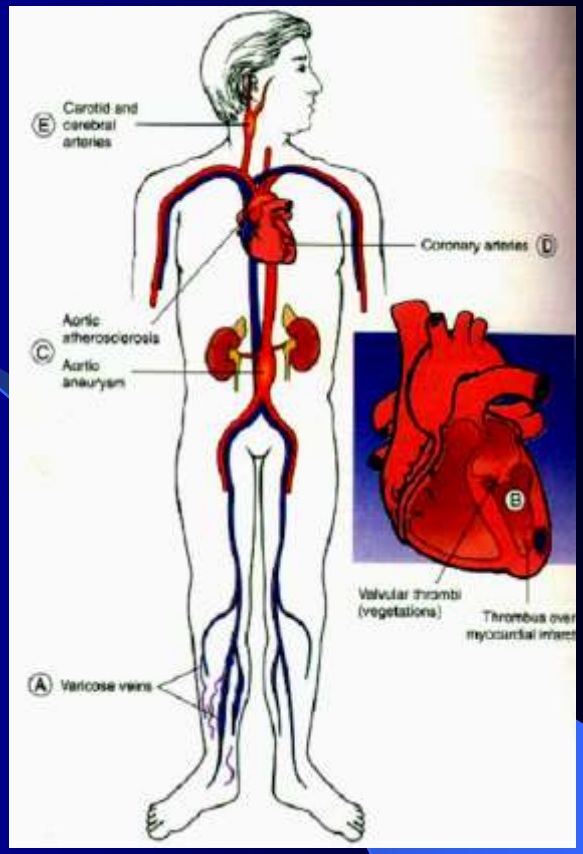
THROMBOSIS



Pathogenesis

- Endothelial injury
- Turbulence of blood flow
- Hypercoagulability

THROMBOSIS



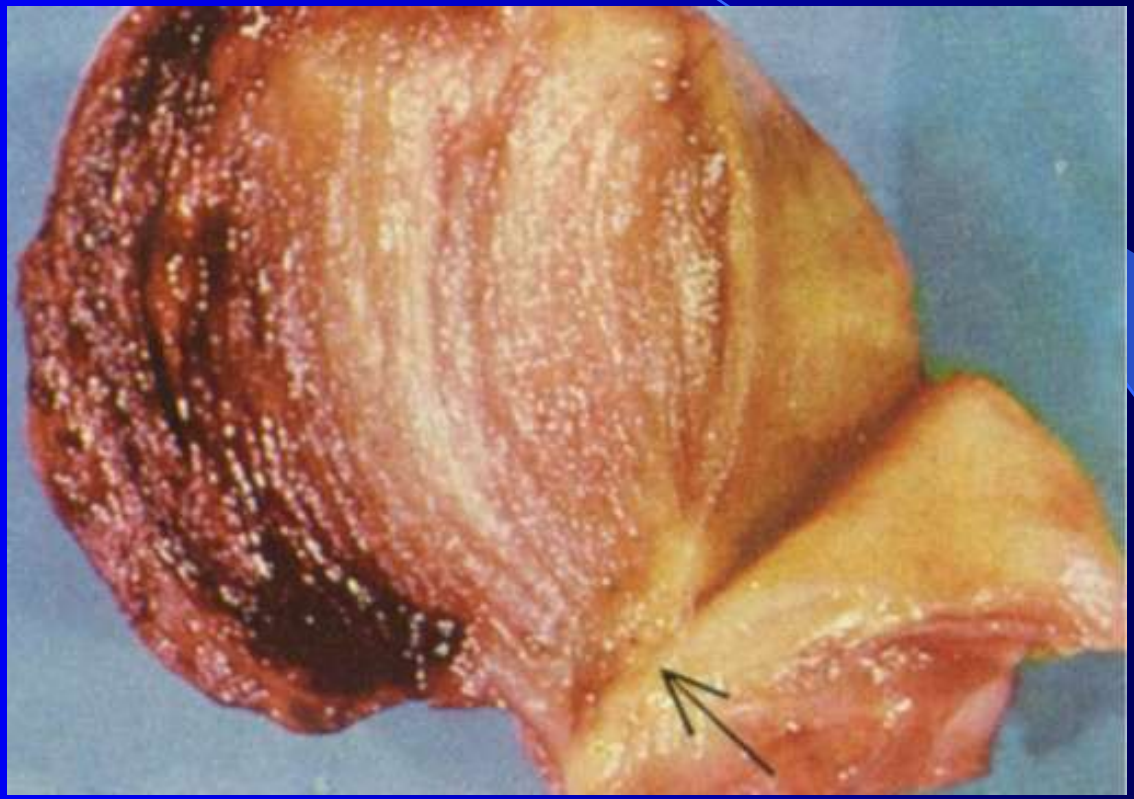
Morphology

- Arterial thrombi
  - Originate from injury sites
- Venous thrombi (phlebothrombi)
  - Originate from the sites of stasis

both extends to the heart

Lines of Zahn { pale platelet and fibrin layers; dark erythrocyte-rich layers

THROMBOSIS



Lines of Zahn

THROMBOSIS

Types

Pale thrombus

Mixed thrombus

Red thrombus

Hyaline thrombus

Mural thrombus

Occlusive thrombus

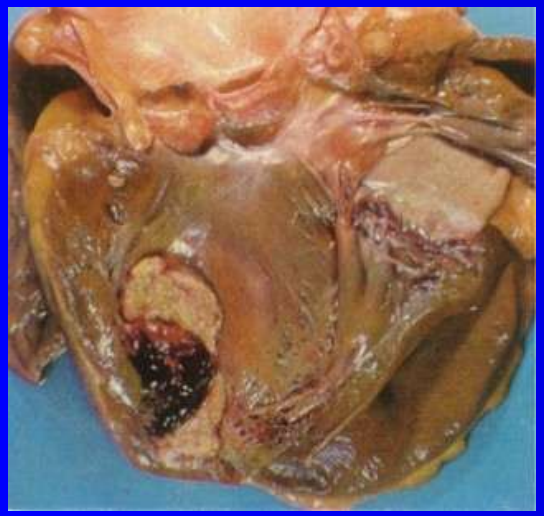
Globular thrombus

Vegetation

Bacterial thrombus

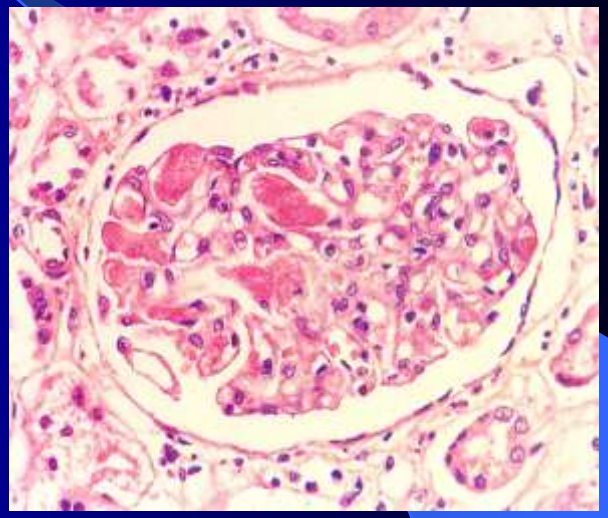
Tumor thrombus

THROMBOSIS



Mural thrombus

Vegetation



Hyaline thrombus

THROMBOSIS

Differentiation between thrombus from ***postmortem clot***

	Thrombus	Postmortum clots
1	Dry	wet and gelatinous “chicken fat” supernatant
2	Rough surface	Smooth surface
3	Hard	Soft
4	Friable	Gelatinous
5	Lines of Zahn	Homogenous
6	Firmly attached	No attachment
7	Slit due to contraction, fragmentation, generate embolus	No slit

5. Embolism

= detached i.v. solid, liguid or gaseous mass carried by blood to distant site from point of origin

- 1. thrombembolism (99%)
  - pulmonary x systemic → infarction
- 2. cellular - amniotic fluid, tumor cells
- 3. subcellular - AS debries, BM bits
- 4. fat
- 5. air
- 6. foreign bodies – catheter

---

paradoxical

retrograde

Fat embolism

- source: fractures of bones with fatty BM + soft tissue trauma + burns
- 1. stage (after 1-3 days)
  - veins → lungs → respiratory insufficiency
- 2. stage
  - lungs → systemic circulation → neurologic symtoms + thrombocytopenia
- 10% fatal
- Mi: fat droplets in lung, brain, kidney capillaries

Air embolism

- 1. systemic veins → lungs
  - obstetric procedures, goiter operation, chest wall injury
- 2. pulmonary veins → systemic circulation
  - cardiosurgery
- 100mL of air → symptoms (dyspnea)
- air bubbles – physical vessel obstruction

- Decompression sickness
  - deep sea divers (nitrogen)
  - chronic form – caisson disease – bone necrosis

Amniotic fluid embolism

- source: abruptio placentae → retroplacental hematoma
- a.f. infusion into maternal circulation → uterine veins → lungs
- dyspnea, cyanosis, hypotensive shock, seizures, coma + lung edema + DIC
- Mi: pulmonary capillaries (mother) - squamous cells + lanugo hair + fat
- + DAD

7. Ischemia / Infarction

= ischemic necrosis due to occlusion of arterial supply (or venous drainage?)

- causes:
  - thrombotic or embolic events (99%)
  - vasospasm, hemorrhage in AS plaque
  - external compression (tumor)
  - twisting (testicular + ovarian torsion, bowel volvulus)

7. Infarction - determinants

- 1. nature of blood supply
  - dual – lung + liver
  - end-arterial – kidney + spleen
- 2. rate of occlusion
  - acute – infarction
  - chronic – collateral circulation, interart. anastomoses
- 3. vulnerability to hypoxia
  - neurons – 3-4 min
  - cardiomyocytes - 20-30 min
  - fibroblasts - hours
- 4. oxygen blood content – heart failure, anemia

7. Infarction - morphology

- 1. red infarcts
  - venous occlusion
  - loose tissue (lung) – blood collection
  - dual circulation – lung + bowel
  - previously congested organs
  - reperfusion (angioplasty, drug-induced thrombolysis)
- 2. white infarcts
  - arterial occlusion
  - solid organs – heart (yellow), spleen, kidney

7. Infarction - morphology

- wedge shape
  - apex to occluded artery
  - base to organ periphery

    + fibrinous exudate (pleuritis, pericarditis epistenocardiaca)
- onset – poorly defined, hemorrhagic
- later – sharper margins + hyperemic rim

7. Infarction - morphology

- ischemic coagulative necrosis – 3 zones
- 1. total necrosis - centre
  - loss of nuclei, eosinophilia of cytoplasm, architecture is preserved
- 2. partial necrosis
  - some cells survive
  - inflammation (neutrophils) – 1-2 day → degradation of dead tissue
- 3. hyperemic rim

7. Infarction - morphology

- healing
  - granulation tissue (5-7 day) → fibrous scar (6-8 weeks)
  - !!! brain – liquefactive necrosis → pseudocyst !

7. Infarction

- septic infarctions
- source
  - infective endocarditis (vegetations)
  - suppurative thrombophlebitis
- infarction → abscess → granulation tissue → scar

Shock

= systemic hypoperfusion due to reduction of cardiac output / effective blood volume circulation

- hypotension → cellular hypoxia
- features – hypotension, tachycardia, tachypnea, cool cyanotic skin (x septic s. – warm)
- initial threat + shock manifestations in organs
- prognosis
  - origin + duration

Shock

- 1. cardiogenic – failure of myocardial pump
  - myocardial infarction, arrhythmias
  - pulmonary embolism
- 2. hypovolemic - inadequate blood/plasma volume
  - hemorrhage
  - fluid loss (vomiting, diarrhoea, burns, trauma)
- 3. septic – vasodilation + endothelial injury
  - Gram+, Gram- bacteria
- 4. neurogenic - loss of vascular tone
  - spinal cord injury
- 5. anaphylactic – IgE–mediated hypersensitivity

Shock - stages

- progressive disorder → multiorgan failure → death
- 1. non-progressive
  - compensatory mechanism (neurohumoral) activation
  - centralization of blood circulation
- 2. progressive
  - tissue hypoperfussion – metabolic dysbalancies
- 3. irreversible
  - incurred cellular damage + tissue injury
  - death

Shock - morphology

- brain - ischemic encephalopathy
  - tiny ischemic infarctions (border zones)
- heart
  - subendocardial hemorrhage + necroses, contr. bands
- kidney - acute tubular necrosis (shock kidney)
  - pale, edematous
  - tubular epithelium necroses → granular casts
- lung – diffuse alveolar damage (shock lung), ARDS
  - heavy, wet
  - congestion + edema + hyaline membranes

Shock - morphology

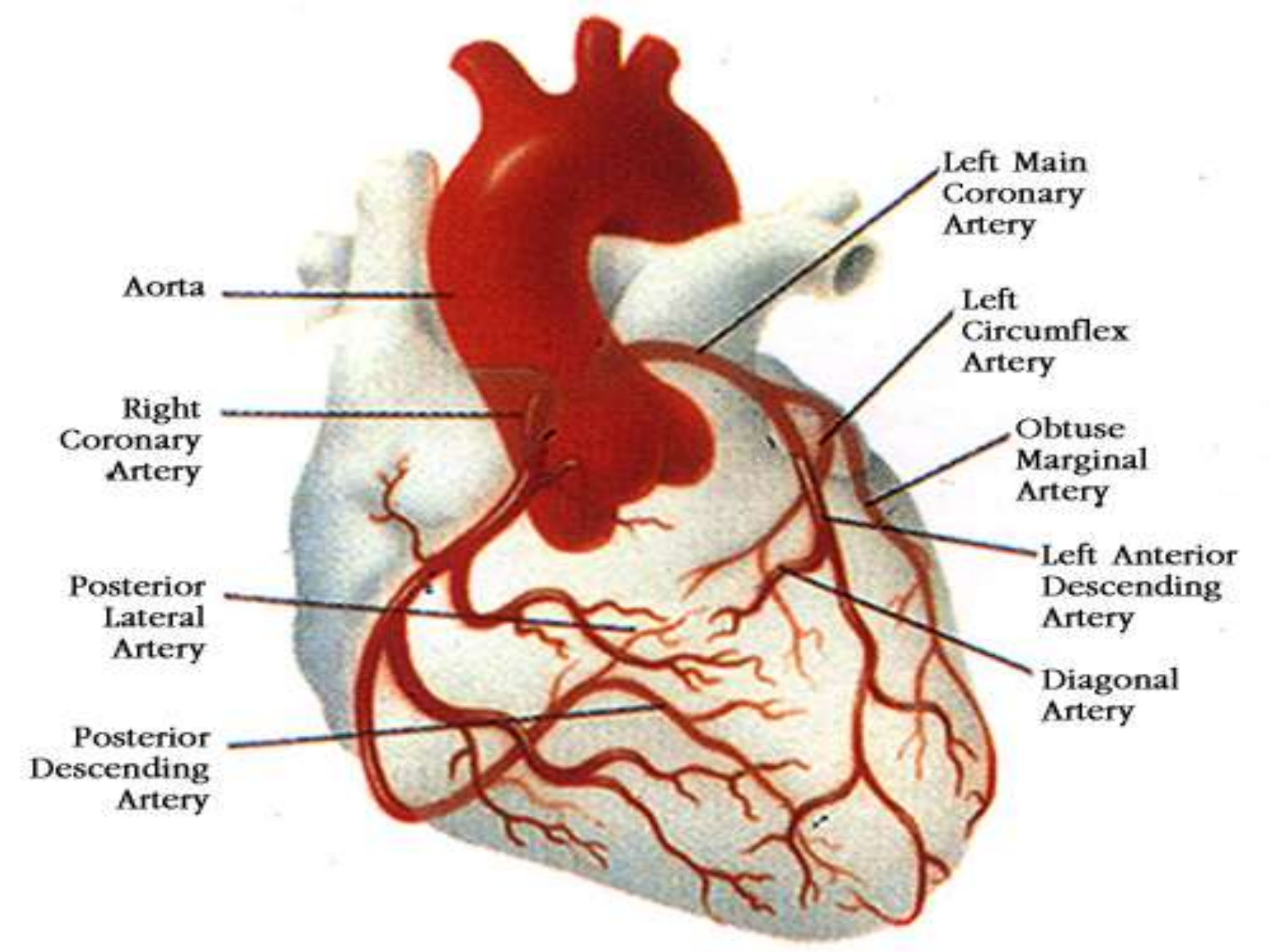
- adrenal gland
  - lipid depletion
- GIT – hemorrhagic enteropathy
  - mucosal hemorrhages + necroses
- liver
  - fatty change, central necrosis

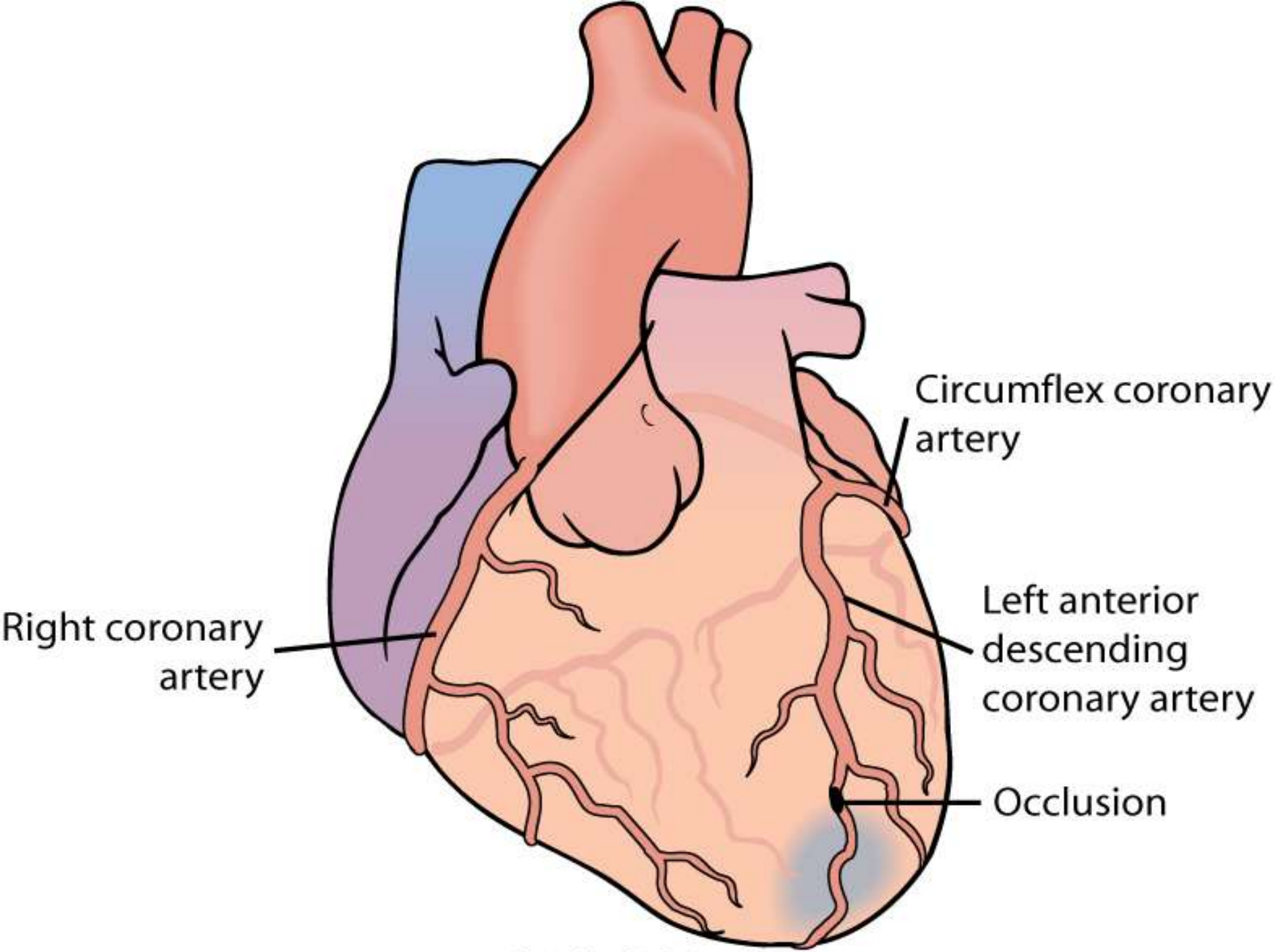
Coronary Artery Disease

& Myocardial infarction

Coronary Arteries

- Coronary Arteries surround and then penetrate the heart muscle
  - Right coronary artery (RCA) (back of heart)
  - Left (Main) coronary artery
    - Left circumflex (Side)
    - Left anterior descending (Front)


Aorta
Right Coronary Artery
Posterior Lateral Artery
Posterior Descending Artery
Left Main Coronary Artery
Left Circumflex Artery
Obtuse Marginal Artery
Left Anterior Descending Artery
Diagonal Artery



(Courtesy Mayo Clinic, Rochester, Minn.)

Atherosclerosis is the leading cause of death and disability in the developed and developing world

Clinical manifestations depend on the particular vascular bed affected

Coronary vasculature	angina, MI, sudden death
Cerebral	TIA, stroke
Peripheral	claudication, gangrene
Renal	hypertension

While transient ischemic attack (TIA) is often labeled “mini-stroke,” it is more accurately characterized as a “warning stroke,”. TIA is caused by a clot; the only difference between a stroke and TIA is that with TIA the blockage is transient (temporary)

What Is Atherosclerosis?

Atherosclerosis is a disease in which plaque builds up inside your arteries.

Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries. This limits the flow of oxygen-rich blood to your organs and other parts of your body.

Atherosclerosis can lead to serious problems, including heart attack, stroke, or even death.

Atherosclerosis

- literally means “hardening of the arteries”; it is a generic term reflecting arterial wall thickening and loss of elasticity.

- There are three general patterns:

  - *Arteriolosclerosis* affects small arteries and arterioles, and may cause downstream ischemic injury.

  - *Mönckeberg medial sclerosis* is characterized by calcific deposits in muscular arteries in persons typically older than age 50.

  - *Atherosclerosis*, from Greek root words for “gruel” and “hardening,” is the most frequent and clinically important pattern.

- **Atherosclerosis is produced by the following pathogenic events:**

- *Endothelial injury*, which causes (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis.

- *Accumulation of lipoproteins* (mainly LDL and its oxidized forms) in the vessel wall.

- *Monocyte adhesion to the endothelium*, followed by migration into the intima and transformation into *macrophages* and *foam cells.*

- *Platelet adhesion.*

- *Factor release* from activated platelets, macrophages, and vascular wall cells, inducing *smooth muscle cell recruitment*, either from the media or from circulating precursors.

- *Smooth muscle cell proliferation and ECM production.*

- *Lipid accumulation* both extracellularly and within cells (macrophages and smooth muscle cells).

Coronary Artery Disease

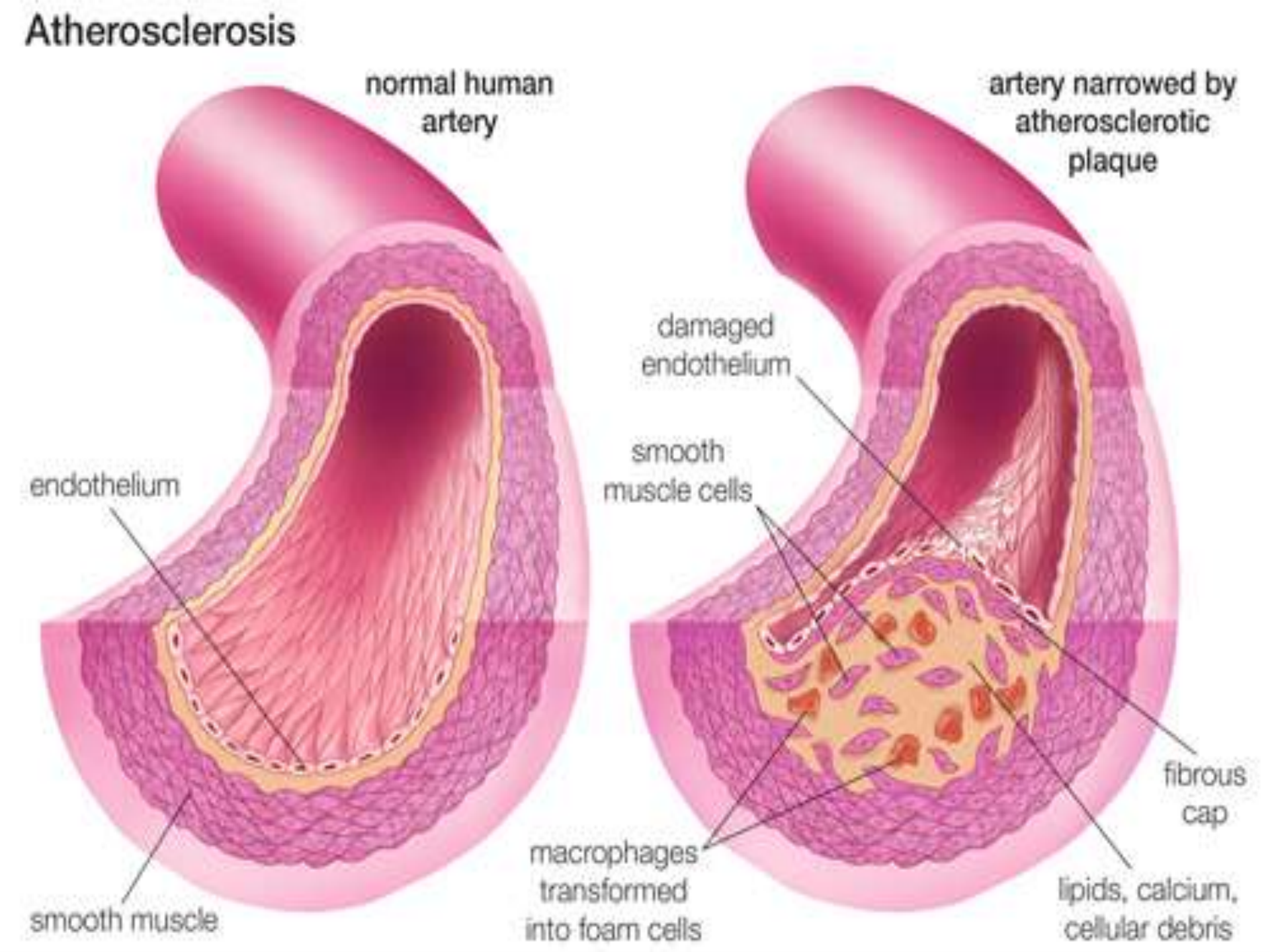
- Most CAD nothing more than ***Atherosclerosis in the coronary arteries***
- Chronic leads to angina pectoris
- Acute is MI

Ischemic Heart Disease

Classification = mainly 4 types

1- Myocardial infarction (MI)
2- Sudden cardiac death
3- Angina pectoris
4- Chronic IHD with heart failure

Atherosclerosis



Risk Factors

- Major nonmodifiable
  - Age/gender
  - Family history
- Major modifiable
  - Dyslipidemia
  - Hypertension
  - Smoking
  - DM, insulin resistance
  - Obesity
  - Sedentary
  - Atherogenic diet

Emerging risk factors:

-Metabolic syndrome

-Triglyceride

-Lp(a)

Lipoprotein(a) is a lipoprotein subclass. Genetic studies have identified Lp(a) as a risk factor for atherosclerotic diseases such as coronary heart disease and stroke.

-Lp-PLA2

Lipoprotein-associated phospholipase (Lp-PL)A2 is a recently described and potentially useful plasma biomarker associated with cardiovascular disease. The enzyme, originally named platelet-activating factor acetylhydrolase (PAF-AH),

-Fibrinogen

-Homocysteine

is a non-protein α-amino acid. It is a homologue of the amino acid cysteine, A high level of homocysteine in the blood (hyperhomocysteinemia) makes a person more prone to endothelial cell injury, which leads to inflammation in the blood vessels, which

-Urine microalbuminuria/creatinine ratio

Dyslipidemia

Better term than hyperlipidemia as it includes the risk of having low HDL

Serum total cholesterol (TC) is a composite of:

- LDL cholesterol- directly related to CVD
- HDL cholesterol- inversely related to CVD
- VLDL cholesterol- related to CVD in patients with DM and low HDL

Best single predictor for CVD risk is TC/HDL ratio.

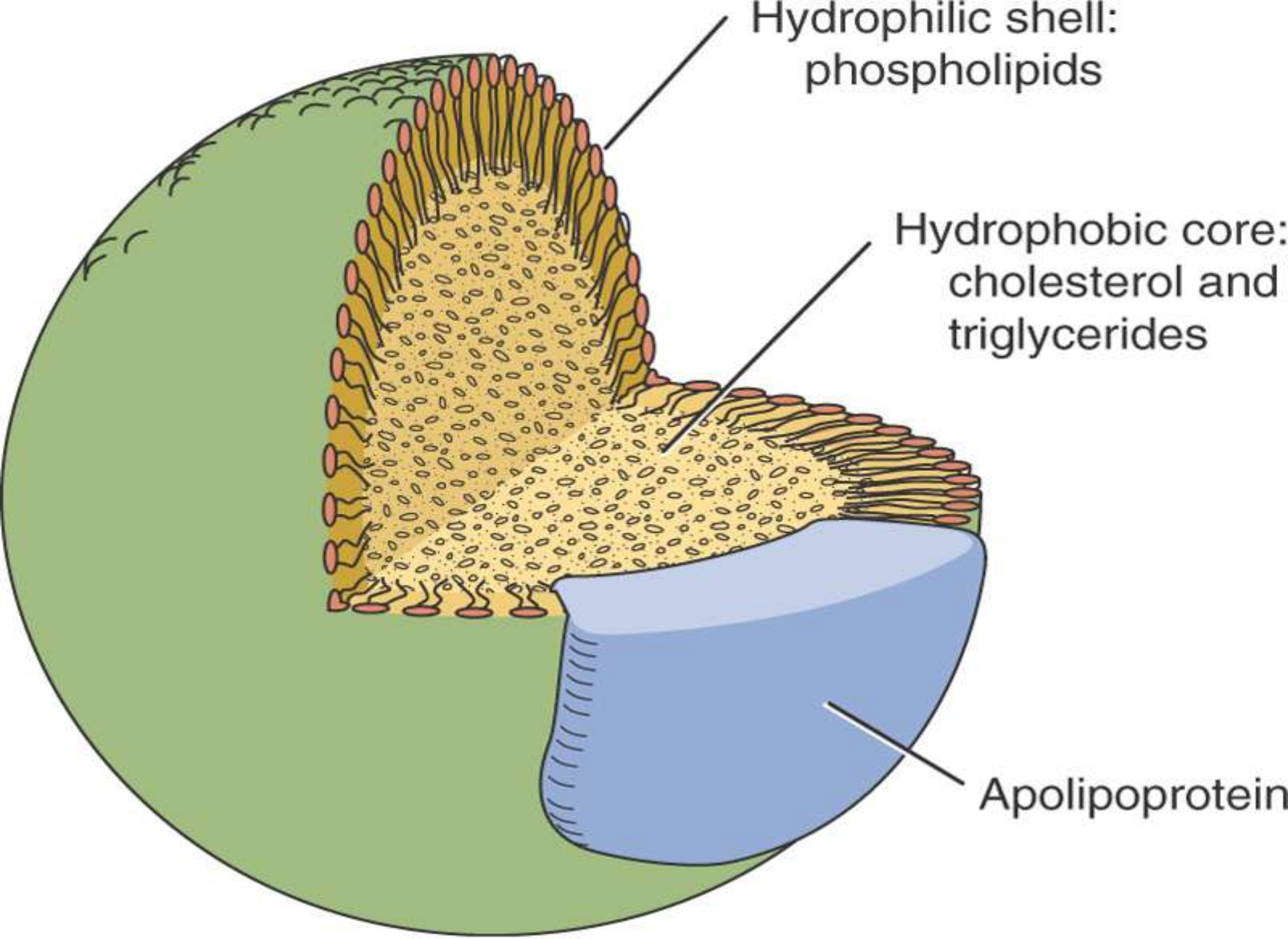
- Ideal ratio is <3, intermediate 3-5, high risk >5
- This ratio is also the best predictor of treatment benefits

Dyslipidemia

- Half of all heart attacks occur in persons with elevated cholesterol
- Lipoprotein
  - Lipids, Phospholipids, Cholesterol, Tryglycerides
- Needed for
  - plasma membrane maintenance
  - Sterol hormones
  - Bile acids
  - Skin (water resistance)

Cholesterols

- Sources of cholesterol
  - Dietary absorption (exogenous)
  - Synthesis of new cholesterol (endogenous)
  - Increased dietary consumption inhibits synthesis
  - Fat substrates
- Triglycerides
  - Storage form of lipids long term storage
  - Adipose tissue



Plasma Lipoproteins

- Function: carrier molecules
- Structure
  - Hydrophobic Core
  - Hydrophillic shell
    - Phospholipids
    - Apolipoproteins
      - Recognition sites for receptors
      - Activate enzymes
      - Increase structural stability
      - A-I, A-II, B-100

Cholesterol Cycle

- Chylomicrons
  - Lipid packages absorbed from intestine
  - Transported to liver
- Liver manufactures
  - VLDL: triglycerides + protein
  - LDL: cholesterol + protein
  - HDL: phospholipids + protein
  - Lipoprotein(a) [Lp(a)]

VLDL

- one B-100 apolipoprotein
- triglyceride core
- deliver triglycerides to muscle and adipose
- Clinical significance
  - Accounts for nearly all triglycerides in blood
  - Normal triglyceride level is <150 mg/dl
  - >150 associated with Metabolic syndrome
  - >400 - 500 associated with pancreatitis

LDL

- One B-100 apolipoprotein
- Cholesterol core
- Deliver cholesterol to nonhepatic tissues
  - Cells that need cholesterol endocytose the LDL molecule
  - If more cholesterol is needed more LDL receptors are produced
- Clinical significance
  - Direct correlation with heart disease
  - 25% reduction of elevated LDL corelated with up to 50% reduction in MI risk

HDL

- Contain apolipoprotein A-I, or A-I and A-II
- Cholesterol core
- Transport cholesterol back to liver
- Clinical Significance
  - Promote cholesterol removal
  - Low cholesterol is associated with increased risk of atherosclerosis
  - Apparently only A-I HDL is cardioprotective
  - Subtype analysis

Role of Cholesterol in Atherosclerosis

- LDL is benign until oxidized in subendothelial (intimal) space
- Oxidized LDL
  - Attract monocytes and promote differentiation to macrophages
  - Inhibit macrophage mobility: chronic inflammation
  - Promote uptake by macrophages
  - Are cytotoxic: damage endothelial cells and contribute to inflammation

Hypertension

Potent risk factor for all CVD and dominant risk factor for stroke.

Graded relationship between level of BP and outcomes.

SBP rises with age, whereas DBP plateaus in the late middle life and decreases somewhat then.

Metabolic syndrome is a group of five risk factors that can increase your chance of developing heart disease, diabetes, and stroke. The five risk factors include:

1- increased blood pressure (greater than 130/85)
2- high blood sugar levels (insulin resistance)
3- excess fat around the waist
4- high triglyceride levels (Triglycerides >150 mg/dl)
5- low levels of good cholesterol, or HDL

Men <40 mg/dl

Women <50 mg/dl

Pathogenesis

Atherosclerosis is a progressive disease

Advanced lesions are a result of three processes:

1. Lipid accumulation
2. Accumulation of intimal SMC, macrophages, T-lymphocytes
3. Formation of connective tissue matrix by proliferated SMC

Atherosclerotic disease can lead to

A- stenosis and occlusion as in most muscular arteries

B- or cause ectasia or aneurysm formation as in elastic vessels (aorta)

Initiation of atherosclerosis

- Lipoprotien accumulation and modification
  - fatty streak formation
  - lipid oxidation
  - nonenzymatic glycation
- Leukocyte recruitment (T lymphocytes, macro)
  - foam cell formation

LDL

↓

Binds to receptor on endothelial cell surface

↓

Internalized

↓

Oxidized to oxidized-LDL

↙ ↘

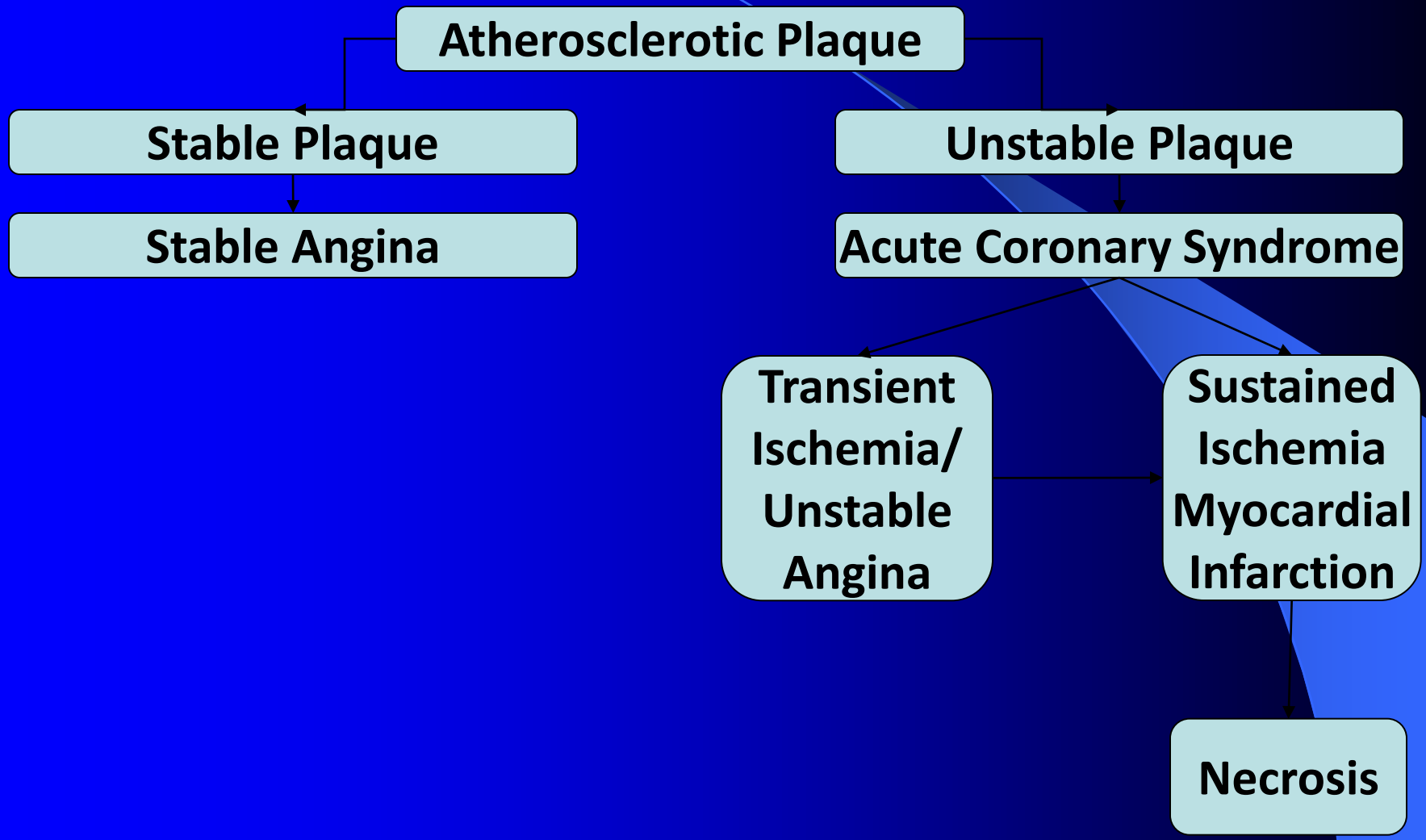
Ingested by Macrophages

↓

Foam Cell

Increased adherence and migration of T-cells, monocytes from the lumen into the wall

Acute Coronary Syndrome



Acute myocardial infarction (AMI)

One of the most common diagnosis in hospitalized patients in industrialized nations

Mortality of acute MI is 30% and one-half of these deaths occur before hospitalization

Mortality after admission has decreased by 30% in last 2 decades

1 in 25 pts (4%) who survive till hospital discharge die within one year

Myocardial Ischemia

- Blood flow must be impeded before heart metabolism is affected
  - Absolute
  - Relative
- Causes
  - Atherosclerosis, Vasospasm
  - Hypotension, Arrythmias, Anemia, V/Q

Myocardial Ischemia

- Myocardium becomes ischemic within 10 seconds of coronary occlusion
- ***Working*** cells remain viable for up to 20 minutes
  - Anaerobic mechanisms kick in
    - Lactic acid
    - Free radical damage, esp after reperfusion

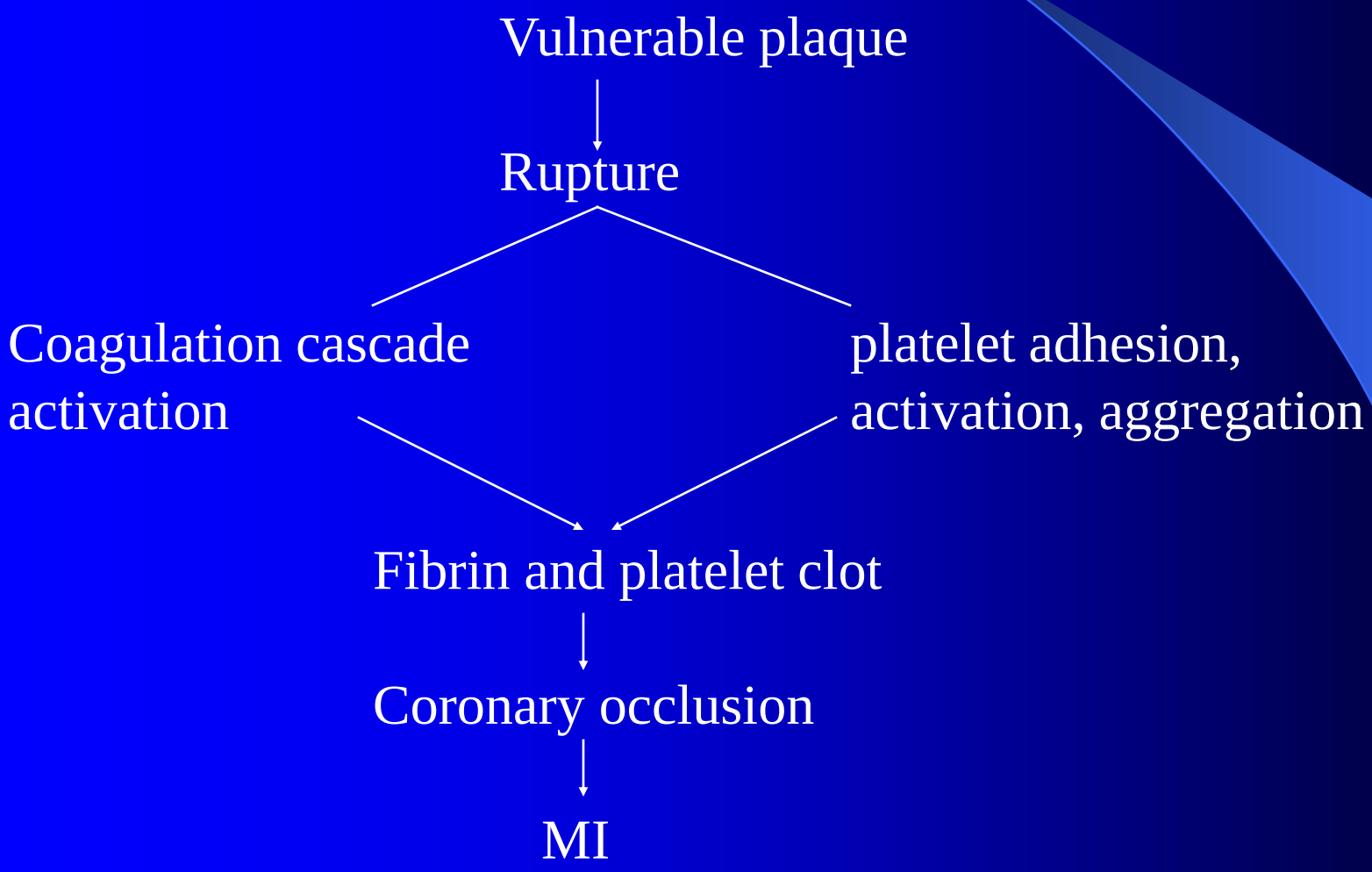
Cardiac Ischemia Manifestation

- **Stable angina**
  - **Chronic obstruction**
  - **Chest pain with exertion**
  - **May radiate, may have diaphoresis**
  - **Relief with rest or nitrates**

- **Prinzmetal angina (also known as variant angina, vasospastic angina (VSA), angina inversa, or coronary vessel spasm) is a syndrome typically consisting of angina (cardiac chest pain) at rest that occurs in cycles**
- **Silent ischemia**
- **Unstable angina**
  - **May become a myocardial infarction**

AMI Pathophysiology

AMI results when thrombus (occlusive/nonocclusive) develops at the site of ruptured plaque

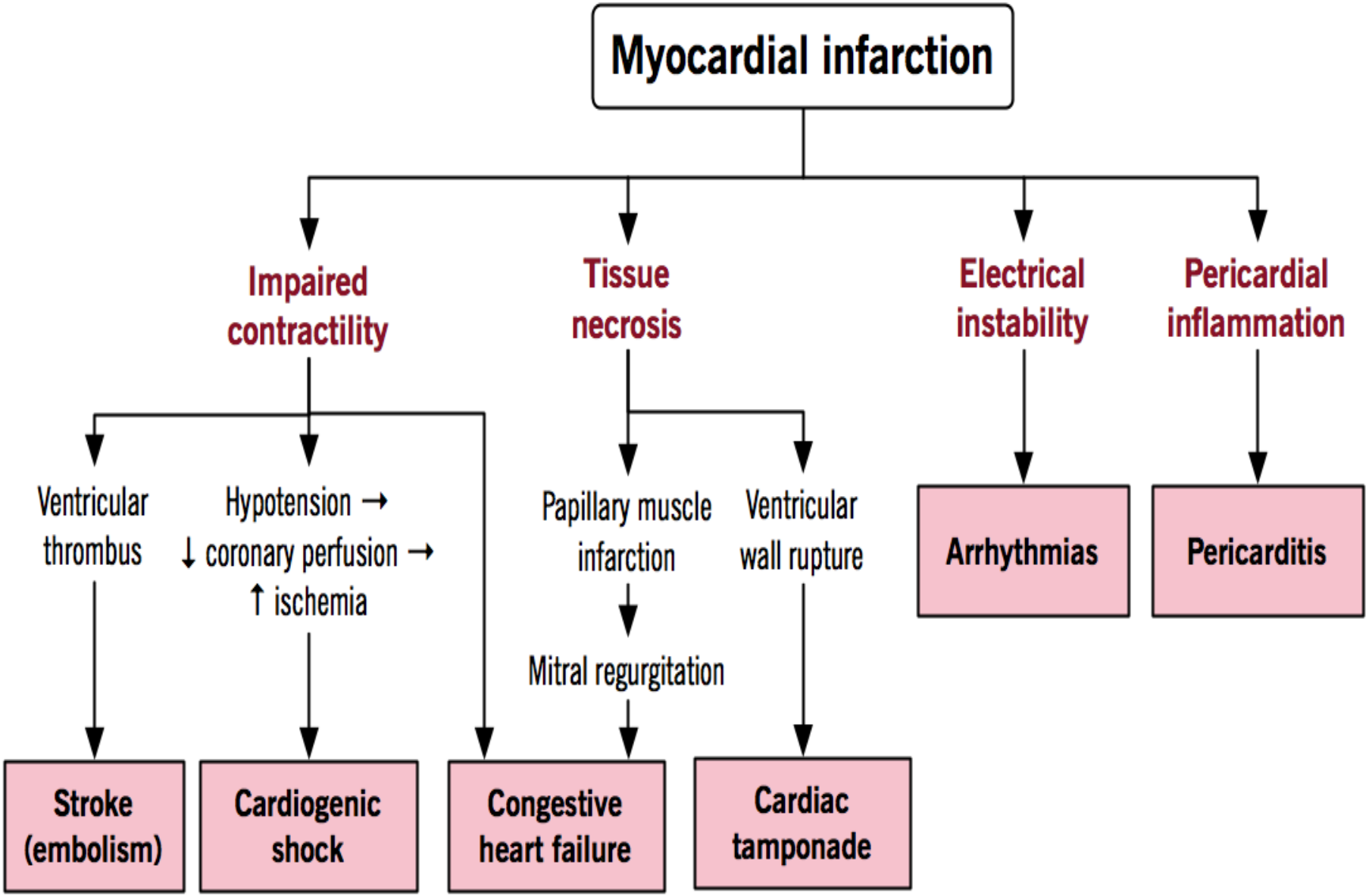


AMI Pathophysiology

- Plaque rupture --> Clotting cascade active
- Thrombus occludes vessel
- Myocardium becomes hypoxic
  - Shift to Anaerobic Respiration
  - Waste products release/hypoxic injury
  - Cardiac output impaired
    - Norepinephrine/Epinephrine Release
    - Renin release

Complications of myocardial infarction

Dominique Yelle



Serum cardiac markers:

Released into the circulation from necrotic heart muscle

CK (creatine kinase) rises 4-8 hrs after onset of MI
and normalize by 48-72 hrs
not specific for myocardial necrosis
MB isoenzyme of CK is more specific

Cardiac specific troponins: more sensitive and specific than CK and CKMB for identification of myocardial necrosis

Myoglobin- first serum marker to rise after MI, but lacks specificity.

Aspirin: 160-325 mg chewable aspirin leads to rapid buccal absorption, inhibition of cyclooxygenase in platelets and reduction of TXA2

Pathophysiology of Rheumatic heart disease

Etiopathogenesis

The cause and subsequent development of an abnormal condition or of a disease

- **Acute rheumatic fever** is a hypersensitivity reaction induced by group A streptococci.
- Antibodies against M proteins of certain strains of streptococci cross react with antigens in heart, joints and other tissues.
- Genetic susceptibility is suggested
- Autoimmune response to self antigens also suggested.

- **Chronic sequelae** are a result of progressive fibrosis (healing process) and blood turbulance in valvular areas

Morphology

ACUTE RH. FEVER--→ *Pancarditis*

- Pericarditis-→ serofibrinous/ Bread and butter type
- Myocarditis → **Aschoff bodies [Anitschkow cells (caterpillar cells]) are often cells associated with rheumatic heart disease. Anitschkow cells are enlarged macrophages found within granulomas (called Aschoff bodies) associated with the disease]**
- Endocarditis →
  - Verrucous vegetations (1-2mm) at lines of closure of valves
  - Fibrinoid necrosis along cusps and tendinous cords
  - MacCallum plaques in left atrium

MacCallum plaques

Mural endocardial lesions can be seen as **MacCallum plaques** in rheumatic heart disease. These **plaques** appear as map-like areas of thickened, roughened, and wrinkled part of the endocardium in the **left atrium**. Perhaps they are caused by regurgitant jets of blood flow, due to incompetence of the mitral valve.

Morphology of chronic Rheumatic heart disease

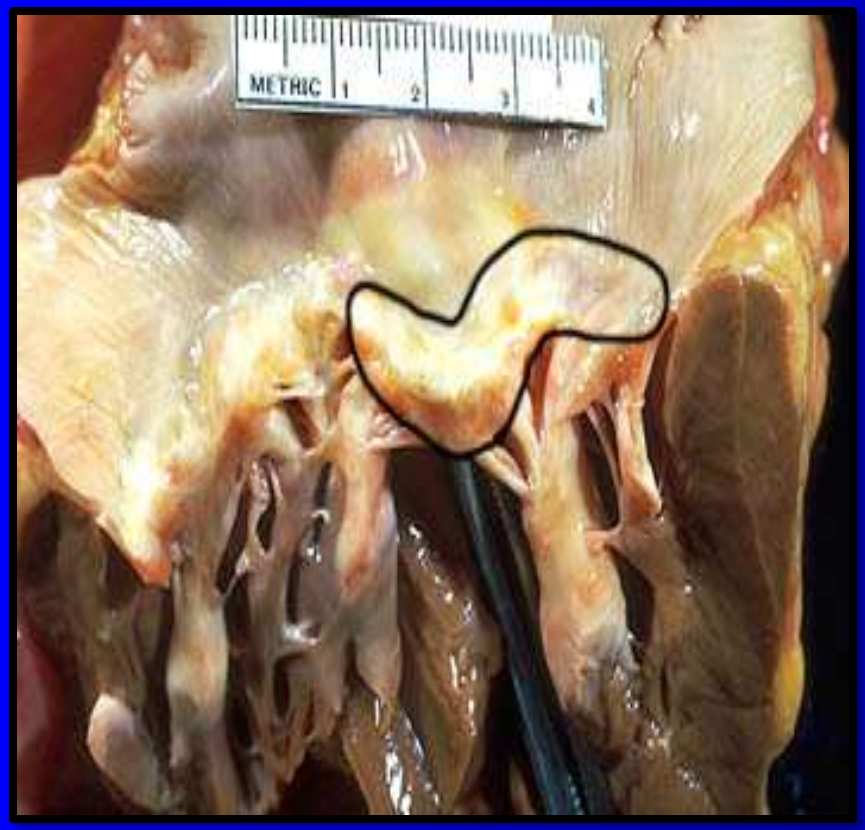
- Mitral valve is most often affected with rheumatic heart disease, followed by mitral and aortic together, then aortic alone, then mitral, aortic, and tricuspid together.
- Mitral stenosis (99% cases)
- Fishmouth/ buttonhole stenosis

Microscopy

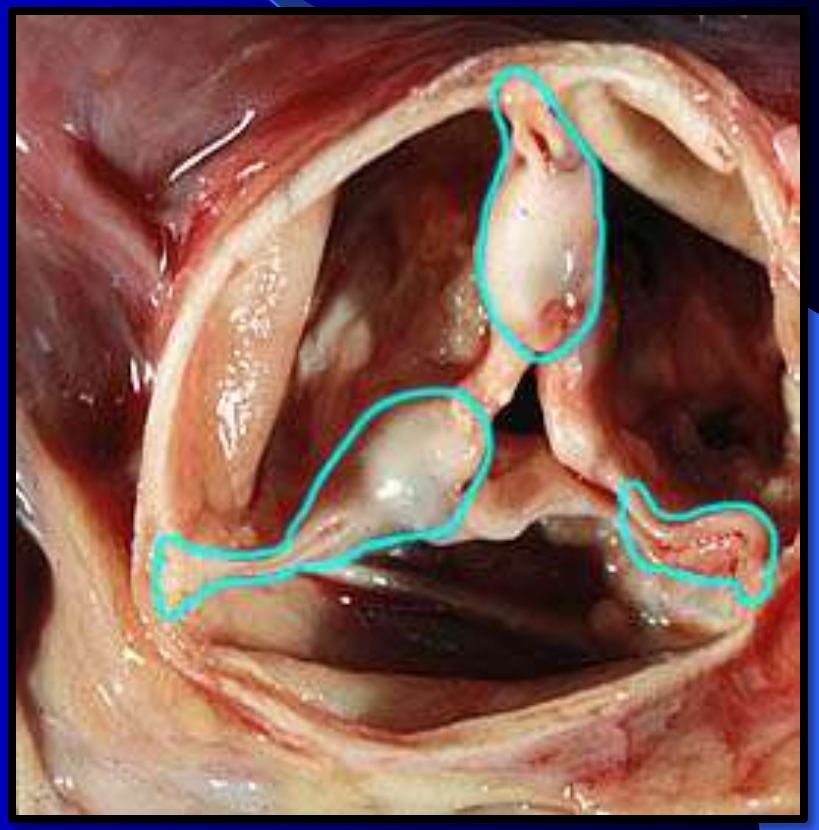
- Fibrosis/ scarring
- Neovascularization

Chronic Rheumatic heart disease

rheumatic mitral valve,



rheumatic aortic stenosis
With fused commisures



ACUTE RHEUMATIC FEVER

- **Autoimmune consequence of infection with Group A streptococcal infection**
- **Results in a generalised inflammatory response affecting brains, joints, skin, subcutaneous tissues and the heart.**
- **The clinical presentation can be vague and difficult to diagnose.**
- **Currently, the modified Duckett-Jones criteria form the basis of the diagnosis of the condition.**

RHEUMATIC HEART DISEASE

- Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune marker and other serologic tests, tissue pathology, and imaging.

RHEUMATIC HEART DISEASE

- Rheumatic Heart Disease is the permanent heart valve damage resulting from one or more attacks of ARF.
- It is thought that 40-60% of patients with ARF will go on to developing RHD.
- The commonest valves affecting are the mitral and aortic, in that order. However all four valves can be affected

CAUSES

- **Rheumatic fever is thought to result from an inflammatory autoimmune response.**
- **Rheumatic fever only develops in children and adolescents following group A beta-hemolytic streptococcal pharyngitis, and only streptococcal infections of the pharynx initiate or reactivate rheumatic fever.**
- **Genetic studies show strong correlation between progression to rheumatic heart disease and human leukocyte antigen (HLA)-DR class II alleles and the inflammatory protein-encoding genes *MBL2* and *TNF-α*.**

- **Both clones of heart tissue–infiltrating T cells and antibodies have been found to be cross-reactive with beta-hemolytic streptococcus.**
- **Interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-10-(+) cells are consistently predominant in valvular tissue, whereas IL-4 regulatory cytokine expression is consistently low.**

PATHOPHYSIOLOGY

The proposed pathophysiology for development of rheumatic heart disease is as follows:

Cross-reactive antibodies bind to cardiac tissue facilitating infiltration of streptococcal-primed CD4+ T cells, which then trigger an autoimmune reaction releasing inflammatory cytokines (including TNF-alpha and IFN-gamma).

Because few IL-4–producing cells are present in valvular tissue, inflammation persists, leading to valvular lesions

PATHOPHYSIOLOGY

- In 0.3-3% of cases, infection leads to rheumatic fever several weeks after the sore throat has resolved.
- The organism spreads by direct contact with oral or respiratory secretions, and spread is enhanced by crowded living conditions.
- Patients remain infected for weeks after symptomatic resolution of pharyngitis and may serve as a reservoir for infecting others.

- Group A *Streptococcus* is a gram-positive coccus that frequently colonizes the skin and oropharynx. This organism may cause suppurative disease, such as pharyngitis, impetigo, cellulitis, myositis, pneumonia, and puerperal sepsis.
- It also may be associated with nonsuppurative disease, such as rheumatic fever and acute poststreptococcal glomerulonephritis.
- Group A streptococci elaborate the cytolytic toxins streptolysins S and O.
- Of these, streptolysin O induces persistently high antibody titers that provide a useful marker of group A streptococcal infection and its nonsuppurative complications

- Rheumatic fever develops in some children and adolescents following pharyngitis with group A beta-hemolytic Streptococcus
- The organisms attach to the epithelial cells of the upper respiratory tract and produce a battery of enzymes allowing them to damage and invade human tissues.
- After an incubation period of 2-4 days, the invading organisms elicit an acute inflammatory response with 3-5 days of sore throat, fever, malaise, headache, and an elevated leukocyte count

- Group A *Streptococcus*, as identified using the Lancefield classification, has a group A carbohydrate antigen in the cell wall that is composed of a branched polymer of *L*-rhamnose and *N*- acetyl-D-glucosamine in a 2:1 ratio.
- Group A streptococci may be subserotyped by surface proteins on the cell wall of the organism.
- The presence of the M protein is the most important virulence factor for group A streptococcal infection in humans

- Acute rheumatic heart disease often produces a pancarditis characterized by endocarditis, myocarditis, and pericarditis.
- Endocarditis is manifested as valve insufficiency.
- The mitral valve is most commonly and severely affected (65-70% of patients), and the aortic valve is second in frequency (25%).
- The tricuspid valve is deformed in only 10% of patients and is almost always associated with mitral and aortic lesions.
- The pulmonary valve is rarely affected.
- Pericarditis, when present, rarely affects cardiac function or results in constrictive pericarditis

- Chronic manifestations due to residual and progressive valve deformity occur in 9-39% of adults with previous rheumatic heart disease.
- Fusion of the valve apparatus resulting in stenosis or a combination of stenosis and insufficiency develops 2-10 years after an episode of acute rheumatic fever, and recurrent episodes may cause progressive damage to the valves.
- Fusion occurs at the level of the valve commissures, cusps, chordal attachments, or any combination of these.

HYPERTENSION
Definition

- A systolic blood pressure **(SBP) >139 mmHg** and/or
- A diastolic **(DBP) >89 mmHg.**
- Based on the average of **two or more** properly measured, seated BP readings.
- On each of **two or more** office visits.

Classification

Table 1. Classification and management of blood pressure for adults*

BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial drug therapy	
				Without Compelling Indication	With Compelling Indications (See Table 8)
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

Alterations of blood pressure

Hypertension is defined as:

a consistent elevation of arterial pressure above the normal range expected for a particular age group.

- **Approximately 90% of all hypertension cases are classified as *primary hypertension. This* form of hypertension is also called *essential* or *idiopathic* hypertension since its etiology is uncertain.**
- **Approximately 5 to 10% of patients are afflicted with *secondary hypertension* in which the cause of the elevated blood pressure is clearly defined.**

Primary or essential hypertension

The cause of primary hypertension is still unknown, however,

Several theories involving:

- **chronic increases in fluid volume**
- **enhanced sympathetic activity**
- **abnormal salt and water excretion by the kidneys.**

A number of key physiologic changes have also been observed in the kidneys of patients with essential hypertension that may contribute to the development of the disorder.

Primary or essential hypertension

For a patient to be diagnosed as hypertensive, he or she must have had blood pressure of:

140 mmHg or above for systolic pressure &

90 mmHg or above for diastolic pressure

at **two successive measurements**.

Systolic blood pressure *= the pressure in the arteries when the ventricles are contracting.*

Diastolic blood pressure *= the pressure in the arteries when the ventricles are relaxed.*

Methods for Measuring Blood Pressure

- Sphygmomanometer (blood pressure cuff) : indirect measure
- Intra-arterial catheter : direct measure

Primary or essential hypertension

Complications

Heart

Chronic elevation of arterial pressure means the heart must now pump blood out against a continually elevated afterload. As compensation for this increased afterload, **left ventricular hypertrophy** occurs. The hypertrophied ventricle will require increased blood, oxygen and nutrient supplies and will be at greater risk for arrhythmia.

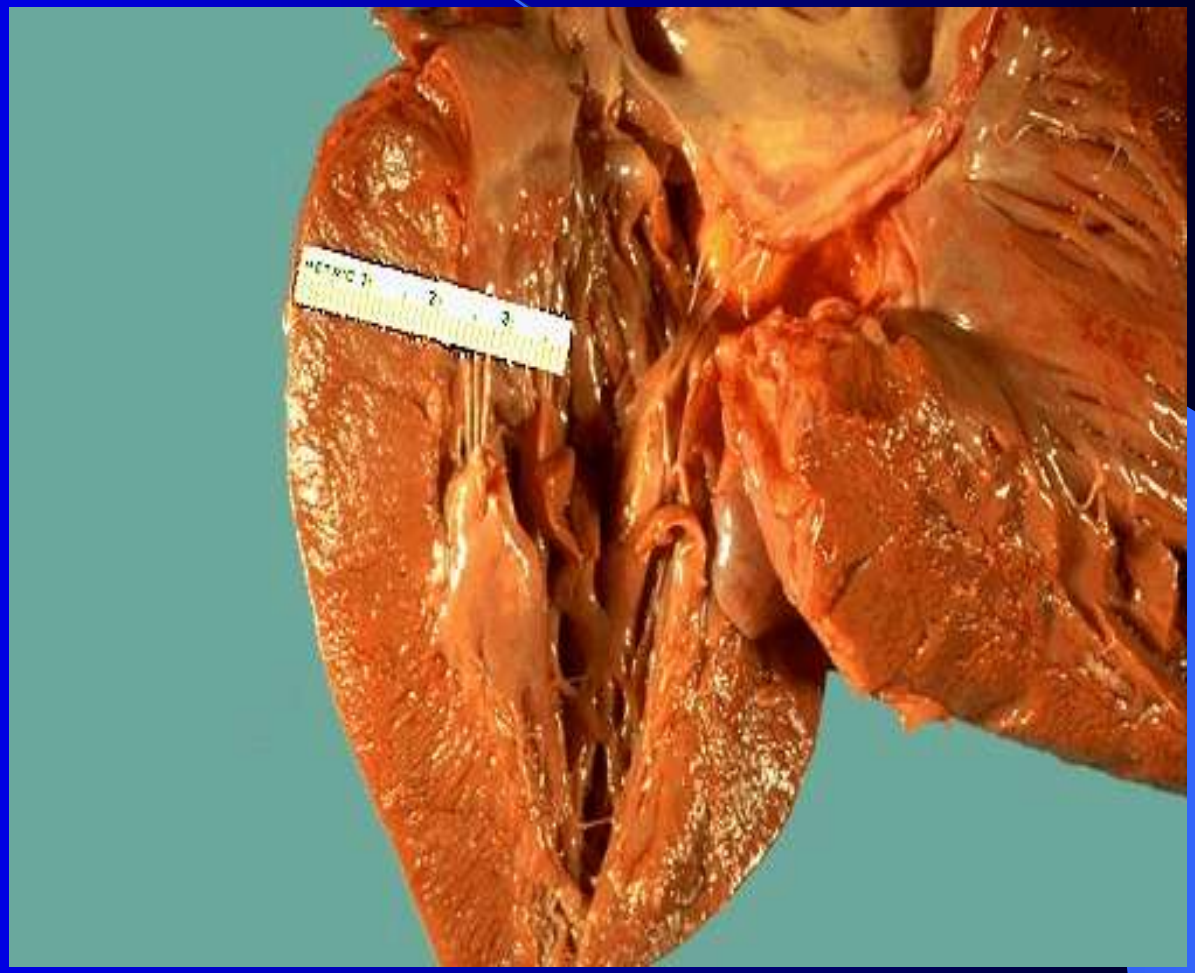
When the ventricular enlargement reaches a certain point, contractile function will no longer be supported and pump failure (congestive heart failure, CHF) will ensue.

Primary or essential hypertension

Complications

Heart

This left ventricle is very thickened (slightly over 2 cm in thickness), but the rest of the heart is not greatly enlarged. This is typical for hypertensive heart disease. The hypertension creates a greater pressure load on the heart to induce the hypertrophy.



Primary or essential hypertension

Complications

Kidneys

Chronically elevated pressure can damage the renal vasculature and compromise renal blood flow, oxygen delivery and filtration. As a result, ***renal insufficiency*** can occur that may eventually progress to ***renal failure***.

Decreased renal blood flow can lead to activation of the renin angiotensin system and contribute to a vicious cycle of increasing blood pressure and decreasing renal function. Hypertension induced renal injury is exacerbated in patients with diabetes.

Secondary Hypertension

- **It represents only a small fraction of all cases of hypertension.**
- **One of the most common causes of secondary hypertension is *renal artery stenosis* which is a narrowing of the renal arteries due to atherosclerosis**

Other causes of secondary hypertension can include:

- ***Hyperaldosteronism* (excess aldosterone production) and**
- ***Pheochromocytoma* (tumor of the adrenal medulla).**

Secondary Hypertension

- **As a result of the reduced renal blood flow that accompanies the narrowed blood vessels, the kidney responds by activating the renin–angiotensin system that in turn leads to vasoconstriction and salt and water retention.**
- **One of the most common causes of secondary hypertension is *renal artery stenosis*, which is a narrowing of the renal arteries due to atherosclerosis.**

Malignant Hypertension

☹***Dramatic increases in blood pressure (greater than 120 to 130 mmHg diastolic pressure) that can occur suddenly.***

☹Occur in a **small % of patients** with chronic essential hypertension.

☹These sudden increases in blood pressure are especially dangerous because dramatic increases in pressure may **damage the retina or kidneys** and lead to **cerebral edema and stroke**.

☹Malignant hypertension requires immediate medical treatment with **powerful intravenous vasodilators** such as *Diazoxide* or *sodium nitroprusside*.

Hypotension

Hypotension is an ***abnormally low blood pressure***.

☞ One common form of hypotension is:

Orthostatic hypotension (also called ***postural hypotension***) that occurs upon standing.

☞ The act of standing initiates a series of reflex responses in the body that are designed to prevent pooling of blood in the lower extremities and a decrease in blood pressure. These reflexes include vasoconstriction in the lower limbs and a reflex increase in heart rate.

Hypotension

Causes of Orthostatic Hypotension

☹ **Aging** : Associated with reduced baroreceptors responses, decreased cardiac output and reduced vascular responsiveness

☹ **Decreased blood or fluid volume** :Caused by dehydration, diarrhea, diuretic use

☹ **Autonomic nervous defects: An** inability to initiate vasoconstriction and increased heart rate reflexes

☹ **Prolonged bed rest** : Associated with reduced plasma volume, decreased vascular tone

☹ **Drug-induced** : Examples: antihypertensive drugs, calcium channel blockers, vasodilators

Complications of Prolonged Uncontrolled HTN

- Changes in the vessel wall leading to vessel trauma and arteriosclerosis throughout the vasculature
- Complications arise due to the “target organ” dysfunction and ultimately failure.
- Damage to the blood vessels can be seen on fundoscopy.

Target Organs

- **CVS (Heart and Blood Vessels)**
- **The kidneys**
- **Nervous system**
- **The Eyes**

Effects On CVS

- Ventricular hypertrophy, dysfunction and failure.
- Arrhithymias
- Coronary artery disease, Acute MI
- Arterial aneurysm, dissection, and rupture.

Effects on The Kidneys

- Glomerular sclerosis leading to impaired kidney function and finally end stage kidney disease.
- Ischemic kidney disease especially when renal artery stenosis is the cause of HTN

Nervous System

- Stroke, intracerebral and subaracnoid hemorrhage.
- Cerebral atrophy and dementia

The Eyes

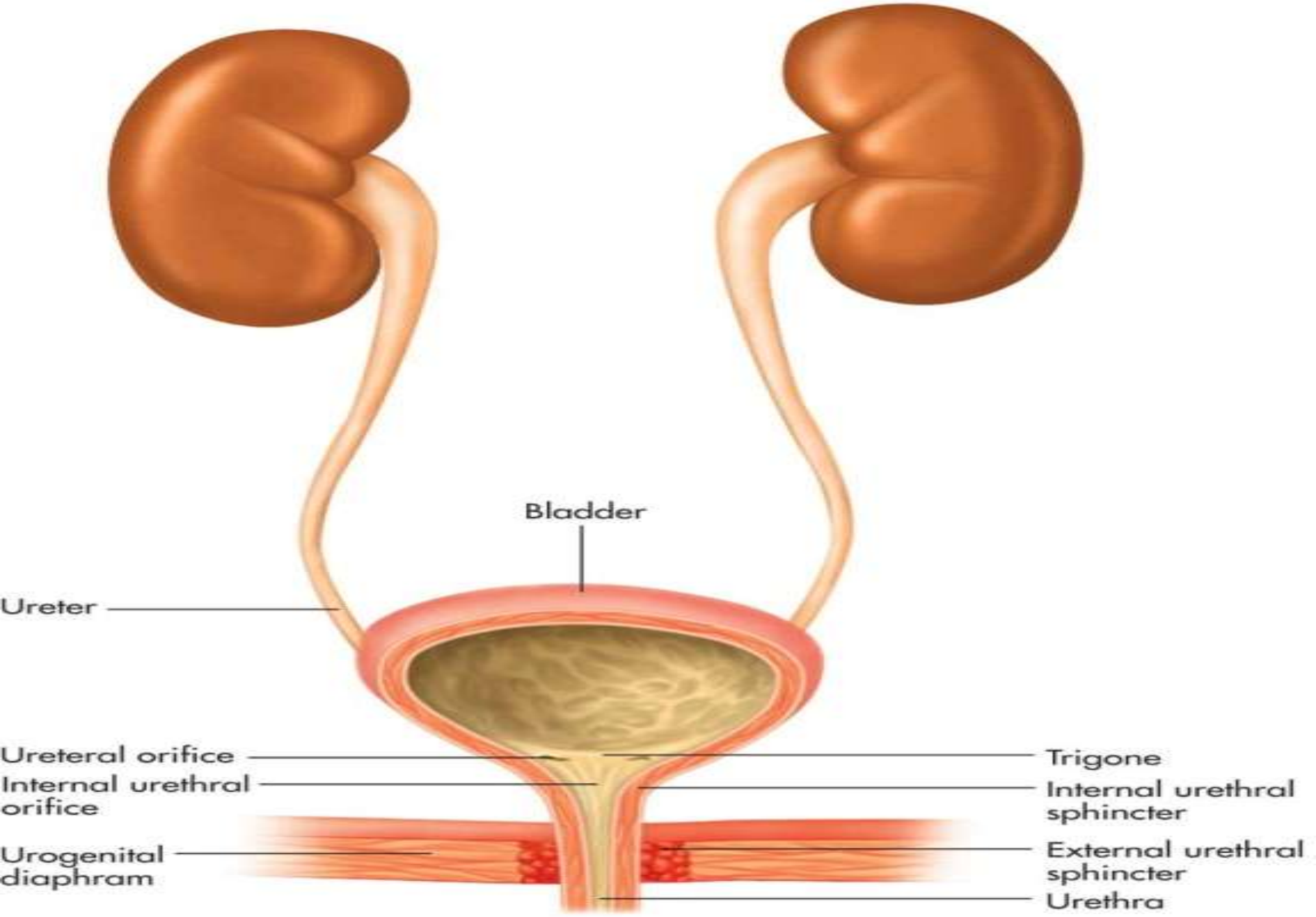
- Retinopathy, retinal hemorrhages and impaired vision.
- Vitreous hemorrhage, retinal detachment
- Neuropathy of the nerves leading to extraoccular muscle paralysis and dysfunction

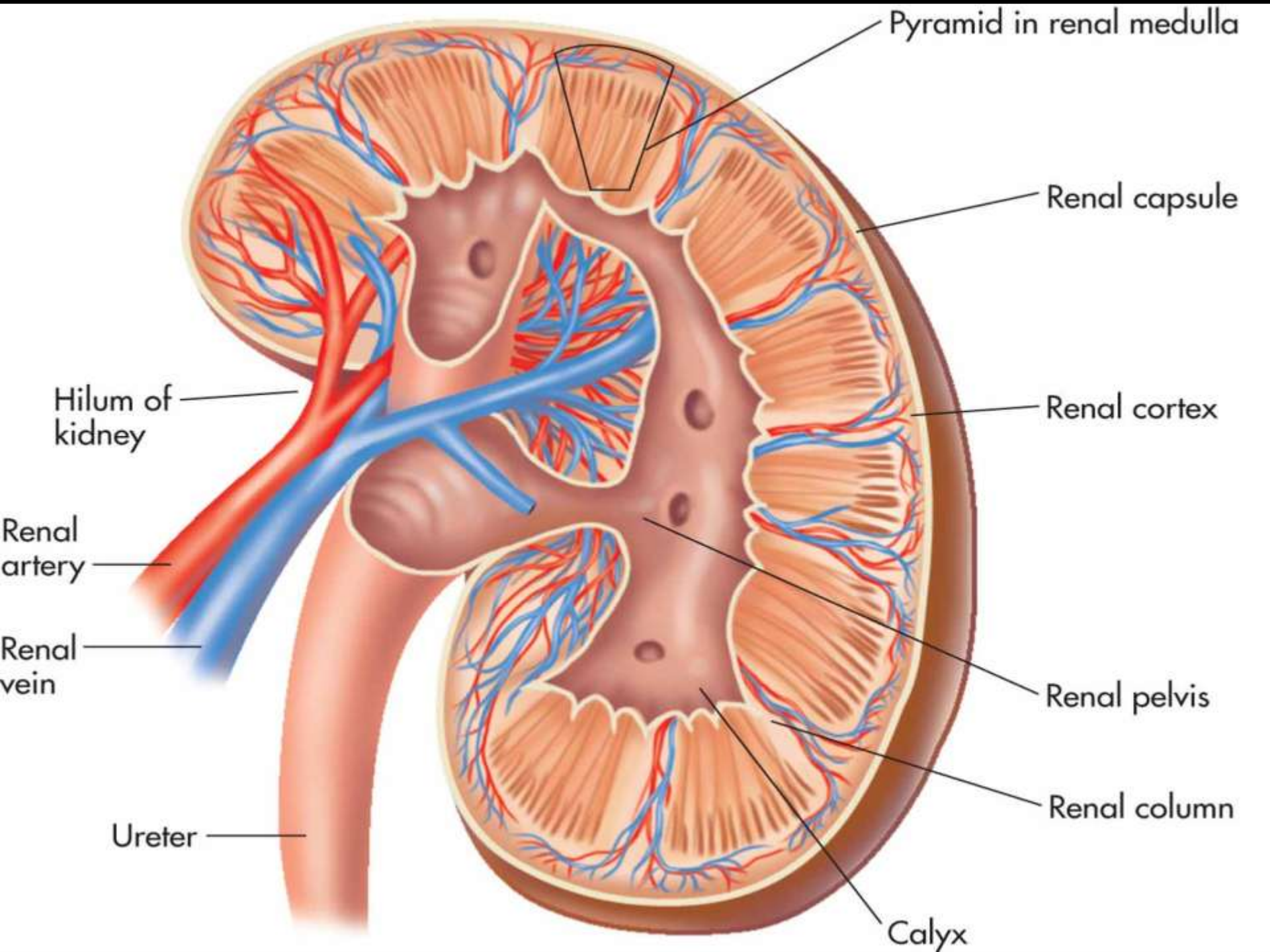
PATHOPHYSIOLOGY OF URINARY SYSTEM DISORDERES

Dr. AJWADASSUMAIDAEE

“When bubbles settle on the surface of the urine, it indicates disease of the kidneys and that the complaint will be protracted”

Hippocrates


Bladder
Ureter
Ureteral orifice
Internal urethral orifice
Urogenital diaphram
Trigone
Internal urethral sphincter
External urethral sphincter
Urethra

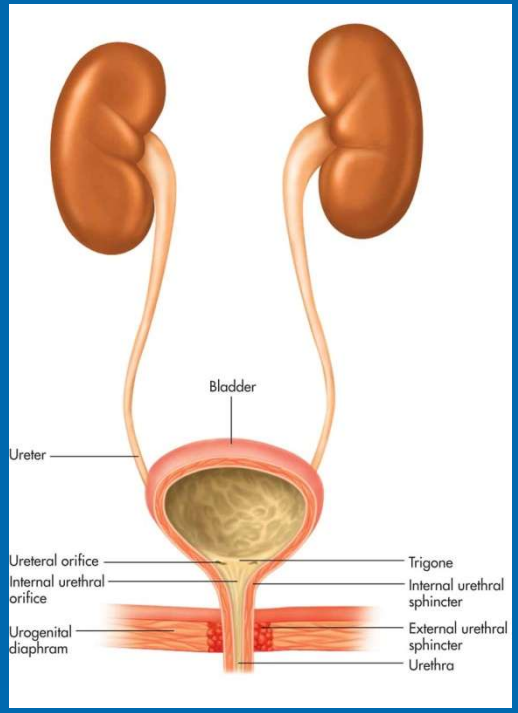

Pyramid in renal medulla
Renal capsule
Hilum of kidney
Renal cortex
Renal artery
Renal vein
Renal pelvis
Renal column
Ureter
Calyx

Introduction

- Kidneys act as purification plant, cleaning blood of waste materials.
- Kidneys control electrolyte (Na, K, Cl, Co2)
- & fluid balances for body.
- Kidneys filter blood, reabsorb & secrete ions, & produce urine.
- Without this important function you would survive only a few days.

Urinary System Overview

- Two kidneys, bean shaped organs located in superior dorsal abdominal cavity that filter blood & make urine, & accessory structures.
- Ureter a tube that carries urine from each kidney to a single urinary bladder, located in inferior ventral pelvic cavity.
- Bladder: expandable sac that holds urine.



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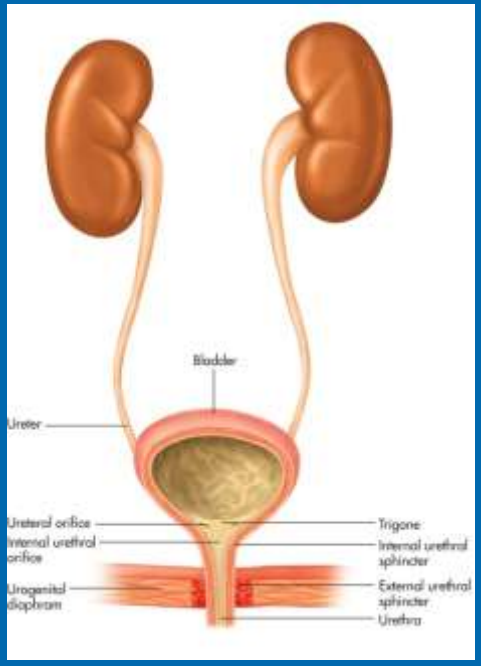
Urinary System Overview con't

- Urethra: a tube that transports urine from bladder to the Meatus.
- Function of urinary system is to make urine, thus controlling body's fluid & electrolyte balance & eliminating waste products.
- To make urine, 3 processes are necessary:
  - Filtration ⟶ purification
  - Reabsorption ⟶ of water
  - Secretion ⟶ of excess water



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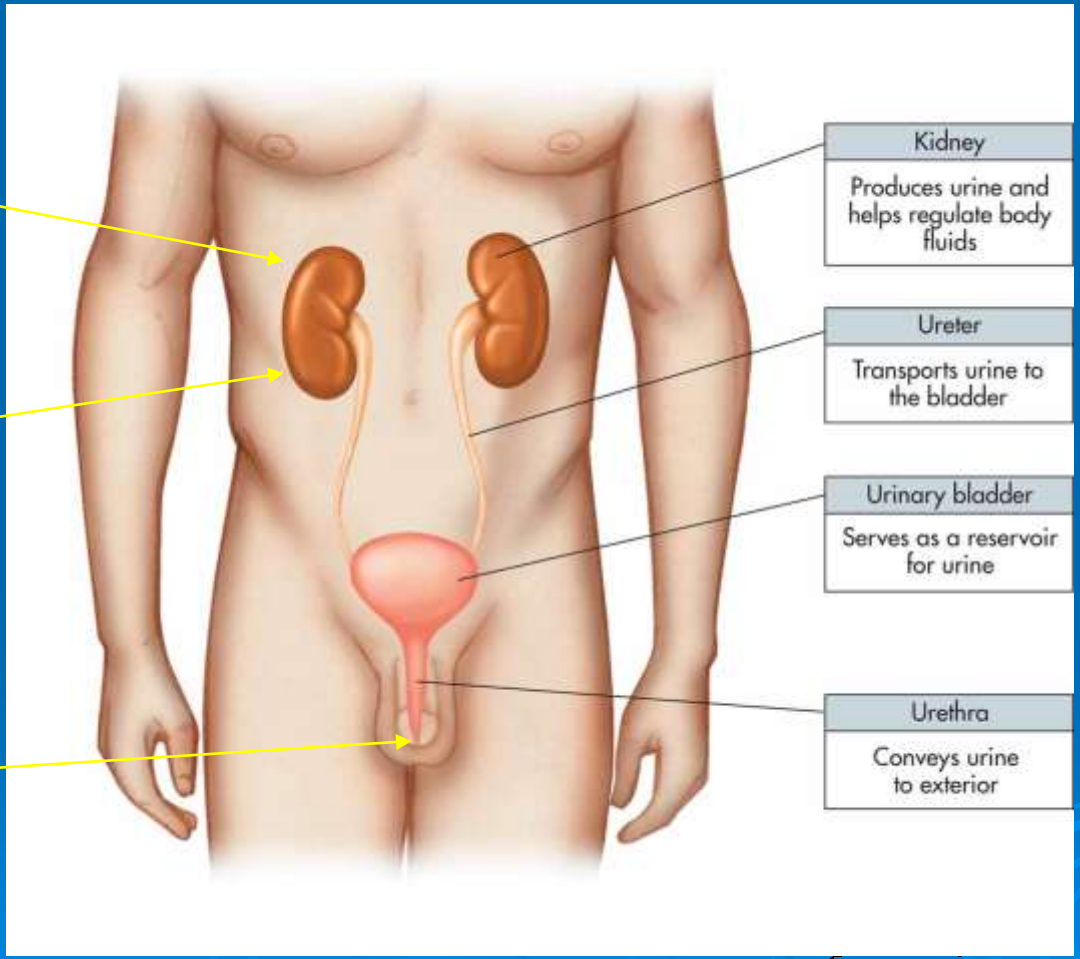
The Urinary System



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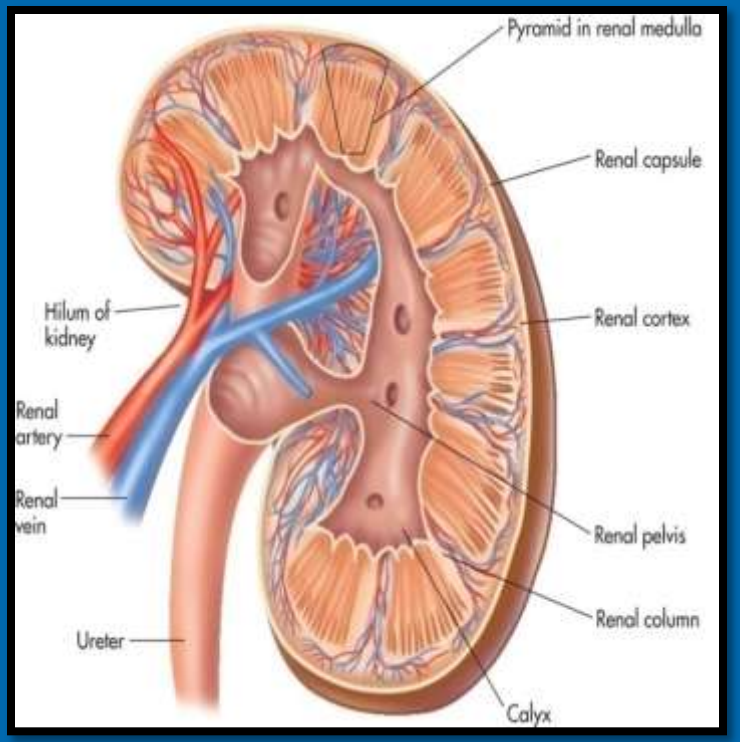
- Renal Capsule: Kidney covered by fibrous layer of connective tissue.
- Renal Hilum: Gives kidney its shape.
- Hilum renal arteries bring blood to kidneys to be filtered and renal veins take filtered blood away from kidney.
- Ureter also attached at hilum to transport urine from kidney to bladder

Kidney divided into 3 layers:

- Renal cortex: outer layer, grainy in appearance, has little obvious structure to naked eye; where blood filtration occurs.
- Renal medulla: middle layer: Transports urine to the renal pelvis via "pyramids."
- Renal pelvis: inner layer. Collects urine.



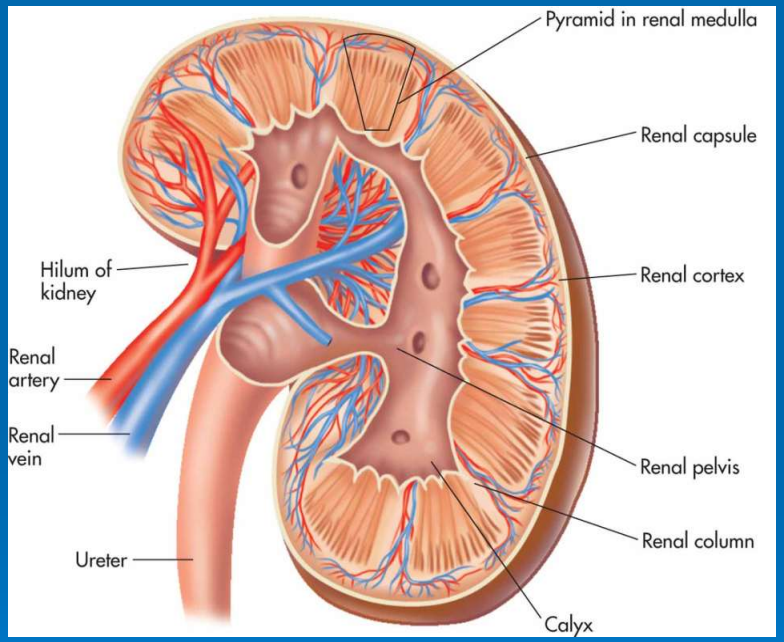
Path of Urine Production

1. Renal Cortex
2. Renal Medulla
3. Renal Pelvis

End Of Slide

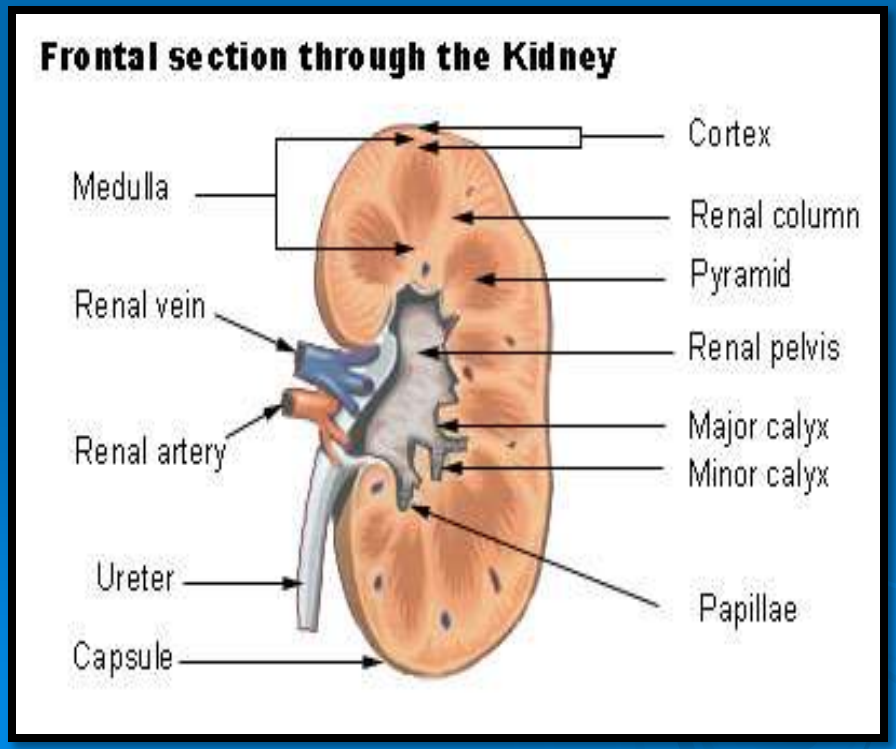
Renal Cortex

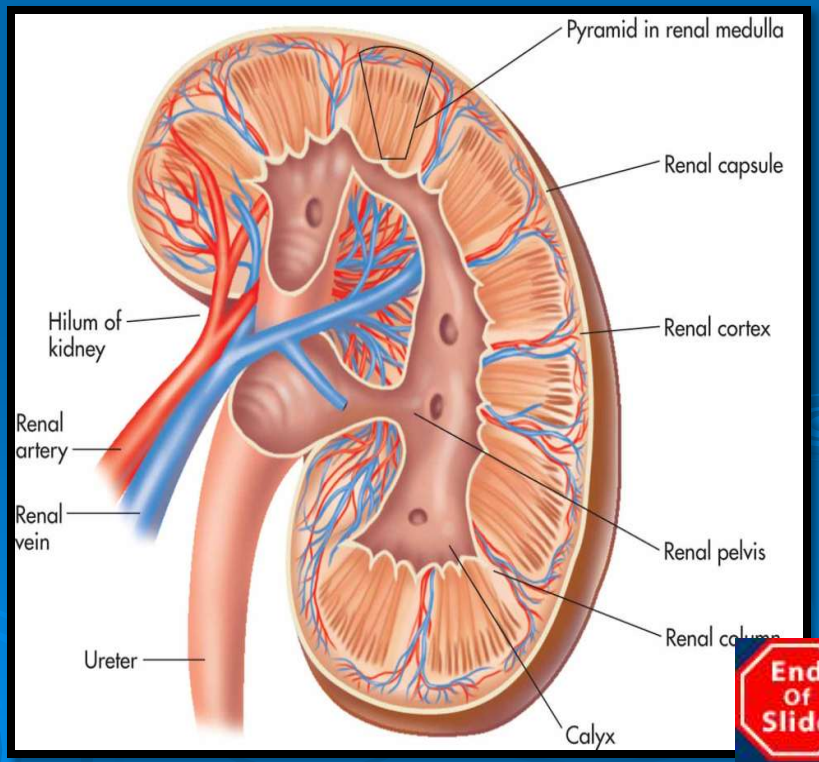
- Outer layer: grainy in appearance, has little obvious structure to naked eye; where blood filtration occurs.



Renal Medulla

- middle layer: Transports urine to the renal pelvis via 7-18 "pyramids," or collecting tubes.
- pyramids composed of collecting tubules for urine that is formed in kidney.





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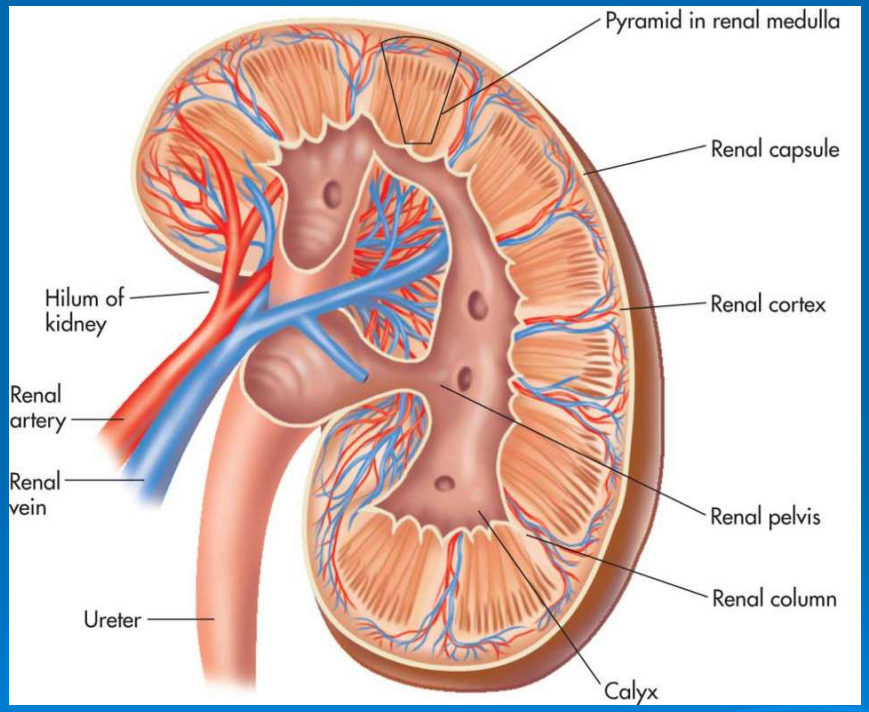
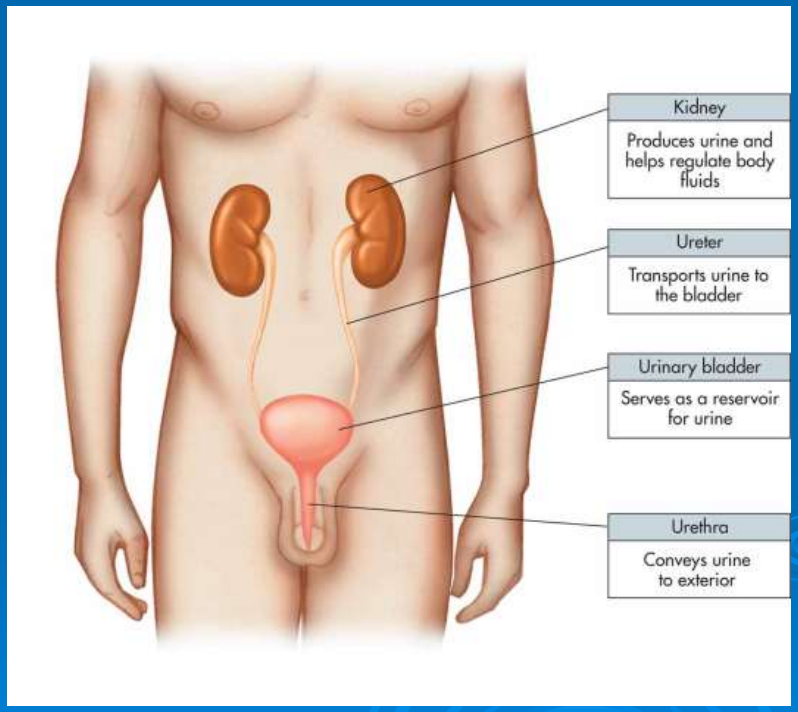
Renal Pelvis

- Inner layer: Collects, then empties urine into proximal Ureter on way to bladder.





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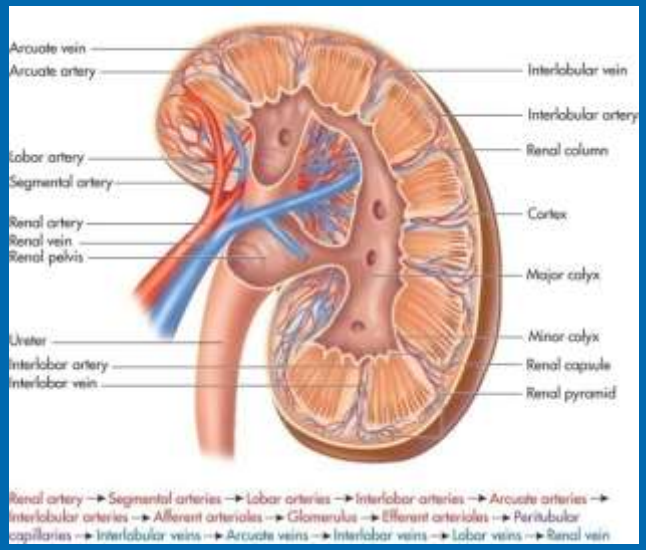
Vasculature of the Kidney

Healthy blood supply to kidney is essential

Arterial System

- Renal
- Segmental
- Lobar
- Interlobular
- Arcuate
- Interlobular
- Afferent arterioles
- Glomerulus
- Efferent arterioles



Venous System

- Renal
- Lobar
- Interlobular
- Arcuate
- Interlobular
- Peritubular capillaries

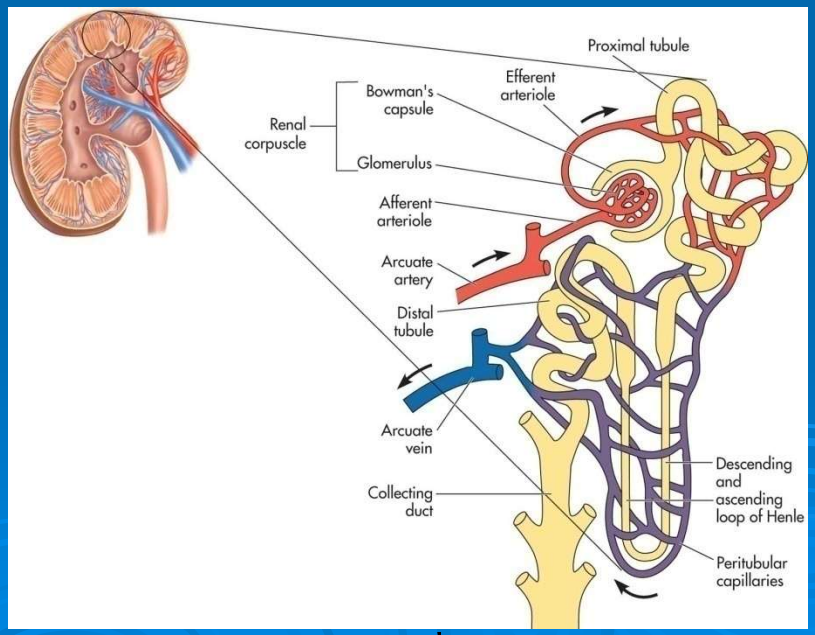
End Of Slide

The Nephron

- Functional unit of kidney: consisting of millions of microscopic funnels and tubules.
- Divided into 2 parts:

a. Renal Corpuscle: a filter

b. Renal Tubule: where reabsorption & secretion take place.



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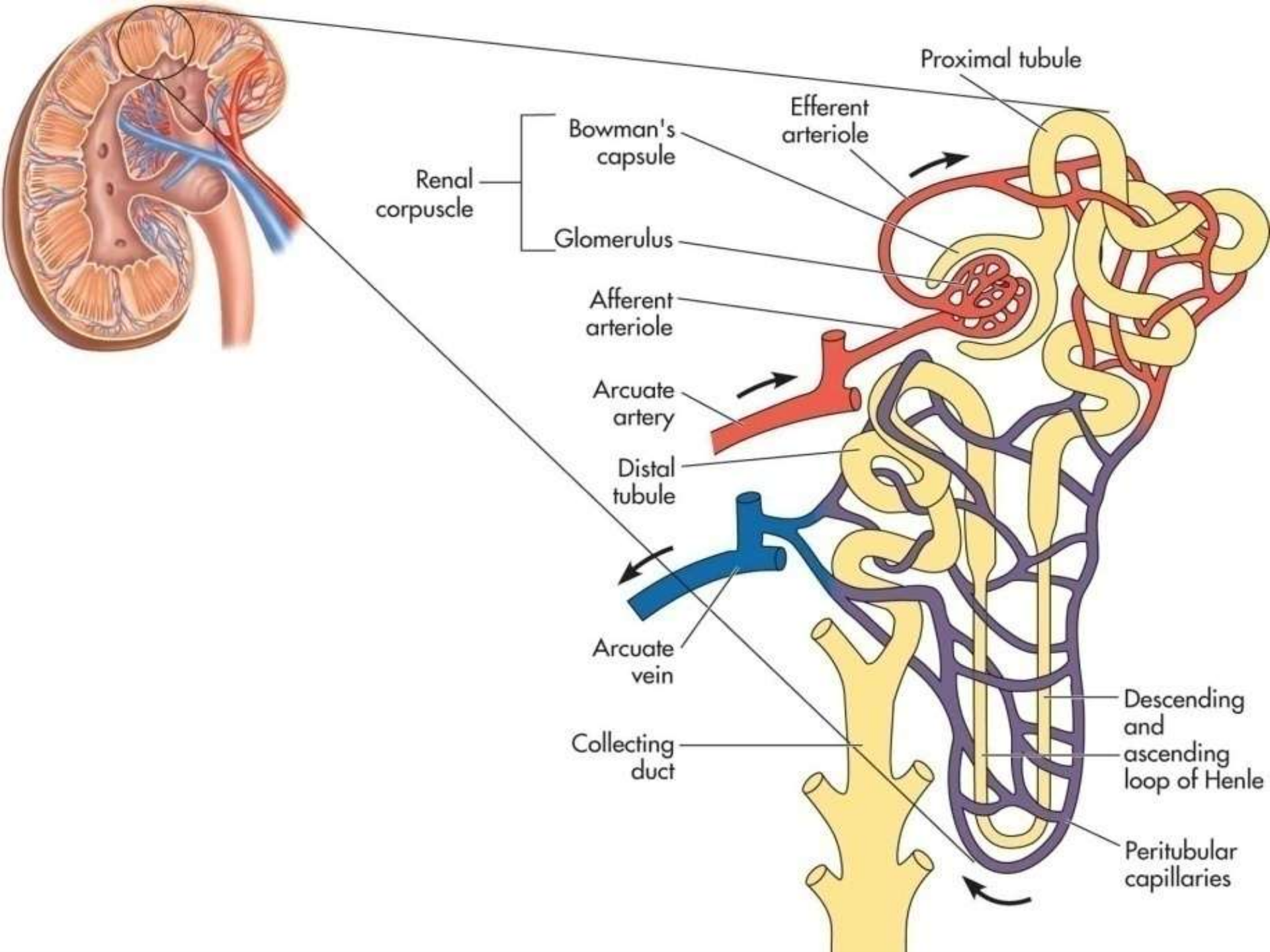
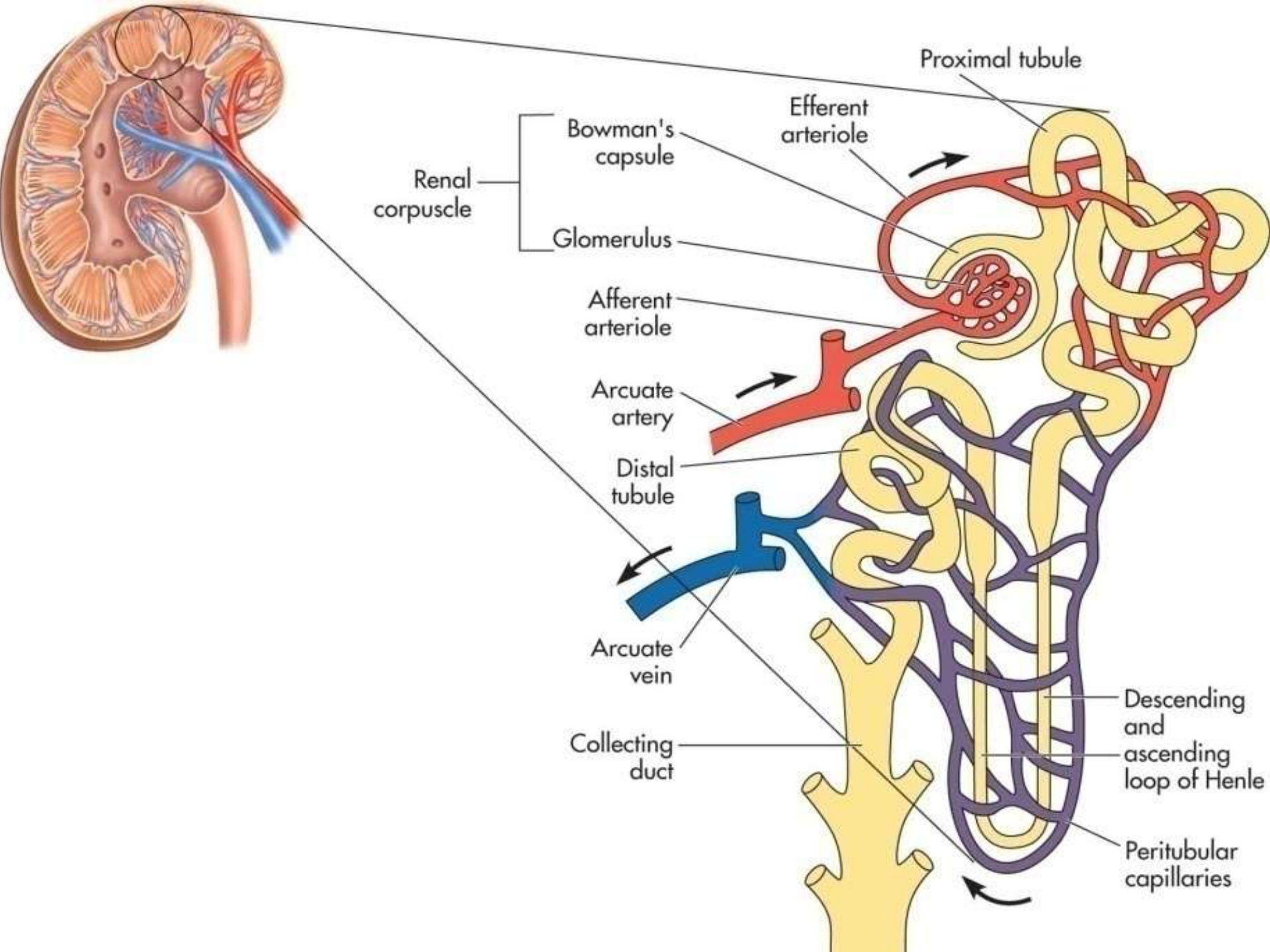

Proximal tubule
Efferent arteriole
Bowman's capsule
Renal corpuscle
Glomerulus
Afferent arteriole
Arcuate artery
Distal tubule
Arcuate vein
Collecting duct
Descending and ascending loop of Henle
Peritubular capillaries


Proximal tubule
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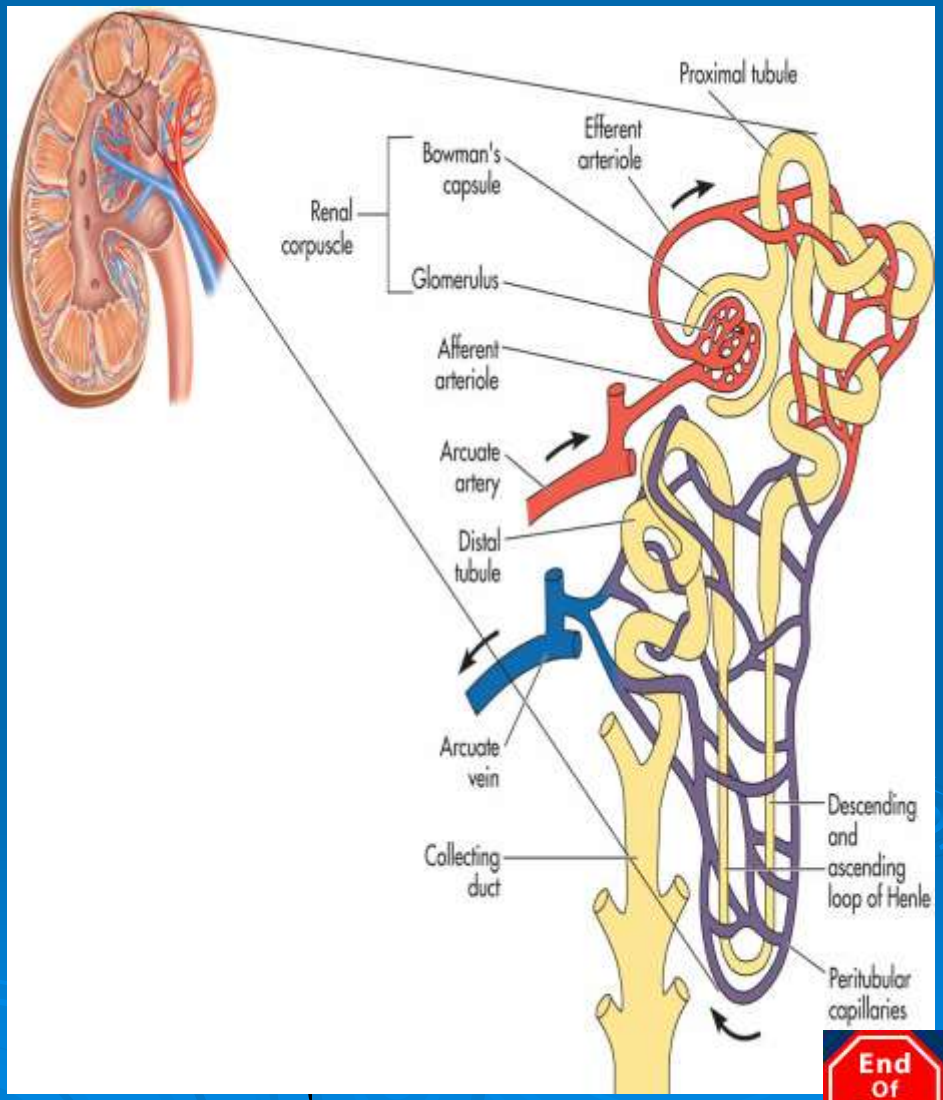
Renal corpuscle
Glomerulus
Afferent arteriole
Arcuate artery
Distal tubule
Arcuate vein
Collecting duct
Descending and ascending loop of Henle
Peritubular capillaries

The Nephron con't

- Blood enters renal corpuscle via glomerulus, ball of capillaries.
- Surrounding glomerulus is double-layered membrane called Bowman's capsule, the filter.

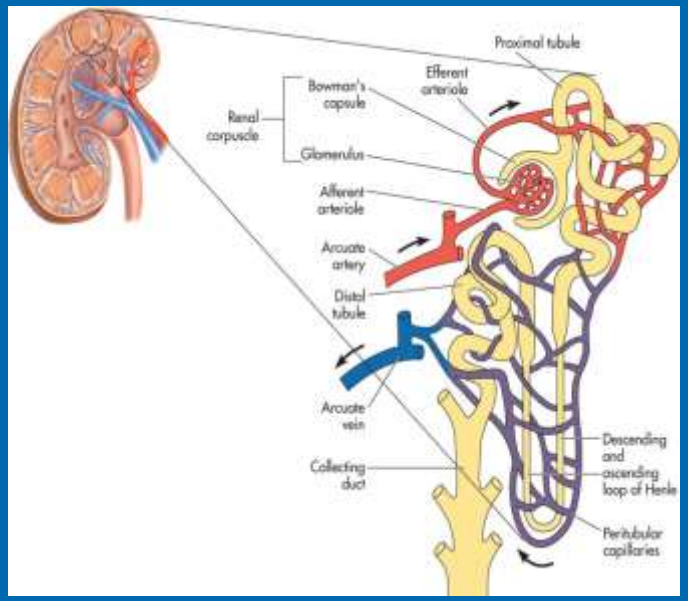


The Nephron con't

- Blood flows into glomerulus & everything BUT blood cells & few large molecules, mainly protein, pushed from capillaries across filter & into glomerular (Bowman's) capsule. Fluid now called "filtrate."
- Protein urea: protein in UA (filtrate)

  or

  Hematuria: blood in UA indicates renal problems!



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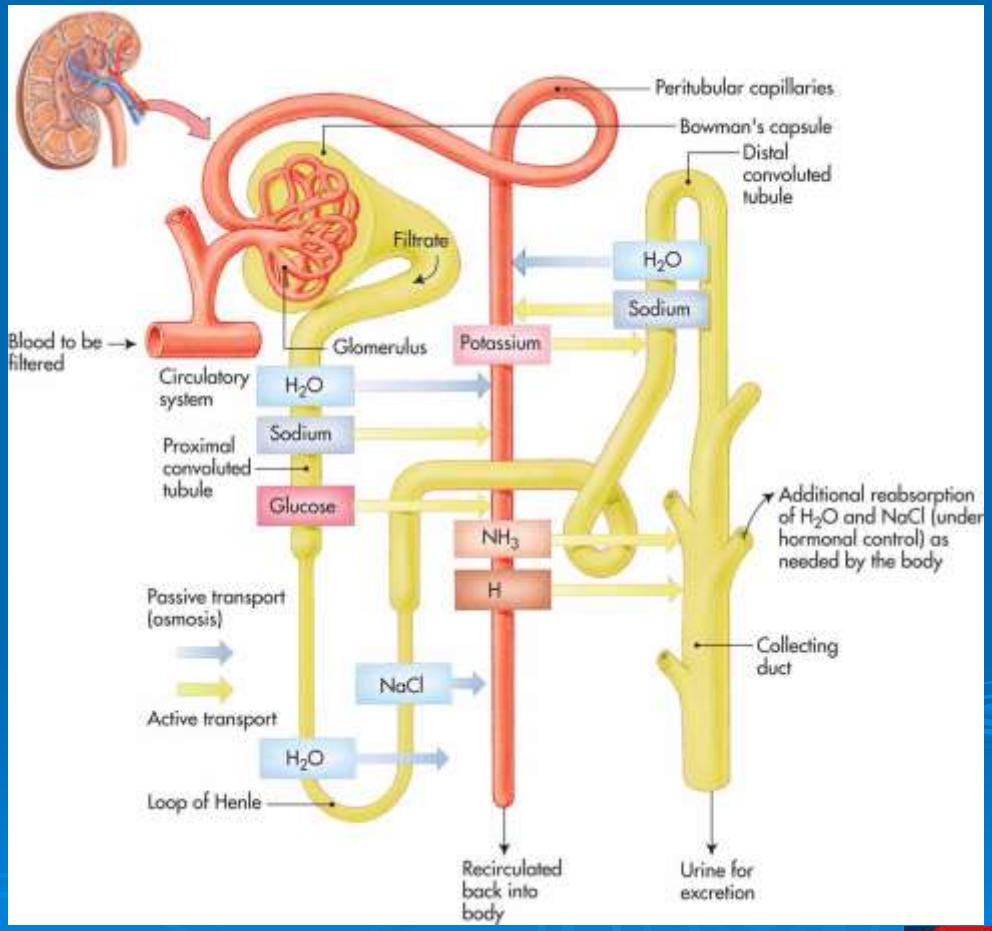
The Nephron con't

Renal Tubules

- Proximal loop
- Loop of Henle
- Distal loop



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How Urine is Formed

3 processes must occur in Nephron:

1. Glomerular Filtration: fluid & molecules pass from glomerular capillaries into glomerular (Bowman's) capsule. Filtrate flows into renal tubule.
2. Tubular Reabsorption: substances reabsorbed pass from renal tubule into peritubular capillaries & return to blood stream.
3. Tubular Secretion: substances that are secreted pass through peritubular capillaries into renal tubule & eventually leave body as urine, no longer filtrate…

End Of Slide

Pathology Connection:
Kidney Stones (Renal Calculi)

- Etiology:

  Calcium, phosphorus, & uric acid crystals, & nephritis.

- S/S:

  Hematuria, flank/abd/pelvic pain. Urgency, fever, Mild to extreme pain 10/10!

Common Disorders of the Urinary System

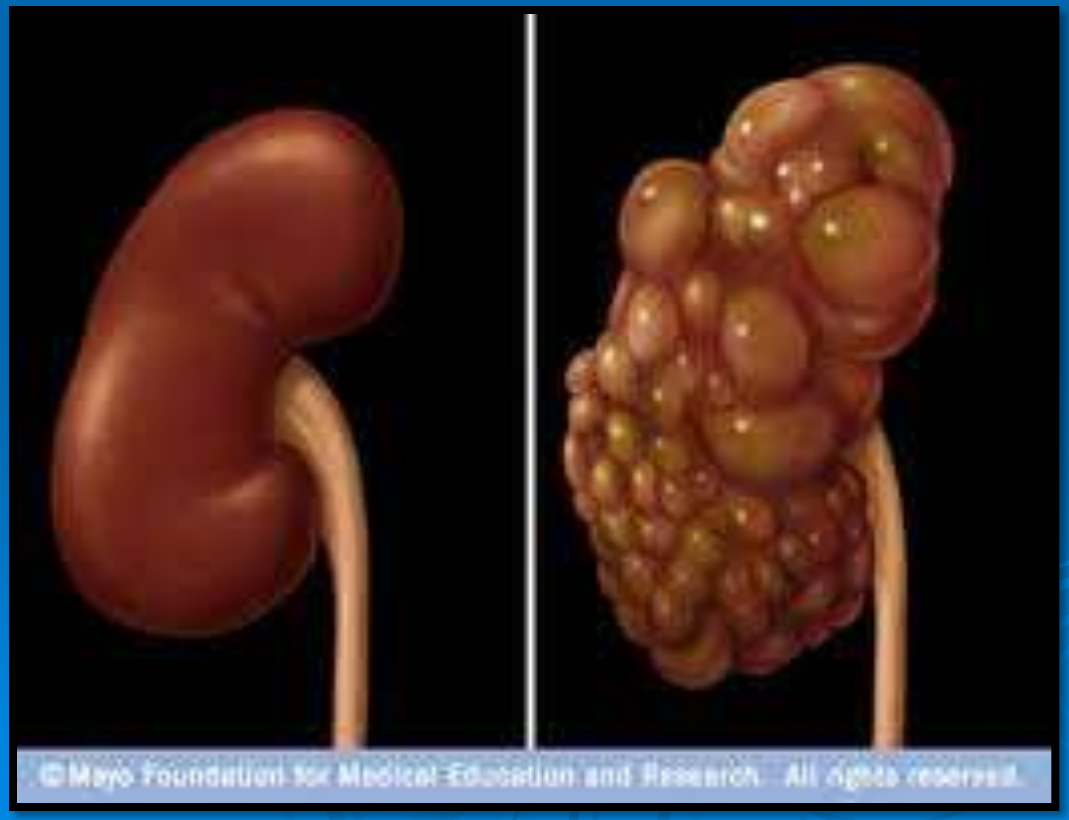
Urinary Tract (Bladder) Infection (UTI)

- Etiology: fecal bacteria into urinary tract
- S/S: freq, dysuria, hematuria, turbid urine, & urine with unusual odor, fever

Common Disorders of the Urinary System

Polycystic Kidney Disease

- Etiology: Genetic
- S/S: enlarged, cystic kidneys, hypertension, UTI, dilute urine, pain, hematuria, aneurysm



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Common Disorders of the Urinary System

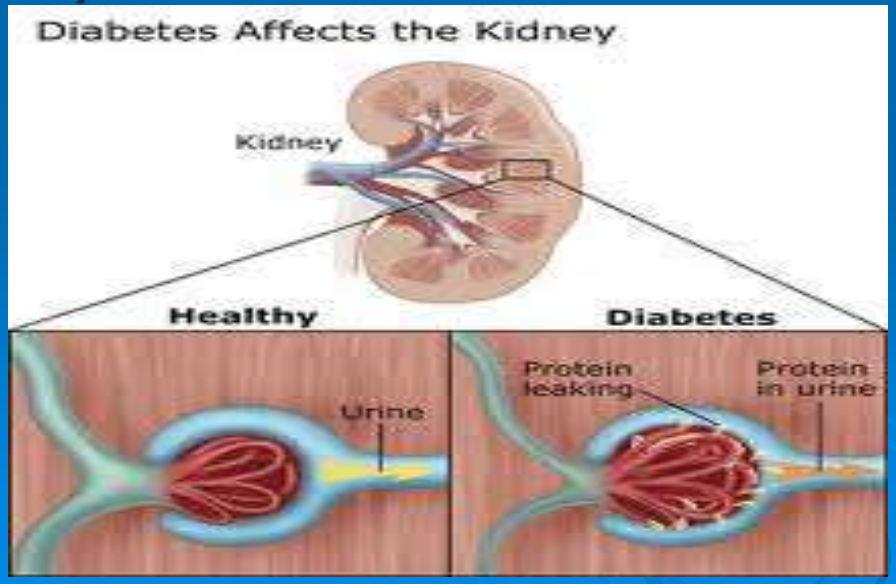
Ischemic Nephropathy

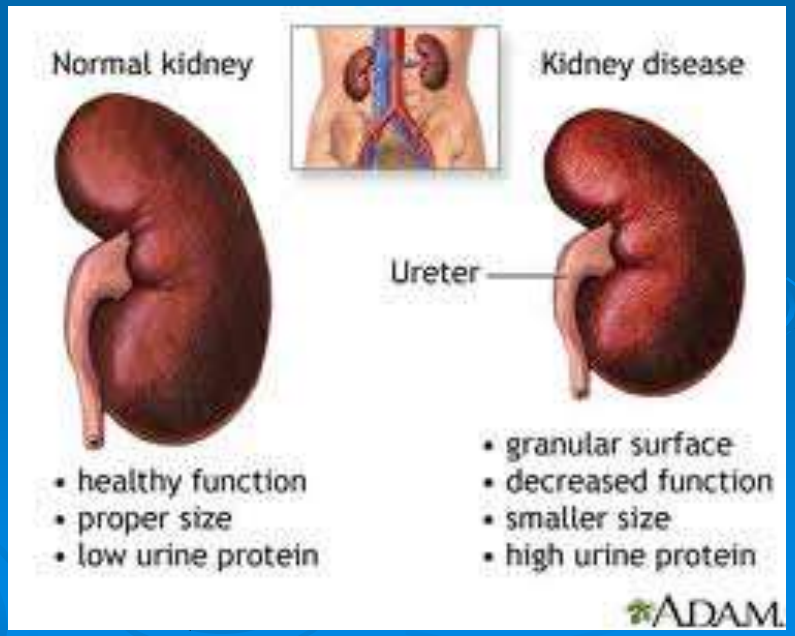
- Etiology: decrease blood flow to kidneys
- S/S: kidney failure, uremia, hypertension or hypotension, oliguria, increase serum creatinine & urea.
- Dx: UA, BUN & Creatinine
- Rx: treat underlying cause & symptoms, possible renal transplantation.
- Prognosis: Poor without treating cause or transplantation.

Common Disorders of the Urinary System

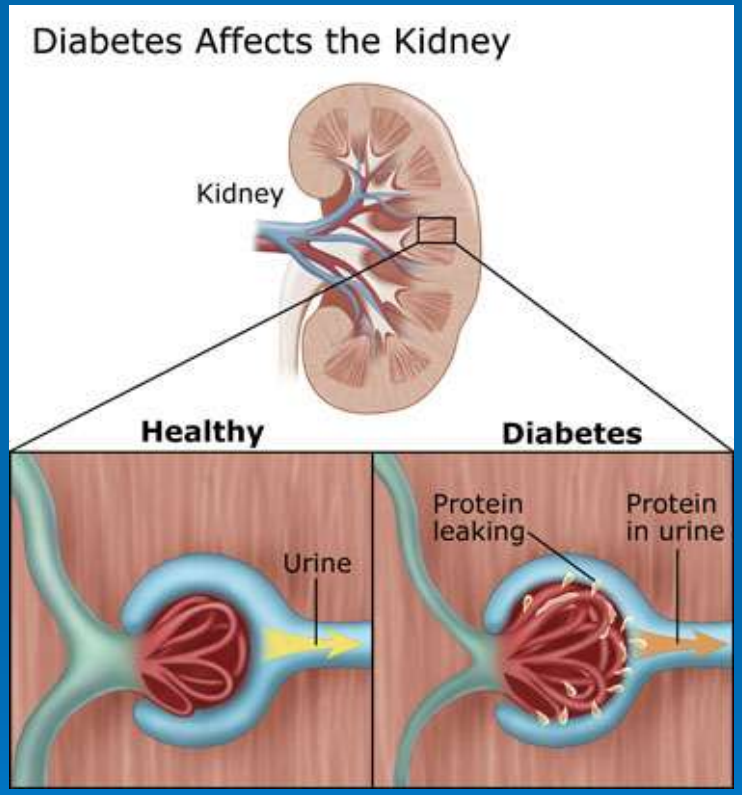
Diabetic Nephropathy

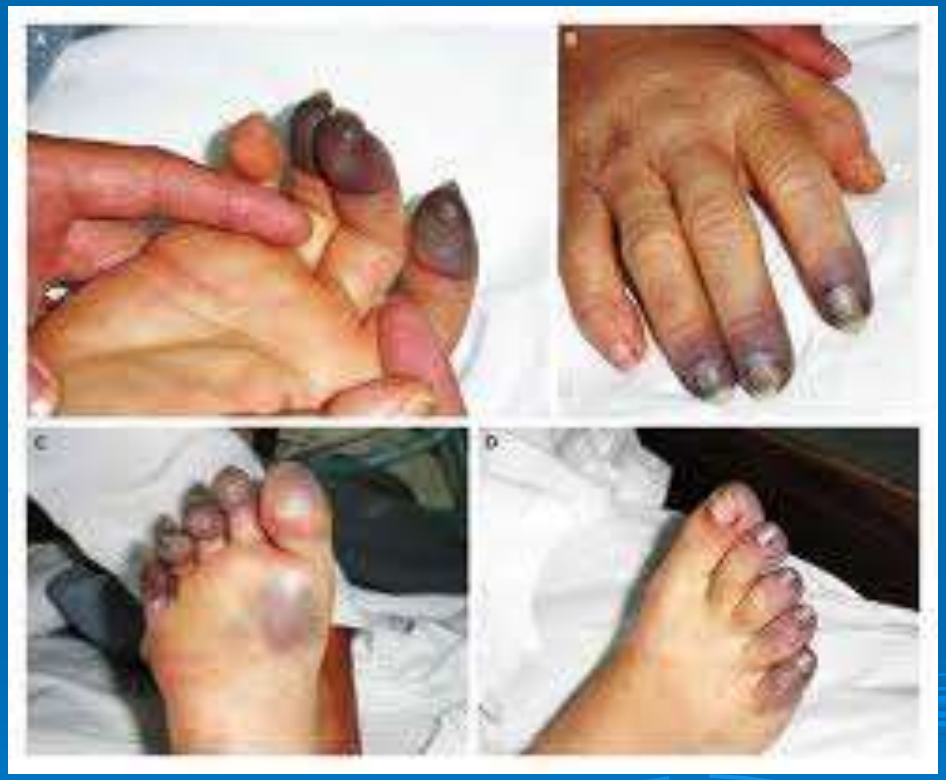
- Etiology: Diabetes Mellitus (type I or II)
- S/S: early stages: increased glomerular filtration, protein in urine, later: uremia, HTN.
- Dx: BUN, Creatinine, UA, 24 hour UA
- Rx: tight glycemic control, lipid control, diet, kidney replacement





Diabetic Nephropathy





Common Disorders of the Urinary System

Drug Induced Nephropathy

- Etiology: drugs toxic to kidney tissue, especially contrast dye & NSAIDs.
- S/S: early stages: increased glomerular filtration, protein in urine, later: uremia, hypertension
- Dx: BUN, Creatinine, UA, 24 hour UA
- Rx: : stop drugs, no contrast dyes for patients with known risk factors, keep patients well hydrated before contrast dye use.

Common Disorders of the Urinary System

Glomerulonephritis

- Etiology: : inflammation & scarring of glomerulus
- S/S: early stages: increased glomerular filtration, protein in urine, later: uremia, hypertension
- Dx: BUN, Creatinine, UA, 24 hour UA

Common Disorders of the Urinary System

Uremia

- Etiology: build up of organic waste products in blood due to renal insufficiency.
- S/S: elevated BUN & Creatinine, fatigue, neuropathy, seizures, lack of appetite, decreased smell & taste, mental confusion, insulin resistance, itching, inflammation, clotting problems.
- Dx: BUN, Creatinine, UA, 24 hour UA
- Rx: dialysis or renal transplantation

Common Disorders of the Urinary System

Diabetes Insipidus

- Etiology: ADH deficiency
  1. Central (Brain) 2. Nephrogenic (Kidneys)
- S/S: polyuria, dilute urine, thirst, dehydration, low K+, lethargy, muscle pain, irritability.
- Dx: UA, 24 UA, BUN, Creatinine
- Rx: Thiazide or Amiloride "Loop" Diuretics or surgery.

Common Disorders of the Urinary System

Renal Failure

- Etiology: acute or chronic decrease in glomerular filtration rate.
- S/S: decrease urine output, uremia, edema, loss of appetite, fatigue, hiccups, nausea, mental confusion, clotting disorder, seizures, coma.
- Dx: UA, BUN & Creatinine.
- Rx: BP meds, glucose & protein control, treatment of underlying condition, prevention CVD, peritoneal or hemodialysis, transplantation.

Common Disorders of the Urinary System

Bladder Cancer

- Etiology: Malignant tumor fm tobacco, radiation
- S/S: Hematuria, UTI's, dysuria
- Dx: UA, cytology, cystoscopy

Staging Cancer

The TNM System

- T: describes the size & whether it has invaded nearby tissues.
- N: describes regional lymph nodes involved
- M: describes distant metastasis

Staging Cancer

- 0: no cancer found
- 1: In-situ (Latin "in the place") in the layer of cells in which they developed.
- 2: Localized: Cancer limited to the organ in which they developed.
- 3: Regional: Cancer spread to nearby lymph nodes or organs.
- 4: Distant: Cancer spread to distant lymph nodes or organs.

Hemolytic Uremic Syndrome

- Etiology: bacterial infection with certain strains of E. coli, toxins damage kidneys
- S/S: fever, abdominal pain, pallor, fatigue, bruising, decreased urination, swelling

Urinary Tract Disorders
overall outline

- Incontinence & retention
- UTI's
- Inflammatory disorders
- Nephrotic syndrome
- Urinary tract obstruction
  - Stones
  - Hydronephrosis
  - Tumors
    - Renal cell carcinoma
    - Bladder cancer
- Congenital disorders
  - Polycystic kidneys
  - Wilm's tumor (nephroblastoma)
- Renal failure
  - Acute
  - Chronic
  - Dialysis

Incontinence, retention, & catheters

- **Urinary Incontinence**
  - Loss of voluntary control of bladder
  - Frequently called “neurogenic bladder”
  - Many causes
  - Enuresis = involuntary control after age 4 or 5
  - Types:
    - Stress
    - Urge
    - Overflow
- **Urinary retention**
  - Called “residual urine”
  - Causes :
    - Anatomical defects
    - Neurogenic defects
- **Treated with “catheterization”**
    - Foley
    - French

Urinary Tract Infections

Urethritis; Cystitis; Pyelonephritis

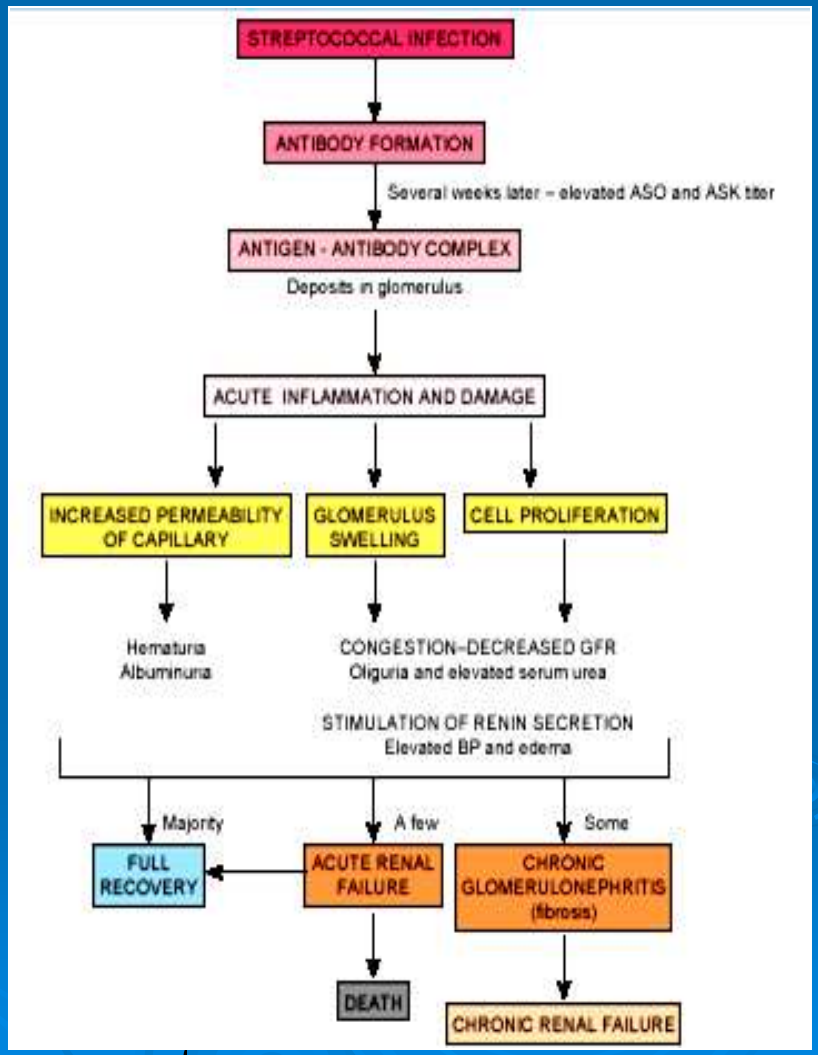
- Etiology
  - Ascending infection ----- women > men
  - Prostatic hypertrophy with urinary retention
  - Incomplete emptying of bladder with urinary stasis
  - Pregnancy associated with stasis
  - Blood borne pathogens
- Pathophysiology of UTI's ----- see next slide
- Dx
  - Dysuria, urgency, & nocturia
  - Systemically get fever & malaise
  - CVA tenderness in pyelonephritis

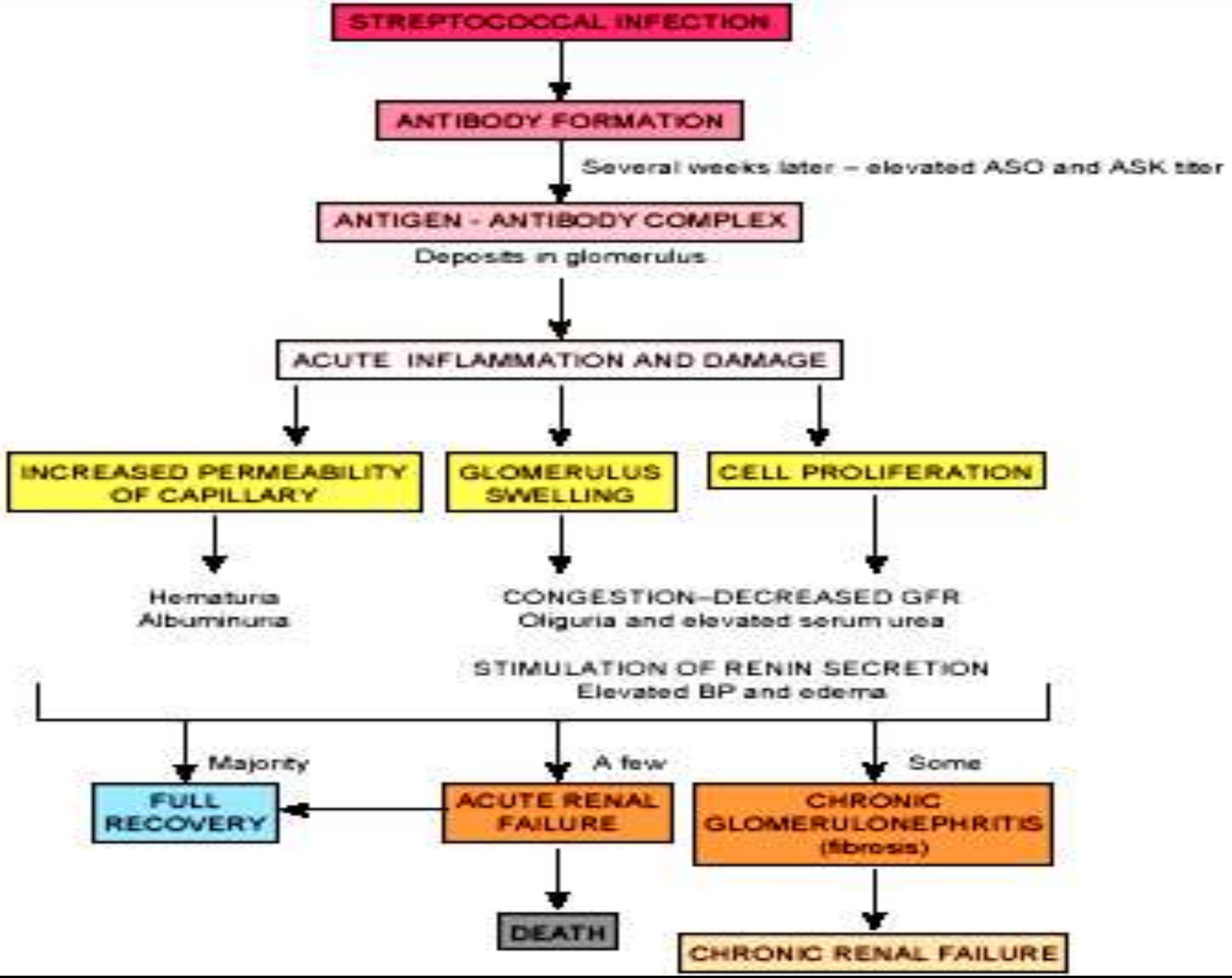
- Note glomerulonephritis is vastly different with regards etiology & pathophysiology

Inflammatory disorders

(1) glomerulonephritis
(2) nephrotic syndrome

- **Glomerulonephritis**
  - Acute
    - Sx = proteinuria, edema, oliguria
    - Etiol = 1-2 weeks post strept infect.
  - Chronic
    - Etiol = autoimmune disease
      - e.g. lupus, diabetes, hepatitis C
    - Can lead to irreversible kidney damage




STREPTOCOCCAL INFECTION
ANTIBODY FORMATION
Several weeks later – elevated ASO and ASK titer
ANTIGEN - ANTIBODY COMPLEX
Deposits in glomerulus
ACUTE INFLAMMATION AND DAMAGE
INCREASED PERMEABILITY OF CAPILLARY
GLOMERULUS SWELLING
CELL PROLIFERATION
Hematuria
Albuminuria
CONGESTION–DECREASED GFR
Oliguria and elevated serum urea
STIMULATION OF RENIN SECRETION
Elevated BP and edema
Majority
A few
Some
FULL RECOVERY
ACUTE RENAL FAILURE
CHRONIC GLOMERULONEPHRITIS (fibrosis)
DEATH
CHRONIC RENAL FAILURE

NEPHROTIC SYNDROME

PROTEINURIA

HYPOALBUMINEMIA

HYPERLIPIDEMIA

+/- EDEMA

Nephrotic-range proteinuria is the loss of 3 grams or more per day of protein into the urine or, on a single spot urine collection, the presence of 2 g of protein per gram of urine creatinine.

Nephrotic syndrome is the combination of 1- nephrotic-range proteinuria with
2- a low serum albumin level
3- and edema.

Nephrotic syndrome has many causes, including
primary kidney diseases such as
minimal-change disease, focal segmental glomerulosclerosis, and membranous glomerulonephritis.

Nephrotic syndrome can also result from systemic diseases that affect other organs in addition to the kidneys, such as
diabetes, amyloidosis, and lupus erythematosus.

Nephrotic syndrome may affect adults and children of both sexes and of any race. It may occur in typical form, or in association with nephritic syndrome. The latter term connotes glomerular inflammation, with hematuria and impaired kidney function.

Classification

Nephrotic syndrome can be primary, being a disease specific to the kidneys, or it can be secondary, being a renal manifestation of a systemic general illness. In all cases, injury to glomeruli is an essential feature. Kidney diseases that affect tubules and interstitium, such as interstitial nephritis, will not cause nephrotic syndrome.

Primary causes of nephrotic syndrome include the following, in approximate order of frequency:

1- Minimal-change nephropathy
2- Focal glomerulosclerosis
3- Membranous nephropathy
4- Hereditary nephropathies

Secondary causes include the following, again in order of approximate frequency:

1- Diabetes mellitus
2- Lupus erythematosus
3- Viral infections (e.g., hepatitis B, hepatitis C, human immunodeficiency virus [HIV])
4- Amyloidosis and paraproteinemias (The presence of a monoclonal gammopathy -abnormal protein- in the blood).
5- Preeclampsia
6- Allo-antibodies from enzyme replacement therapy
Substitution of the defective lysosomal enzyme in lysosomal storage disorders (LSDs) often elicits antibody formation towards the infused protein.

For years, pathologists found no changes when viewing specimens under light microscopy, hence the name "minimal change disease." With the advent of electron microscopy, the changes now known as

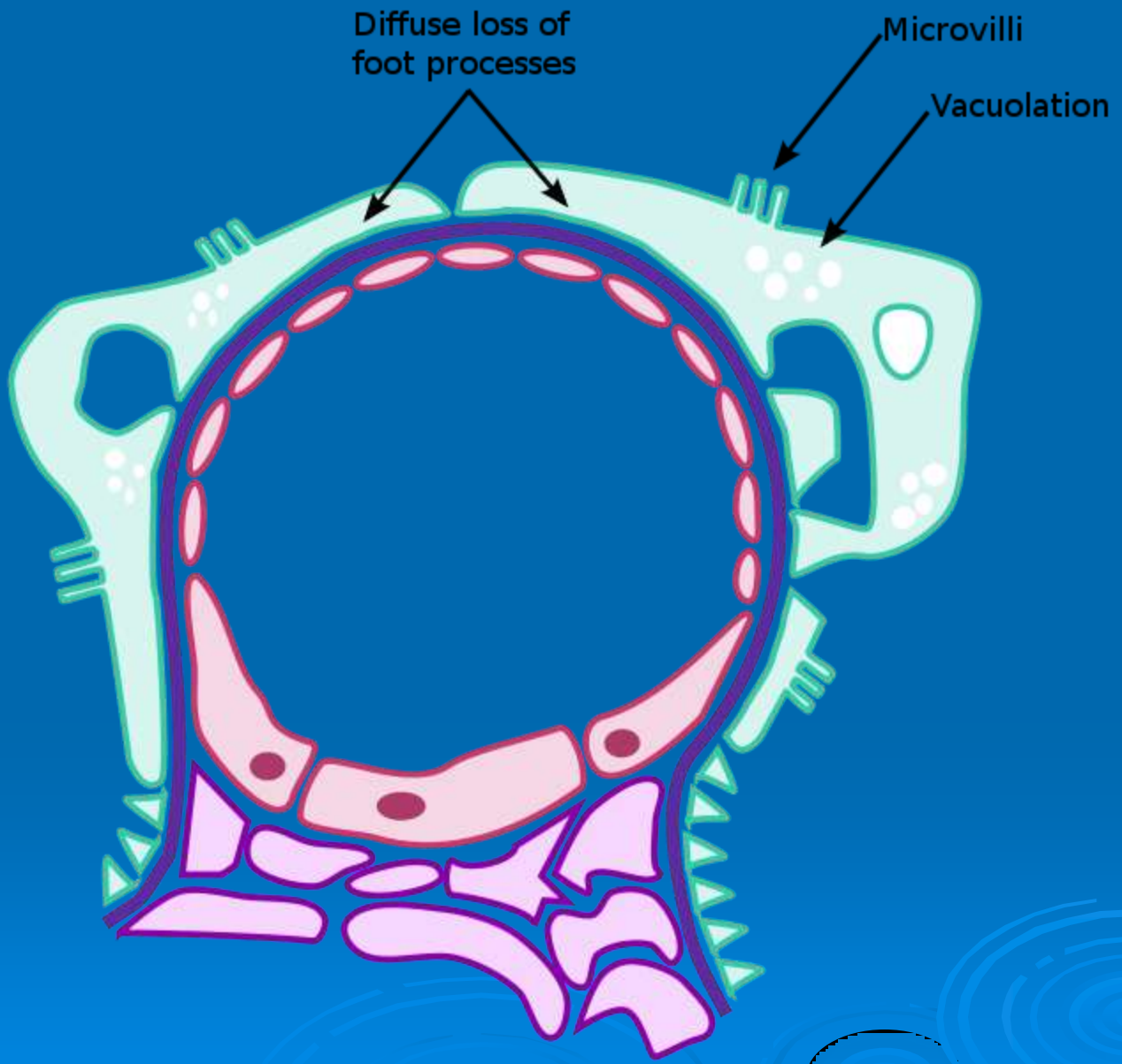
the hallmarks of the disease were discovered. These are

1- diffuse loss of visceral epithelial cells' foot processes (i.e., podocyte effacement),

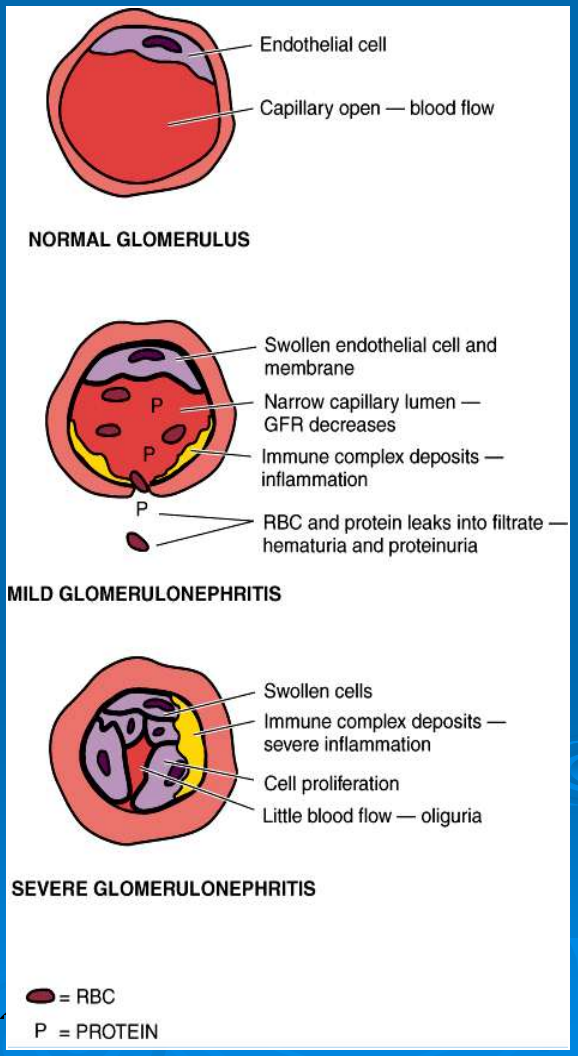
2- vacuolation,

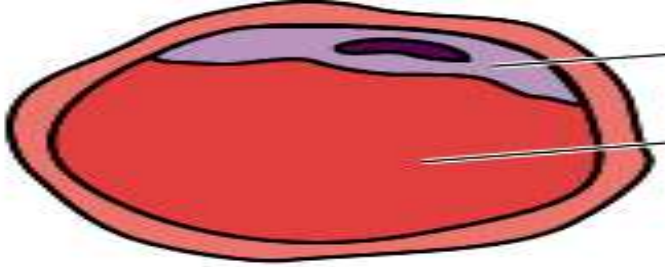
3- and growth of microvilli on the visceral epithelial cells.

The cause and pathogenesis of minimal change disease is unclear and it is currently considered idiopathic


Diffuse loss of
foot processes
Microvilli
Vacuolation

- **Nephrotic Syndrome**
  - Glomerular disorder where one loses the capacity to retain protein, especially albumin
  - Sx
    - severe edema (anasarca)
      * can get skin breakdown since impaired arterial flow
    - proteinuria
    - hypoalbuminemia
    - oliguria
  - Etiol:
    - » Toxic agents (lead, mercury)
    - » Toxic drugs (aminoglycosides)
    - » Diseases (diabetes, lupus
  - » Key = any significant problem with glomerulus can lead to nephrotic syndrome

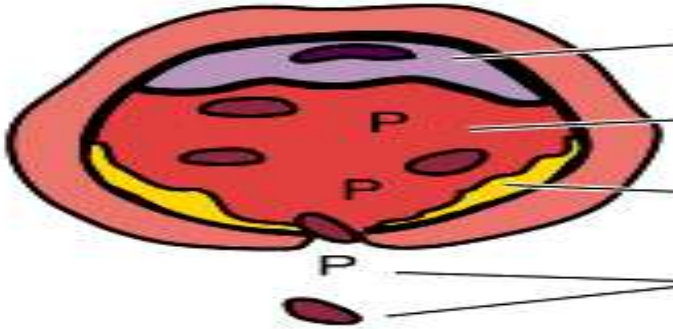




Endothelial cell

Capillary open — blood flow

NORMAL GLOMERULUS



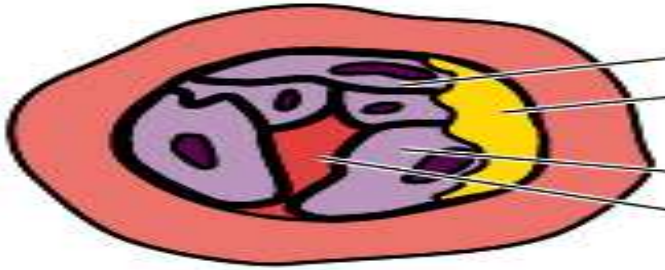
Swollen endothelial cell and membrane

Narrow capillary lumen — GFR decreases

Immune complex deposits — inflammation

RBC and protein leaks into filtrate — hematuria and proteinuria

MILD GLOMERULONEPHRITIS



Swollen cells

Immune complex deposits — severe inflammation

Cell proliferation

Little blood flow — oliguria

SEVERE GLOMERULONEPHRITIS

= RBC

P = PROTEIN

Pathophysiology of oedema in nephrotic syndrome

The mechanism by which loss of serum proteins into the urine causes expansion of extracellular fluid volume and oedema has become clearer. A key initiating abnormality is avid sodium retention by the kidney, leading to increased whole-body sodium and increased extracellular fluid volume. This appears to be driven primarily by overactivation of the amiloride-sensitive epithelial sodium channel (ENaC) in the collecting duct, activated proteolytically through abnormal filtration of plasminogen, and its activation to plasmin in the nephron. Conventional explanations for nephrotic oedema focused on low colloid osmotic pressure as a consequence of loss of serum proteins, leading to egress of extracellular fluid from the intravascular compartment. It was hypothesized that this led to sodium retention. While low osmotic pressure may play a part in the clinical picture of nephrotic syndrome, a variety of observations suggest that underfilling is not a common feature except in the most severe nephrotic syndrome. Furthermore the gradient in colloid osmotic pressure between serum and interstitium tends to be preserved in nephrotic syndrome.

Complications

Possible complications of nephrotic syndrome include:

Blood clots. The inability of the glomeruli to filter blood properly can lead to loss of blood proteins that help prevent clotting. This increases your risk of developing a blood clot (thrombus) in your veins.

High blood cholesterol and elevated blood triglycerides. When the level of the protein albumin in your blood falls, liver makes more albumin. At the same time, liver releases more cholesterol and triglycerides.

Poor nutrition. Loss of too much blood protein can result in malnutrition. This can lead to weight loss, but it may be masked by swelling. You may also have too few red blood cells (anemia) and low levels of vitamin D and calcium.

High blood pressure. Damage to glomeruli and the resulting buildup of wastes in the bloodstream (uremia) can raise blood pressure.

Acute kidney failure. If your kidneys lose their ability to filter blood due to damage to the glomeruli, waste products may build up quickly in the blood.

Chronic kidney disease. Nephrotic syndrome may cause kidneys to gradually lose their function over time. If kidney function falls low enough, you may require dialysis or a kidney transplant.

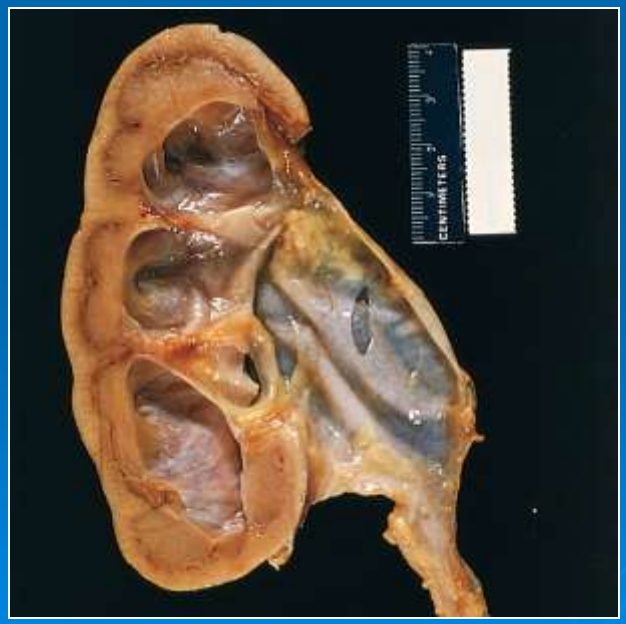
Infections. People with nephrotic syndrome have an increased risk of infections.

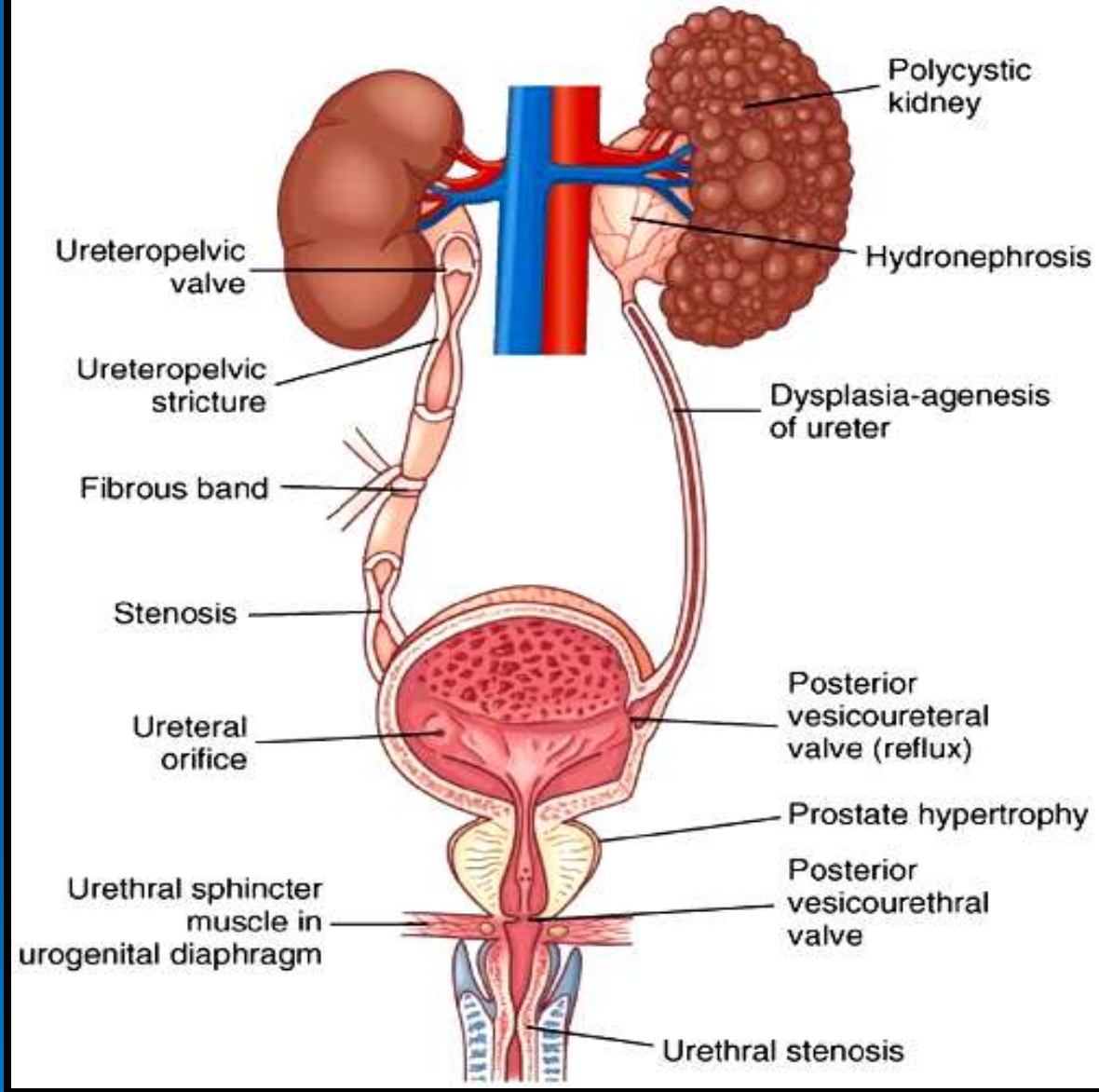
Obstructive Disorders

- **Renal Calculi**
  - Etiology: Calcium, Uric acid, Urine crystals
  - Symptoms: renal colic, N&V, chills, fever
  - Risk factors: prolong dehydration, prolong immobilization, infection
  - Treatment: surgery,lithotripsy
- **Anomalies**
  - Strictures
  - Kinks
  - Ptosis
  - Pelvic kidney

- **Tumors**
  - Note that primary symptom = hematuria
  - Renal Cell Ca = most common, unilateral, adeno Ca from tubular epithelium
    - See picture
  - Bladder Ca = usually from transitional epithelium
- **Neurogenic bladder**

- These result in:
  - Hydronephrosis
  - Hydroureter
- If these conditions exist longer than 2 months get destruction of kidney





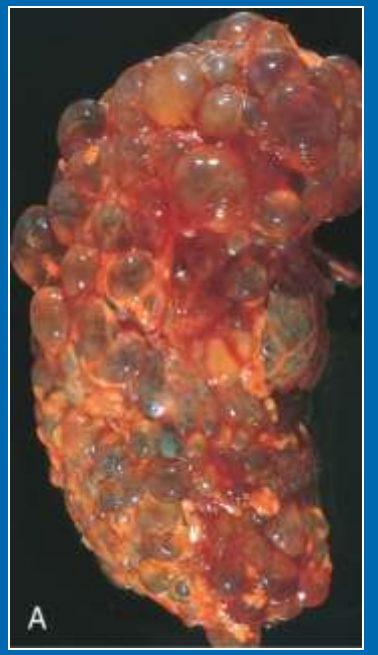
Major sites of urinary tract obstruction

Congenital Diseases

- **Vesicoureteral reflux**
  - Due to ectopic insertion of ureter into bladder
  - Incidence: 1/1000
  - Girls> boys; 10:1 ratio
- **Ectopic kidney**
  - May get kinking of ureter
  - Usually in pelvis
  - Asymptomatic
- **Renal agenesis**
  - Usually unilateral & left kidney
  - Asymptomatic
  - Remaining kidney becomes large since compensatory hypertrophy

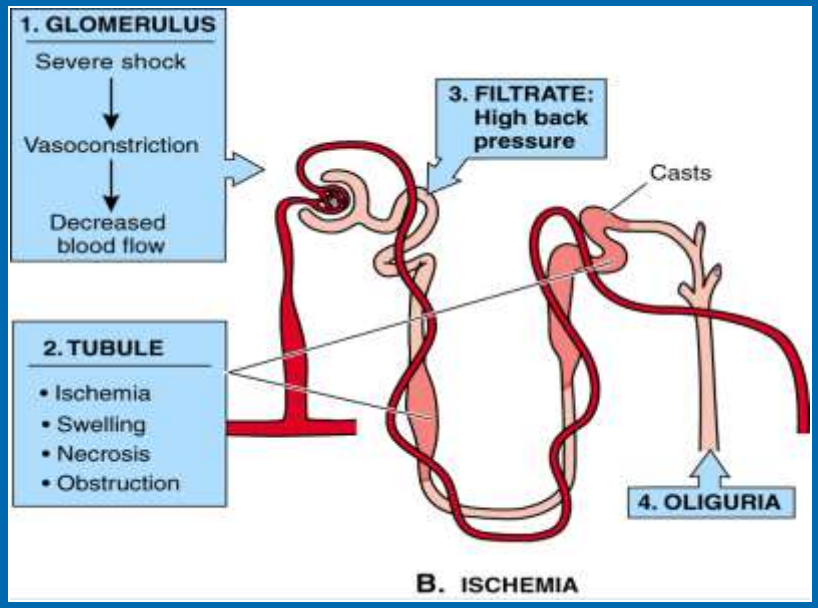
Congenital Diseases (cont)

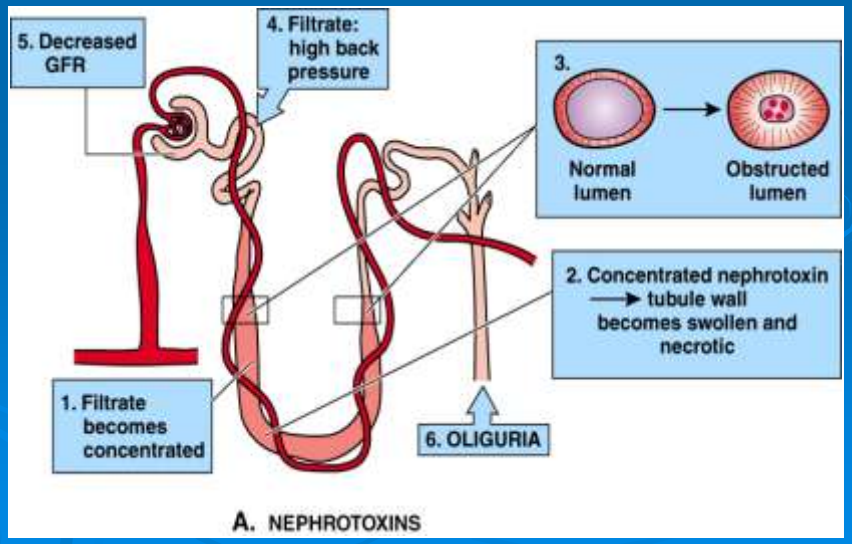
- **Polycystic kidney (2 types**
  - In adults
    - Genetic etiol ----- autosomal dominant
    - Clinically seen in adults
      - Between age 30 – 40 one begins to get renal failure
  - In children
    - Genetic etiol --- autosomal recessive
    - Manifest at birth; usually fatal or infant stillborn
    - Rare
- **Wilm's tumor (nephroblastoma)**
  - Most common tumor of children; usually unilateral
  - Etiol = autosomal recessive (on chromosome 11)
    - May produce hypertension



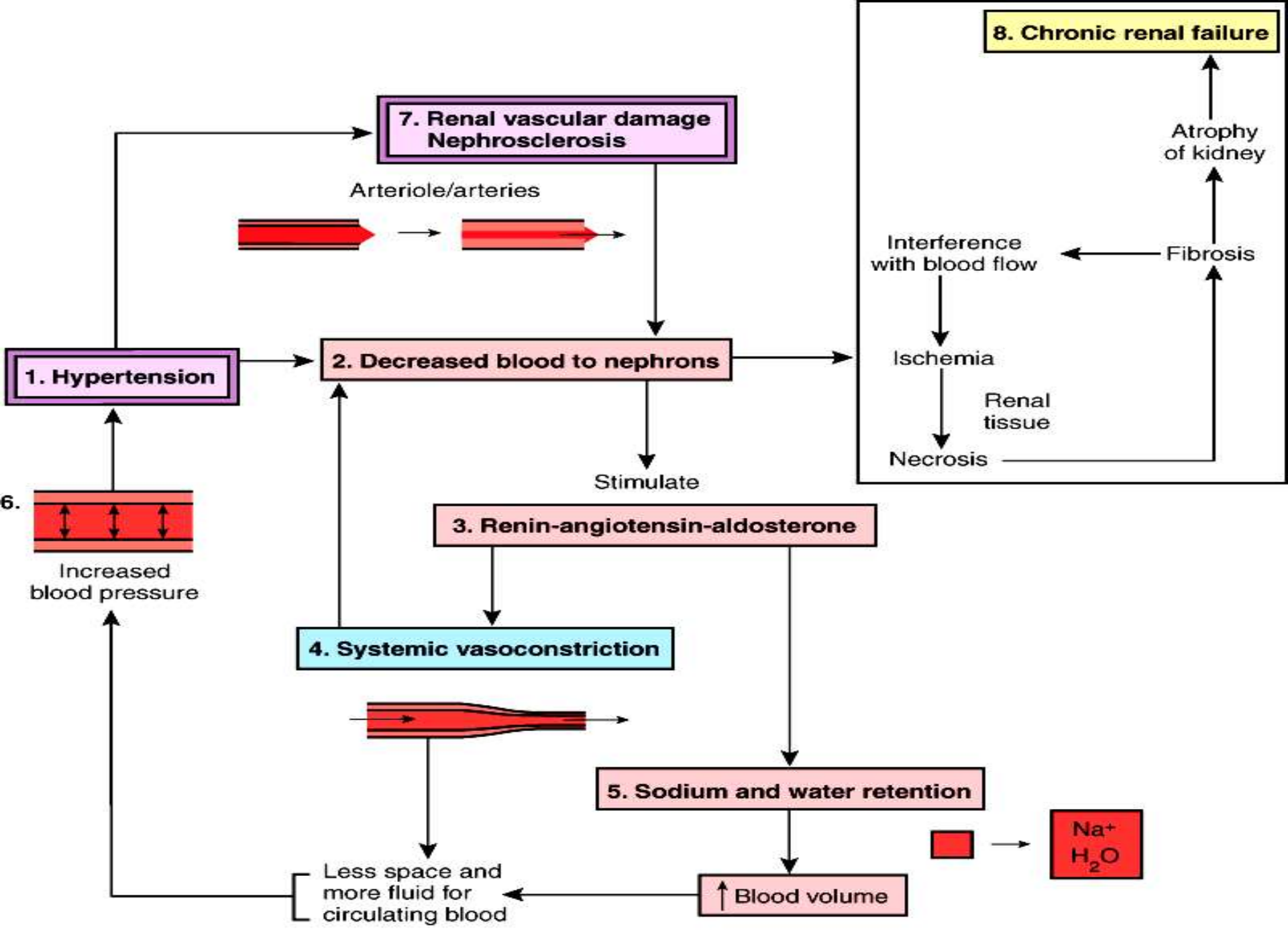
Renal Failure

- **Acute renal failure**
  - Abrupt decrease in renal function
    - Nitrogenous wastes accumulate
  - Usually reversible
  - Sx:
    - Oliguria
    - Drowsiness
    - Altered levels of consciousness
  - Etiol:
    - Glomerular disease
    - Severe pyelonephritis
    - Nephrotoxins that damages tubular epithelium
    - Ischemic causes
      - shock
    - ATN (acute tubular necrosis)
      - e.g. burns(hgb accumulates)
      - e.g. trauma (myoglobin accumulates)





- **Chronic Renal Failure**
  - Get slow progressive loss of nephrones
  - Usually irreversible
  - Course = gradual
  - Etiol:
    - Vascular disease
      - e.g. hypertension
      - Disease called nephrosclerosis
    - Glomerular disease
      - e.g. diabetes
    - Tubular disease
      - e.g. toxins


8. Chronic renal failure
Atrophy of kidney
7. Renal vascular damage Nephrosclerosis
Arteriole/arteries
Interference with blood flow
Fibrosis
1. Hypertension
2. Decreased blood to nephrons
Ischemia
Renal tissue
Necrosis
Stimulate
6.
3. Renin-angiotensin-aldosterone
Increased blood pressure
4. Systemic vasoconstriction
5. Sodium and water retention
Na+
H2O
Less space and more fluid for circulating blood
Blood volume