INTRODUCTION, TISSUE PROCESSING, MOLECULAR AND CLINICAL PATHOLOGY

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Pathology

pathology is the study (logoy) of suffering (patho).

Pathology: is the branch of medical science that studies the causes , nature and effects of diseases"

Disease: any abnormality in the **structure** and /or **function** of an organ or tissue.

Specialties of pathology

Histopathology .
 Hematology
 Clinical pathology
 Immunpathology
 Experimental pathology
 Molecular pathology

Biopsy: examination of tissue taken from living body (gross & microscopical examination).

Autopsy

Also known as a post-mortem examination.

Is a procedure that consists of a thorough examination of **C CCC body** to determine the cause and manner of death and to evaluate any disease or injury that may be present.

Types of biopsy

1) Incisional biopsy: a portion of tissue from a large lesion is taken-only diagnostic

2) Excisional biopsy: the entire lesion is removed with a margin of adjacent normal tissue-diagnostic & herapeutic.

3) Punch biopsy: by biopsy forceps in the uterus , cervix, oral cavity & esophagus.

4) Core needle biopsy: by wide bore needle used percutaneously for sampling of internal organs.

5) Curettage biopsy :

for diagnosis of internal diseases e.g. curettage of endometrium as diagnostic procedure.

Handling of biopsy:

Once a biopsy is taken, it should be put in plastic or metal container with adequate amount of fixative (10% formalin) which causes rapid denaturation of cellular proteins & prevents autolysis. It should be sent to the lab. with a request form including patient's name, age, sex, short clinical notes, type of biopsy, name of tissue submitted, findings of operation & provisional diagnosis.

Gross examination



General principles for gross examination:

- 1) Proper identification & orientation of the specimen.
- 2) Place the specimen on a cutting board & record all the following data
- Type of specimen
- Dimension (in centimeters)
- Weight
- Shape
- Consistency
- Surgical margins whether included or not involved by the tumor.

Histopathological techniques

Deals with tissue deals with preparation of tissue for histopathological examination, **the aim of these technique is to preserve microscopic anatomy of tissues** & to cut tissue in very thin sections(4-5 microns) this is achieved by passing tissue in a series of process. Tissue processing can be done manually or mechanically & includes the following processes

- 1) Fixation.
- 2) Dehydration.
- 3) Cleaning.
- 4) Embedding.
- 5) Cutting.
- 6) Staining.



1- Fixation

Most fixatives act by **denaturating or** precipitating cellular proteins which form meshwork that hold other structures & prevent autolysis.

The most widely used fixative is 10% formalin.

2- Dehydration

Is removal of water molecules from tissues and is achieved by graded alcohol.

3- Cleaning

Alcohol replace water in the tissues, removal of alcohol from tissues is by Xylene which creates empty tissue spaces to be infiltrated by wax.

4- Embedding with wax

Parafin Wax is used for embedding of tissue which form tissue blocks after cooling. It can be trimmed into thin sections (4-5microns) using the microtom the sections are placed on glass slides and become ready for staining.











5- Staining \ Hematoxylin
& Eosin (H&E) is the most widely used stain in histopathology
Nuclei appear dark blue.
Collage & cytoplasm appear pink.
Keratin appears pink to red.







Special stains

- 1) PAS (periodic acid schiff) stain for glycogen & mucin .
- 2) Congo-red for amyloid.
- 3) Sudan-black for fat.
- 4) Gimsa stain for Helicobacter pylori.

H. pylori stained dark blue with Gimsa stain

Cytology: is the study of normal & abnormal morphologic characteristics of **human Cells**.

e.g. fluid cytology , Pap smear from the uterine cervix , FNAC.

Frozen section

In this technique the tissue is frozen rapidly (Using

Cryostat) to -20°C ten sections are cut and stained (without passing in the steps of tissue processing) so that tissue can be examined microscopically within 5-10 minutes of removal from the body.

It allows rapid diagnosis of the nature of the lesion whether benign or malignant to decide the next step in surgery.

Molecular Pathology

Definition

- The study of biochemical and biophysical cellular mechanisms as the basic factors in disease.
- Use of nucleic acid based tests to determine diagnosis or prognosis
 - Includes hybridization (FISH), blotting and sequencing
 - Generally doesn't include protein assays or antibody detection (however some define it more broadly).
 - The field typically includes both molecules testing in tubes and slides (cytogenetics).





Diagnosis
Prognosis
Prenatal testing
Pharmacotherapy

What is clinical pathology?

Branch of pathology studying changes in chemical composition of the body fluids which help in diagnosis of a disease

Covers the use of laboratory aids to assess the health, detect a disease state

Referred to as laboratory medicine because it is a component of the investigative process that leads to the diagnosis and treatment of medical conditions

SPECIFIC OBJECTIVES OF CLINICAL PATHOLOGY

1.Disease diagnosis:

Especially when disease is at sub-clinical stage

e.g. Examples of tests include tuberculin test for TB and Rose Bengal test for brucellosis

2. Differential Diagnosis:

e.g., if patient has red urine, it may due to hematuria(intact red blood cells) or hemoglobinuria (lysed RBCs)

3.Determination of the drug effectiveness & toxicity:

4. Prognosis (outcome) of the disease:



Lect.2

CELL INJURY, CELLULAR ADAPTATION & CELL DEATH

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Cellular response to injury

•Acute cell injury

- Reversible injury
- Ireversible injury (Cell death) include:
- Necrosis
- Apoptosis
- Cellular adaptations
- Atrophy: decrease cell mass
- Hypertrophy: increase cell mass
- •Hyperplasia: increase numbers
- •Metaplasia: change from one mature cell type to another
- Intracellular accumulations: Ca, Lipofuscin, hemosiderin

Factors that determine fate of cells

Type of injury.
 Severity of injury.
 Duration of exposure.
 Type of cells.

According to capacity of cell to division it divided into

• High capacity (labile cell)

- Epidermis
- Gastrointestinal epithelium
- Respiratory epithelium
- Bone marrow

• Low capacity (stable cell)

- Hepatocytes
- Pancreas
- Kidney
- Smooth muscle
- Bone
- cartilage

Nil capacity (permanent cell) Neurons Cardiac muscle Skeletal muscle



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Acute Cell Injury

 Reversible cell injury: indicates that the cellular changes will regress and disappear when the injurious agent is removed; the cell will return to normal both morphologically and functionally

• Irreversible cell injury: occurs when the injury persist or when it is severe from the start. Here the cell reaches the point of no return and progression to cell death is inevitable.

Types of injurious agent for cell injury

1-Hypoxia

- Ischemia
- Cardiac & respiratory diseases
- Low O2 carrying capacity (anemia)

2-Physical injury (temp, radiation, electrical shock, trauma, change in atmospheric pressure)

- **3-Chemical agents & drugs**
- **4-Microbial agents** (virus, bacterial,etc)

5-Immunologic reactions (hypersensitivity reaction , anaphylactic shock & autoimmune diseases)

6-Genetic derangement (Down's syndrome & sickle cell anemia)

7-Nutritional imbalance (vitamin deficiency, protein deficiency, increase fat, alcoholism)

Mechanism of cell injury (pathogenesis)

The susceptible targets in cell

1-Cell membrane destructed by phospholipase which secreted for example by certain bacteria. Cell membrane damage play the Key factor in the pathogenesis of irreversible cell injury mediated by excessive influx of calcium into the cell.

2-ATP production lost by e.g., cyanide which inactivate cytochrome oxidase in mitochondria causing decrease ATP production

3-Protein synthesis4-Genetic apparatus

Free radical induced injury

FR are chemical species with unpaired electron in the outer shell

Source of free radicals

1-endogenous (leukocytes, macrophages & endothelial cells)

- 2-metabolites of drugs & chemicals
- 3-Absorption of radiant energy
- Types of free radicals
 - Superoxide, nitroxide, hydroxyl, hydrogen peroxide, carbontrichloride

Example of FR induced injury

- **Reperfusion** injury to a partially ischemic cells reperfusion cause release of FR from leukocytes
- Aging process decrease ability to handle FR
- O2 toxicity e.g., diffuse alveolar damage in lung
- Radiation
- Chemical & drug injury e.g., CCL3 cause severe injury in the liver

Chemical injury

There are 2 general classes of chemical injury

1- Direct interaction with cellular component e.g., mercuric chloride cause membrane damage by binding to sulfhydryl group of cell membrane

2-Indirect by converted in cell into toxic metabolite e.g., carbon tetrachloride change to carbon trichloride free radical result in either fatty change or lipid peroxidation

Microbial injury

1-Direct induced injury e.g., poliovirus cause direct destruction of cell membrane of the host cell by insertion of the virus to the cell membrane

2-Indirect induced injury e.g., hepatitis B virus cause destruction of cell membrane of the cell by stimulation of the immune system against the viral protein that exposed on the cell membrane

Morphological changes in irreversible cell injury By LM: Nuclear changes including:

- Pyknosis (nuclear shrinkage + increase basophilia of the nucleus)
- Karyorrhexis (fragmentation with nuclear dust)
- Karyolysis (nuclear loss)

Liver cell necrosis: Nuclear changes





normal

pyknosis

karyorrhexis





karyolysis

Necrosis:

Morphologic changes that follow cell death in the living tissue or organs due to **action of degradative enzymes or protein denaturation**

- **Mechanism of necrosis:**
- Denaturation of proteins
- Enzymatic digestion by
 Autolysis By lysosomal enzyme of the cell itself
 Heterolysis by surrounding inflammatory cells (Neutrophils & Monocytes)
- It is passive process
- Associated with inflammation
- Randomly occurs

Involve a group of cells

Always pathologic

• Causes : ischemia, chemical injury or infarction(cell death due to cut of blood supply), nutritional....etc

Types of necrosis:

- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Gangrenous necrosis (Gangrene)
- Fat necrosis
- Fibrinoid necrosis
- Gummatous necrosis (Gumma)

Coagulative necrosis

- The commonest type of necrosis
- Infarcts (ischemic necrosis) in all **solid organs** except the brain & spinal cord result in liquefactive necrosis

• Grossly:

• Whitish-gray or red-hemorrhagic firm wedge shape area of infarction

• Histology:

- Preservation of the tissue architecture & cellular outline for sometime with loss of internal details including nuclei
- Result from denaturation of all proteins including enzyme as a result of ischemia & acidosis

• Fate: after several days fragmentation & phagocytosis then healing.

Liquefactive necrosis

Early softening & liquefaction of the necrotic tissu

- Proteolytsis over protein denaturation
- Seen in
 - Ischemic necrosis of CNS
 - Abscess formation in pyogenic infection
- Gross
 - Soft liquid like
- Histology • Loss of original tissue .

Liquefactive necrosis- Brain infarction

Caseous necrosis

- Being soft & yellow white appears as cheese-like gross appearance
- Histology:
 - Tissue architecture is completely loss.
 - Appears as a brightly eosinophilic & amorphous structureless material
- Characteristic of tuberculosis(TB):
- Coagulative necrosis modified by capsule lip- polysaccharide of TB bacilli
- It could be seen in other lesions so it is not pathognomonic of TB.





Fat necrosis

1-Enzymatic fat necrosis:

- acute hemorrhagic pancreatitis cause activated **lipase** leading to adipose tissue destruction causing releasing of triglycerides & fatty acid
- Deposition of calcium ending in calcium soap

2-Traumatic fat necrosis:

- Trauma to the Dreast causing rupture of fat cells resulting in foreign body reaction
- Ending in fibrosis & calcification causing stony hard lump which is easily misdiagnosed by carcinoma of breast clinically.



Fibrinoid necrosis

Intense eosinophilic staining of involved (necrotic) tissue, like fibrin

• Example:

 Fibrinoid necrosis of blood vessels in malignant hypertension & vasculitis

 Fibrinoid necrosis of collagen tissue in connective tissue disease as in rheumatoid arthritis

Fibrinoid necrosis

is caused by immune-mediated vascular damage. It is marked by deposition of fibrin-like proteinaceous material in arterial walls, which appears eosinophilic or light microscopy.

Artery, fibrinoid necrosis

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Gangrene

It is coagulative necrosis plus putrefaction by saprophytes (anaerobic bacteria

- Either wet gangrene which has large amounts of fluid as in DM.
- Or dry gangrene drying & mummification of dead tissue, seen in distal parts of the lower limbs associated with peripheral vascular diseases (atherosclerosis, vasculitis). Necrosis is separated by a line of demarcation from viable tissue





• GANGRENE

It can be classified into two types according to the cause of the tissue necrosis:

- Primary gangrene
- Secondary gangrene

- PRIMARY GANGRENE

 It is brought by infection with pathogenic bacteria which both kill the tissue by secreting exotoxins & then invade & digest the dead tissue.

SECONDARY GANGRENE

 This type of gangrene is characterized by necrosis due to some other causes, usually loss of blood supply from vascular obstruction or tissue laceration & saprophytic bacteria then digest the dead tissue, there are two types :

Dry gangrene

•Wet gangrene

Gangrenous necrosis It is a form of a necrosis of the tissue with superadded putrefaction.

Dry gangrene -Ischemia

Wet gangrene – D.M

DRY GANGRENE

- Due to gradual cut of blood supply.
- The line of demarcation between dead and living tissue is clear.
- The lesion remains localized .

WET GANGRENE

- The infected tissue are edematous due to large amount of subcutaneous fluid.
- The demarcation between dead and living is indistinct.
- May extend proximally beyond the site of infective. Wet gangrene is seen in the bowel due to mesenteric vascular occlusion and in diabetic limb.

WET GANGRENE

- The infected tissue are edematous due to large amount of subcutaneous fluid.
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 Wet gangrene is seen in the bowel due to mesenteric vascular occlusion and in diabetic limb.

Fate of necrotic tissue

- Body treats necrotic tissue as a foreign materials
- It stimulates an inflammatory reaction that eventually removes the necrotic tissue & prepare the scene for the process of repair
- Repair process by
 - Regeneration
 - Organization
- These required proliferation, migration, differentiation of cells & production of extracellular matrix

Apoptosis (Programmed cell death)

 Death of single cell as a result of the activation of a genetically programmed (suicide) pathway through which the cell removed with minimal damage to the tissue containing them.

How the process of apoptosis is initiated?

• Different types of stimuli causing activation of caspases enzymes, which play the key role in the apoptosis, this activate cytoplasmic endonuclease, proteases & transglutaminase

Examples where apoptosis occurs include: <u>Pathological;</u>

- 1. Atrophy of the prostate after castration.
- 2. Virally infected cells attacked by cytotoxic T lymphocytes, as in acute viral hepatitis (Councilman body)
- 3. Neoplasia.
- 4. Radiation
- 5. Cytotoxic drugs
- 6. Some mature B & T lymphocytes cannot distinguish self from non self antigens, if that remain, will lead to destroy healthy body cells (autoimmune).

Virally infected cells attacked by cytotoxic T lymphocytes, as in acute viral hepatitis (Councilman body)



So, failure of cells to undergo apoptosis may result in **undesirable effects** that includes:

1-Anomalous development of various organs and tissues.

2-Progressive acceleration of tumor growth.

3-Autoimmune diseases e.g. SLE., rheumatoid arthritis.

DIFFERENCES BETWEEN APOPTOSIS & NECROSIS

Apoptosis

- Active process
- Occur in single cells
- Physiological & pathological
- No inflammatory reaction
- Step-ladder appearance on gelelectrophoresis for DNA material
- Programmed process
- Mechanism;
- Gene activation
- Caspases activation causing activation of activate cytoplasmic endonuclease, proteases & transglutaminase

Necrosis

- Passive process
- Affects mass of cells
- Always pathological
- Stimulate inflammation
- Smudge pattern appearance of DNA material on gelelectrophoresis
- Random process
- Mechanism;
 - ATP depletion
 - Cell membrane injury

DIFFERENCES BETWEEN APOPTOSIS & NECROSIS

Apoptosis

Necrosis

- Morphology:
 - Cell shrinkage
 - Nuclear condensation & fragmentation
 - Formation of apoptotic bodies
 - Apoptotic bodies engulf by macrophages

- Morphology
 - Cell swelling
 - Nuclear changes (pyknosis, karyorrhexis & karyolysis)
 - Eosinophilic cytoplasm
 - Necrotic area infiltrate & cleaned by inflammatory cells
Cellular adaptations

The adaptive responses include

1-Atrophy

2-Hypertrophy.

3-Hyperplasia.

4-Metaplasia.

Atrophy

refer to the decrease in the size the organ as a result of decrease in size of cells with loss of cell substances.

- Cells exhibit autophagy with increase in number of autophagic vacuoles & lipofuscin pigment
- causes: Pathological & physiological
- ► 1-Decrease in the workload
- 2-Denervation: e.g. paralysis of limb due to nerve injury or poliomyelitis.
- >3-Under nutrition as in starvation
- ► 4-Loss of endocrine stimulation e.g. atrophy of the gonads in hypopituitarism.
- ►5-Aging
- ► 6-Diminish blood supply

Hypertrophy. Refer to increase in the size of organ as a consequence of

Increase of cell size

- It can be physiological or pathological e.g.,
 - Uterus in pregnancy,
 - Skeletal mm. In athletes, or manual workers,



- left ventricular hypertrophy (pathological).
- Hepatocytes hypertrophy in barbiturate drug therapy
- Compensatory mechanism after nephrectomy

Hyperplasia:

Is refer to the increase in the size of the organ as a result of increase in the **number of cells**

- Cells that undergo hyperplasia are those capable of cell division (labile cells)
- Hyperplasia is divided into:
- Physiological: which is
 - either hormonal (proliferation of the breast glandular epithelium of female at puberty, or during pregnancy.
 - or compensatory (e.g. after partial hepatectomy).

• Pathological:

• Extensive hormonal stimulation (e.g. endometrial hyperplasia). Or effect of growth factors as in healing of wounds forming keloid (exaturated scar)

Metaplasia; this refer to replacement of one

mature cell type by an other mature cell type, which could be either epithelial or mesenchymal

• It is an adaptive reversible process

- It may represents an adaptation of cells more sensitive to stress by other that are more resistant to the adverse environment. E.g.
- Squamous metaplasia of the laryngeal and bronchial respiratory epithelium due to habitual smoking.
- Columnar metaplasia of esophageal sq. epithelium. as a result of prolonged reflux esophagitis.
- Squamous metaplasia of urothelium of the bladder due to bilharzias or stone.



Metaplasia of normal columnar (left) to squamous epithelium (right) in a bronchus

Pathological Calcification

This refer to abnormal deposition of calcium salt. there are two forms of calcification;

1- Dystrophic calcification:

- refer to deposition of calcium in non viable or dying tissues in the presence of normal serum level of calcium with normal calcium metabolism. E.g.,
 - Areas of necrosis (caseous, coagulative or fat necrosis)
 - Wall of artery in atherosclerosis
 - Disease of valve (aging or damage valve)
 - Dead parasites & their ova

DYSTROPHIC CALCIFICATION



Calcific aortic valvular stenosis



2-Metastatic calcification:

refer to deposition of calcium in viable tissue in the presence of high serum calcium level.

Causes of hypercalcaemia >Hyperparathyrodism Vitamin D intoxication Sarcodosis Metastatic cancer to the bone Some other non metastatic cancer ► Organ affected are: kidneys, stomach, lungs, pulmonary veins& systemic arteries

Metastatic Calcification Hypercalcemia - Lung



Fatty changes

- Is abnormal accumulation of fat of triglyceride type within parenchymal cells rather than adipocytes.
- It is an example of reversible cell injury,
- seen often in the liver in which fat centrally metabolized & to less extend in heart & kidney

Causes of fatty change

- Toxins including alcohol
- Starvation & protein malnutrition
- Diabetes mellitus
- Oxygen lack (anemia & ischemia)
- · Drugs & chemicals e.g., CCL4
- Obesity
- Complicated pregnancy
- Reye syndrome

Morphology of Fatty liver

- **Gross features** : In the liver mild fatty changes shows no changes, but with further accumulation the organ enlarges & become increasingly yellow, soft & greasy to touch.
- Microscopically : In the early stages there are small fat vacuoles around the nucleus (microvesicular steatosis). With progression the vacuoles fuse together creating large clear space that displaces the nucleus to the periphery (macrovesicular steatosis).



Fatty changes in hepatic steatosis

PIGMENTS

Exogenous which include carbon or coal dust, and these deposit are called anthracosis when accumulated in the pulmonary macrophages and lymph node

Endogenous i.g Melanin and Hemosiderin

Melanin are endogenous non-hemoglobin derived brown black pigment which is formed by enzymatic oxidation of tyrosine to dihydroxyphenylalanine in melanocytes (DOPA reaction)

HEMOSIDRIN:

- Is a hemoglobin-derived, golden-yellow to brown granules.
- Excess iron in the body causes hemosiderin to accumulate within the cell. Excess deposition is termed as hemosiderosis which is either localized or systemic.
- Special stain for iron is Prussian blue or Perl's stain

• Localized hemosiderosis: result from local hemorrhage e.g. bruise, cerebral hemorrhage.

H & E Stain

Special stain for iron is **Prussian blue or Perl's stain**







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DEFINITION:

- It is the reaction of a tissue & its microcirculation to a pathogenic insult. It is characterized by elaboration of inflammatory mediators and movement of fluid & leukocytes from the blood into extravascular tissues. •This response eliminates the cause of the injury (foreign particles, microorganisms, and antigens) & altered cells, and paves the way for

- Inflammation serves to destroy, dilute, or wall off the injurious stimuli & sets into motion series of events that try to heal & reconstitute the damaged tissue. Without inflammation, wounds and infections would never heal.
- Despite it's beneficial effects, inflammation may cause harm, especially if the reaction is very strong, prolonged, or inappropriate (directed against self-antigens)

TYPES OF INFLAMMATION:

- Acute inflammation:
- Chronic inflammation:
- Clinical signs of inflammation are 5:
- Rubor (Redness)
- Calor (Heat)
- Tumor (Swelling)
- Dolor (pain)
- loss of function





The cardinal signs of inflammation are 5. Seen here is skin with erythema, compared to the more normal skin at the far right.

This example of a fluid collection, a friction blister of the skin, is an almost trivial example of edema.



Here is marked redness and congestion in case of acute appendicitis



Acute inflammation

 Is a rapid response to injury or microscopes and other foreign substances that is designed to deliver leukocyte and plasma protein to site of injury.

Acute inflammation has two major components

- •A- Vascular change : ultration in vessels caliber resulting in increased blood flow "vasodilation" and structural change that permit plasama protein leave the circulation " increased vascular permeability"
- •B- Cellular events : a migration of leukocyte from the microcirculation and accumulate in focus of injury.
- •The principle leukocyte in acute inflammation are neutrophils

Triggers of Acute inflammation

- 1. Infection (bacterial viral fangus parasitic) "most common of inflammation.
- 2. Truma (physical and chemical agent with irradiation.
- 3. Tissue necrosis (Schemia)
- 4. Foreign bodies.
- 5. Immunreaction (hypersensitivity reaction and autoimmune disease.

Vascular Change of Acute inflammation

- •Acute inflammation has two major components a vascular response & a cellular reaction :
- VASCULAR RESPONSE:

Blood vessels (microcirculation) undergo series of changes including:

- Vasodilation
 - increased vascular permeability

1-VASODILATION:

•After transient vasoconstriction lasting for few second arteriolar vasodilation occur.

• Alterations in vessel caliber causing increased blood flow, resulting in heat & redness characteristically seen in acute inflammation.

•Mechanism: results from the action of several chemical mediators



2- Increased vascular permeability:

Structural changes in the microcirculation that permits the out flow of fluid &proteins into the interstitial tissue resulting in edema (swelling).



Fluid exchange occurs normally between intravascular and extravascular spaces, with the endothelium forming a permeability barrier.



Endothelial cells are connected to each other by tight junctions and separated from the tissue by a limiting basement membrane





Acute inflammation is marked by an increase in inflammatory cells. Perhaps the simplest indicator of acute inflammation is an increase in the white blood cell count in the peripheal blood, here marked by an increase in segmented neutrophils (PMN's).



Seen here is vasodilation with exudation that has led to an outpouring of fluid with fibrin into the alveolar spaces, along with PMN's.

-Several definitions are important for understanding the consequences of inflammation:

* Edema : it means accumulation of fluid within the extravascular compartment and interstitial tissue

Effusion : it is fluid collection into a body cavity. e.g plural effusion, pericardial effusion or ascites.

Transudate : it is edema fluid with low protein content (S.G < 1.015) it tends to occur with inflammatory condition

Exudate : it is edema fluid with high proiten content, (S.G > 1.015) which frequently contain inflammatory cell and oxidase are observed in acute inflammatory reaction.



Formation of transudates and exudates. **A**, Normal hydrostatic pressure (*blue arrows*) is about 32 mm Hg at the arterial end of a capillary bed and 12 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg (*green arrows*), which is equal to the mean capillary pressure. Therefore, the net flow of fluid across the vascular bed is almost nil. **B**, A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure. **C**, An exudate is formed in inflammation because vascular permeability increases as a result of increased interendothelial spaces.

ABSCESS:

A localized collection of pus, which usually develops following extensive tissue damage especially that caused by pyogenic bacteria as *staph aureus*.

PUS:

A thick yellow viscous fluid resulting from the liquefaction of tissue due to the action of lysosomal enzymes. It contains dead & dying neutrophils, necrotic tissue debris, microorganisms & fluid component of acute inflammation.



CELLULAR EVENTS OF ACUTE INFLAMMATION

LEUKOCYTE CELLULAR EVENTS:

- Immigration of leukocytes from microcirculation & accumulation at the site of injury. It is divided into the following steps:
 - 1. Margination
 - 2. Adhesion & rolling
 - 3. Transmigration (diapedsis)
 - 4. Chemotaxis:
 - 5. Activation, phagocytosis & degranulation:
- Margination: the process of leukocyte accumulation at the periphery of vessels.
- Adhesion to endothelium; rolling along the vessel wall; firm adhesion to the endothelium



The diagram shown here illustrates the process of exudation, aided by endothelial cell contraction and vasodilatation, which typically is most pronounced in venules



As stasis develops, leukocytes (principally neutrophils) begin to accumulate along the vascular endothelial surface, a process called *margination*. This is the first step in the journey of the leukocytes through the vascular wall into the interstitial tissue



- Both rolling & adhesion are mediated by binding of complementary adhesion molecules on leukocytes & endothelial surface like lock & key.
- Chemical mediators affect these processes by modulating surface expression of these adhesion molecules, example TNF, IL-1.



- Chemotaxis: (directional movement in interstitial tissues toward a chemotactic stimulus). After extravasation, neutrophils emigrate toward the site of injury. This movement is mediated and directed by chemical agents (chemotactic) which include exogenous factors (as bacterial products) and endogenous factors (as C5a, Lt-B4, IL-8).
- Such factors also cause leukocytes activation (production of arachidonic acid metabolites & release of lysosomal enzymes).

Phagocytosis: The ultimate effect of

- recruitment of PNL is to phagocytose
- microbes with subsequent killing.
- Phagocytosis is facilitated by host proteins
- called opsonins that coat microbes and
- target them for phagocytosis (a process
- Kickinedapsohization, tieg IgGreictsbes:
- Such killing is achieved by 2 factors:
 - Generation of free radicals (reactive O2
 - species- oxidative burst and reactive
 - nitrogen species) and lysosomal enzyme

CHEMICAL MEDIATORS OF ACUTE INFLAMMATION:

These are chemical substances that play vital roles in the inflammatory process.
Many mediators are known, and this knowledge has been used to design a large armamentarium of anti-inflammatory drugs.

-Sources of mediators:

* Cell derived mediators: produced locally by cells at the site of inflammation.

Circulating in the plasma (typically synthesized by the liver) as inactive precursors that are activated during inflammation.

-Cell-derived mediators are normally sequestered in intracellular granules and are rapidly secreted upon cellular activation (e.g., histamine in mast cells) or are synthesized de novo in response to a stimulus (e.g., prostaglandins and cytokines)

SOURCES OF CHEMICAL MEDIATORS:



) -

-EFFECTS OF CHEMICAL MEDIATORS:

☐ Production of chemical mediators is triggered by microbial products & damaged tissues.

☐ Chemical mediators perform their function by binding to a specific receptors on the target cells.

□ One mediator can stimulate the release of other mediator from the target cell (2ry).

☐ Mediators can act on one or few target cells, & may have different effects on different types of cells.

□ The action of chemical mediators is firmly controlled, once they perform their function they decay quickly or rapidly inactivated.

Major Cell-derived Mediators

- **Vasoactive amines:** histamine, serotonin; main effects are vasodilation and increased vascular permeability
- Arachidonic acid metabolites: prostaglandins and

leukotrienes; several forms, involved in vascular reactions, leukocyte chemotaxis, and other reactions

- **Cytokines:** proteins produced by many cell types; mediate multiple effects, mainly in leukocyte recruitment and migration; e.g TNF, IL-1, and chemokines
- Reactive oxygen species: role in microbial killing, tissue injury
- Nitric oxide: vasodilation, microbial killing

• Lysosomal enzymes: role in microbial killing, tissue injury

• Otherst as DAE

-BENEFICIAL EFFECTS OF ACUTE INFLAMMATORY EXUDATE:

-Beside elimination of injurious stimuli & participation in the removal of necrotic tissues, inflammatory exudate is protective through:

- Dilution of toxins:
- Protective antibodies:
- Fibrin formation:
- Plasma mediator system:
- Cell nutrition:
- Promotion of immunity:

OUTCOMES OF ACUTE INFLAMMATION

The outcome may be:

- **Complete resolution:**
- ***** Scarring & fibrosis:
- ***** Abscess formation:

Progression to chronic inflammation:

MORPHOLOGICAL FEATURES IN ACUTE INFLAMMATION:

Depending on the type & severity of the injury & on the type of tissue affected, we can have the following types:

1 - Mild acute (catarrhal) inflammation:

* Characteristic for mild infection of the mucous membrane (as viral upper respiratory tract infection).

- * Hotness, redness and swelling.
- * Complete resolution.

<u>2</u>- Serous inflammation:

* Excessive accumulation of protein-poor fluid resulting in blister formation.

* As in burn and viral infection of skin.

3-Fibrinous inflammation:

* Characteristic of more severe injury (greater vascular permeability with exudation of large amount of fibrinogen.

* The outcome either: Complete resolution or organization (deposition of fibrin followed by ingrowth of new capillary & fibroblast ending in fibrosis.

* Common in inflammation of serosal membranes & joints.

4-Suppurative (purulent) inflammation:

* Characteristic by accumulation of large amount of pus with abscess formation.

* Certain bacterial infection.

5-Acute ulceration:

* When infection is severe & affecting surface epithelium, it causes loss of part of the epithelium.

6-Pseudomembranous inflammation:

* Necrotizing infection of surface epithelium of the colon caused by certain bacteria *(clostridium difficile)*.

Collection of fluid in a space is a transudate. If this fluid is protein-rich or has many cells then it becomes an exudate. The large amount of fibrin in such fluid can form a fibrinous exudate on body cavity surfaces. Here, the pericardial cavity has been opened to reveal a fibrinous pericarditis with strands of stringy pale fibrin between visceral and parietal pericardium.





Here is an example of bilateral pleural effusions. Note that the fluid appears reddish, because there has been hemorrhage into the effusion. This is a serosanguinous effusion.



The abdominal cavity is opened at autopsy here to reveal an extensive purulent peritonitis that resulted from rupture of the colon. A thick yellow exudate coats the peritoneal surfaces. A paracentesis yielded fluid with the properties of an exudate: high protein content with many cells (mostly PMN's).



The abdominal cavity is opened at autopsy here to reveal an extensive purulent peritonitis that resulted from rupture of the colon. A thick yellow exudate coats the peritoneal surfaces. A paracentesis yielded fluid with the properties of an exudate: high protein content with many cells (mostly PMN's).

Systemic Manistifesticaiton of inflammation

- Local injury may result in prominent systemic effects that can themselves be debilitating.
 - •e.g : systemic effect are likely to results when a pathogen enters the blood stream, a condition known as **sepsis**.
 - the systemic symptoms associate with inflammation include fever, myalgia, arthralgia, anorexia which are attributable to cytokines.
 - Fever and leukocytosis are clinical and laboratory Hallmark of inflammation

CHRONIC INFLAMMATION

Dr. Abdelkarim Y. Altaie Associate Professor on Pathology Al-Noor University College 2022-2023 Lecture 4

CHRONIC INFLAMMATION

Definition:

Inflammation of prolonged duration in which active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously.

Causes of Chronic inflammation It results from:

- 1. Persistent infection by microbes that are difficult to eradicate . e.g:
 - mycobacteria bacilli 🔶 T.B
 - •T-pallidum Syphilis
 - Certain virus and fungi
 - 2. Prolonged exposure to potentially toxic agent e.g:

□ Inhalation of silica particles → silicosis

3. Under certain condition immunoreaction develop against

the individual own tissue _____toimmune diseases like SLE , RA

Characters of Chronic inflammation

- In contrast to acute inflammation, which is distinguished by vascular changes, edema, and a predominantly neutrophilic infiltrate, chronic inflammation is characterized by:
- •Infiltration with mononuclear cells, including; macrophage, lymphocyte, plasma cell.
- •Tissue distraction induced by products of inflammatory cell.
- •Repair involving new vessels proliferation (angiogenesis) granulation tissue and fibrosis.



-Here is chronic cervicitis. Prolonged acute inflammation or repeated bouts of acute inflammation may lead to the appearance of more mononuclear cells, and chronic inflammation. In this case the inflammation is severe enough to produce mucosal damage with hemorrhage.



-Chronic inflammation is more difficult to understand, because it is so variable. Seen here is chronic endometritis with lymphocytes as well as plasma cells in the endometrial stroma. In general, the inflammatory infiltrate of chronic inflammation consists mainly of mononuclear cells ("round cells"): lymphocytes, plasma cells, and macrophages.



-Certain etiologic agents such as viruses are more likely to lead to chronic inflammation, as seen here in the lung of a patient with influenza A. Note also that the inflammatory infiltrates of chronic inflammation are more likely to be interstitial (mainly lymphocyte) rather than exudative (above surfaces or in spaces) like acute inflammation.



-Chronic inflammation with destruction of the bronchial wall is seen here. An inflammatory infiltrate extends from the lumen to the left.



-Sometimes the inflammatory reaction is mainly one of scarring, as seen here with a silicotic nodule of the lung. The inhaled silica persists indefinitely and produces an inflammatory reaction that is marked by prominent fibrosis. Dense pink collagen is seen in the center of the nodule.

Chronic Inflammatory Cells and Mediators

macrophage

- Lymphocyte
- Eosinophil
- mast cell

Role of macrophages:

□ Monocytes emigrate into the extravascular space (by expression of specific adhesion molecules & secretion of specific chemotactic factors).

Differentiate into larger macrophages:

Then macrophages activated by cytokines (interferon $\gamma - type$), such activated macrophages secrete a variety of active products (chemical mediators) which result in:

- Tissue injury and Fibrosis

Lymphocytes : are mobilized to the setting of any specific

immune stimulus (i.e., infections) Both **T** and **B lymphocytes** migrate into inflammatory sites using some of the same adhesion molecule pairs and chemokines that recruit other leukocytes. Lymphocytes and macrophages interact in a bidirectional way, and these interactions play an important role in chronic inflammation. Macrophages display antigens to T cells that stimulate them . Activated T lymphocytes, in turn, produce cytokines, and one of these, IFN-y, is a powerful activator of macrophages

Eosinophils

are characteristically found in inflammatory sites around parasitic infections or as part of immune reactions mediated IgE, typically associated with allergies. by Their recruitment is driven by adhesion molecules similar to those used by neutrophils, and by Eosinophil granules contain major basic protein, a highly charged cationic protein that is toxic to parasites but also causes epithelial cell necrosis.

Mast cells

- Widely distributed in connective tissues throughout the body, and they can participate in both **acute** and **chronic inflammatory** responses. In atopic individuals (individuals prone to allergic reactions), mast cells are "armed" with IgE antibody specific for certain environmental antigens.
- When these antigens are subsequently encountered, the IgE-coated mast cells are triggered to release histamines that elicit the early vascular changes of acute inflammation. IgE-armed mast cells are central players in allergic reactions, including anaphylactic shock.
- Mast cells can also elaborate cytokines such as TNF and chemokines and may play a beneficial role in some infections.

Mediators of chronic inflammation

Agent Action Source Migration inhibition factor (MIF)

Aggregation of macrophages at site of injury

urce Activated T lymphocytes

Macrophage activating factor (MAF)

Increased phagocytosis by macrophages Activated T lymphocytes

> Complement C5a Chemotatic for macrophages Complement system

Eosinophil chemotactic factor of anaphylaxis (ECF A)

Chemotactic for eosinophils in parasite infection Mast cells and basophils


Definition:

A distinctive pattern of chronic inflammatory reaction that characterized by formation of granuloma which is an aggregate of modified macrophages having a characteristic epithelial-like appearance (so called epithelioid histiocytes).

Types of granulomatous inflammation?

Granulomatous inflammation is important to be recognized

because it is encountered in a few pathological conditions as in:

Infections : TB, syphilis, brucellosis

Reaction to poorly digestible materials as inorganic
 metals, irritant lipids and some foreign materials

Unknown immune disorder as sarcoidosis.

Granuloma:

It is a focal area of granulomatous inflammation. It consists of a microscopic aggregation of epithelioid macrophages surrounded by a collar of lymphocytes & externally bounded by fibroblasts. Frequently several epithelioid macrophages fuse together to form a large multinucleated cells called giant cell. The central part of granuloma may exhibits necrosis.

-Grossly, a granuloma tends to be a focal lesion. Seen here in a hilar lymph node is a granuloma. Granulomas due to infectious agents such as mycobacteria are often described as "caseating" when they have prominent caseous necrosis.





-Giant cells are a "committee" of epithelioid macrophages. Seen here are two Langerhans type giant cells in which the nuclei are lined up around the periphery of the cell. Additional pink epithelioid macrophages compose most of the rest of the granuloma.



-The focal nature of granulomatous inflammation is demonstrated in this microscopic section of lung in which there are scattered granulomas in the parenchyma. A biopsy could miss such lesions from sampling error, too.



-Here is a foreign body type giant cell at the upper left of center adjacent to a segment of vegetable material aspirated into the lung. Such foreign body giant cells have nuclei scattered haphazardly about the cell



-Two foreign body giant cells are seen just to the right of center where there is a bluish strand of suture material from a previous operation.

INFECTION (1)

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OBJECTIVE

- We study Infections because it is an important health problem and one the leading cause of death (2 out of top 10 causes).
- 2. To study these diseases in a scientific way i.e to know the types, etiology, pathogenesis , gross & microscopic appearance of each disease so that you can understand the signs & symptom , and to plan therapy and prevention.

WHAT IS INFECTION ?

- Infection is defined as the invasion of living tissue by m.o. or its products(toxins) followed by local reaction which may be associated with general reaction.
- •Numerous microorganisms can infect human body some are present normally & harmless called commensals, others cause diseases called pathogens

BASIS OF CLASSIFICATION OF INFECTIONS

• Infections are classified in multiple ways. They are classified by the causative agent as well as by the constellation of symptoms and medical signs that are produced.

Types of Infectious Agents

- Viral and small prion protein PPr. infection .
- Bacterial infection
- Fungal infection
- Parasitic
- Protozoan

Route of Transmission

It involves

- Direct contact
- Respiratory droplet
- Faeco-oral route
- Blood born contact
- Sexual transmission
- Vertical transmission (Mother Fetus)
- Insect/ Arthropod vector

Strategies of microorganism to evade immune response

- Remaining inaccessible to host defense .
- Constantly changing antigen repertories.
- Inactivating a.b or complement, resisting phagocytosis.
- Suppressing the host adaptive immune response by inhabiting MHC expression and antigen presentation.

- Pathogenicity and Virulence
- Pathogenicity
- The ability of a microbe to cause disease This term is often used to describe or compare species
- Virulence: degree of pathogenicity of specific microbe
 - Based on:
 - Invasive qualities
 - Toxic qualities
 - Presence of pili or fimbriae for adherent.
 - Ability to avoid host defence .

Acute infection vs. chronic infection -

- Acute Infection
- An infection characterized by sudden onset, rapid progression, and often with severe symptoms
- Chronic Infection
- An infection characterized by delayed onset and slow progression

Primary infection vs. Secondary infection Primary Infection

An infection that develops in an otherwise healthy individual Secondary Infection

An infection that develops in an individual who is already infected with a different pathogen.

Localized infection vs. systemic infection

• Localized Infection

• An infection that is restricted to a specific location or region within the body of the host

• Systemic Infection

• An infection that has spread to several regions or areas in the body of the host

Clinical infection vs. subclinical infection

- Clinical Infection
- An infection with obvious observable or detectable symptoms
- Subclinical Infection
- An infection with few or no obvious symptoms

Opportunistic infection

- An infection caused by microorganisms that are commonly found in the host's environment
- This term is often used to refer to infections caused by organisms in the normal flora
- The suffix "-itis"
- A suffix meaning "inflammation of"
- Examples:
 - Pharyngitis = Inflammation of the pharynx
 - Endocarditis = Inflammation of the heart chambers
 - Gastroenteritis = Inflammation of the gastrointestinal tract



- Reservoir of Infection
 - •The source of an infectious agent .
- •Carrier
 - •An individual who carries an infectious agent without manifesting symptoms, yet who can transmit the agent to another individual.

DEVELOPMENT OF INFECTION: CLINICAL SIGNS AND SYMPTOMS

• Local signs

- Inflammation
- Purulent exudate if bacterial infection; serous exudate if viral
- Tissue necrosis
- Lymphadenopathy
- Respiratory effects

-Systemic signs

- Fever, fatigue, headache, nausea

FACTORS INFLUENCING THE INFECTION:

I- Micro-organism factors

I. Access: entry of m.o to the body cells & tissues, most m.o. enter via inhalation, ingestion, sexual .parentral.

- 2. Dose & virulence: number of m.o entering the body & their capacity to cause diseases.
- **3. Invasiveness:** ability of m.o to multiply & spread in the body through the use of endotoxin & exotoxin
- 4. Transmission: ability of m.o to pass to another suitable host.

2-HOST FACTORS:

- I. Mechanical barriers: Intact skin, keratin, mucous membrane & their secretary products .
- 2. Physical Forces: movement of cilia, mucus, flow of urine & saliva.
- 3. Chemical: Acidic pH in the stomach which are lethal for many GIT pathogens.
- 4. Phagocytosis: by macrophages & neutrophils.
- 5. Immune response: by cell-mediated & humeral immunity.
- 6. Local factors: e.g. ischemia & foreign body promote infection.
- 7. Systemic factors: e.g., malnutrition, diabetes mellitus, chronic alcoholism & malignancy.

8. Age: both very young & very old have increasing risk of infection.9. Drug .

RESULTS OF INFECTION:

- **1. Eradication:** most infections end by total eradication at the site of entry.
- **2. Persistence of infection:** either in form of carrier state or mild chronic forms e.g. typhoid fever, hepatitis infection.
- 3. Spread: to other parts of the body.e.g. Direct spread as in cellulitis,
- lymphatic spread as in lymphangitis & lymphadenitis, blood spread as in
- bacteremia, septicaemia & pyaemia.
- 4. Host death: in severe infection e.g. tetanus & diphtheria.

HOW DO INFECTIONS SPREAD INSIDE THE BODYP

I - Local spread: by the action of lytic enzyme.e.g Streptococci secrete hyaluronidase enzyme which degrades the extra cellular matrix between host cells.

2-Lymphatic spread: to the Lymph nodes.

3-Hematogenous spread: causing:

- Bacteremia: Presence of m.o in the blood.
- Septicemia: actively multiplying m.o in the blood.

4-Through body fluids: e.g., sexual transmitted disease

(gonococcus).

5-Through excretions: e.g., from kidney to lower urinary tract.

6-Through nerves ; e.g. rabies virus, varicella zoster virus.

7-Through placental- fetal route.

Patterns of Inflammatory Response to Infection

- I-Suppurative inflammation characterized by production of pus .
- 2-Mononuclear & Granulomatous characterized by interstitial inflammation & formation of granuloma
- 3-Cytopathic- Cytoproliferative inflammation. These reactions are usually produced by viruses.
- 4-Necrotizing inflammation caused by powerful toxins e.g. Cl. Perfringens lead to gangrene .
- 5-Chronic inflammation & scarring, is the final common pathway of many infections, e.g.
 HBV lead to cirrhosis, Schistosomal eggs lead to fibrosis of U.B. wall.

SPECIAL TECHNIQUES FOR DIAGNOSIS OF INFECTION

- H&E stain e.g CMV inclusion bodies *Candida*
- Gram stain e.g Most bacteria
- Acid fast for T.B.
- PAS e.g fungi and Amoebae
- Silver stain e.g fungi and pneumocystis
- Culture e.g all classes
- Molecular diagnostic tests e.g. PCR , for Viruses , bacteria and protozoa

HOW MICRO-ORGANISMS CAUSE DISEASE

Infectious agents damage tissues by.

- Entering cells and directly causing cell death
- Releasing toxins that kill cells at a distance
- Releasing enzymes that degrade tissue components or damage blood vessels
- Inducing host inflammatory cell responses that may directly contribute to tissue damage, including suppuration, scaring, hypersensitivity reactions

VIRAL INFECTION

- Viruses are relatively simple, small, obligatory intracellular parasite which replicates within host cells.
- Viruses are classified by their nucleic acid genomes into
- DNA viruses
- RNA viruses .
 - Viral infection can be transient (e.g mumps)
 - Chronic latent e.g Varicella-zoster virus
 - Chronic productive e.g HBV.
 - Virus can promote cellular transformation and malignancy e.g EBV, HBV and human T-cell lymphotropic viruses (HTLV-1)

MECHANISM OF VIRAL INJURY

Viruses kills the host cells by

- Inhibiting host DNA, RNA, or protein synthesis (poliovirus)
- Damaging the plasma membrane (HIV)
- Lysing cell (rhinoviruses and influenza viruses)
- Inducing the host immune response to virus infected cells (HBV) Routs of infection
 - Inhalation ;e.g influenza viruses
 - Ingestion : polio viruses
 - Parentral : AIDs
 - Transplacental .many types
 - Following infection the virus is transmitted by blood, cells, along nerves and become localized in certain tissue which it prefer (tropism) e.g. polio, rabies etc.

MICROSCOPICAL PICTURE OF VIRAL INFECTION

- Mononuclear infiltration
- Tissue necrosis
- Giant cell formation
- Inclusion body formation.(Intranuclear or intracytoplasmic)
- . Viral particles aggregate within the cells they infect & form

characteristic (Inclusion bodies)

. nuclear inclusion surrounded by a clear halo as in Herpes virus

cytoplasmic inclusions as in small pox and rabies virus

. Many viruses do not give rise to inclusions e.g. EBV.

THIS IS CYTOMEGALOVIRUS (CMV) INFECTION IN THE LUNG. NOTE THE VERY LARGE CELLS THAT HAVE LARGE VIOLET INTRANUCLEAR INCLUSIONS WITH A SMALL CLEAR HALO. BASOPHILIC STIPPLING CAN BE SEEN IN THE CYTOPLASM.



Body response to viral infection

- Lymphocytosis
- Production of interferon
- Production of neutralizing antibody
- Cell mediated immunity plays a role in controlling viral infection

BACTERIAL INFECTIONS

Classification of Bacteria

Bacteria are classified on several criteria:

- •Gram stain: bacteria are either gram (-) or gram(+)
- Shape: bacteria are classified as cocci, bacilli (rods), vibrios, spirochetes.
- •Growth requirements: bacteria are classified as:
- Aerobic
- Anaerobic

MECHANISM OF BACTERIAL INJURY (PATHOGENESIS) (HOW BACTERIA PRODUCE DISEASE)

- 1- Release toxins that kill cells.(exotoxin&Endotoxin)
- 2- Release lytic enzymes,
- includes proteases, hyaluronidase, coagulase & fibrinolysins that destroy the tissue & facilitate the spread of bacteria
- **3- Elicit an inflammatory reaction that may destroy not only the bacteria but also the infected tissue.**
- 4-Elicit an immune reaction that may damage the tissues carrying the same antigen as the bacterium ("cross reactivity").

MECHANISM BACTERIAL INJURY

- Bacterial damage depends on the ability of the bacteria to :
- Adhere to host cells
- Invade cells and tissues
- Deliver toxin

Endotoxin (lipopolysaccharide) is a cell wall component of gram negative Bactria

it causes septic shock by inducing high levels of TNF , IL1 and IL12 $\,$

Exotoxin are proteins released by bacteria that damage host tissue by several mechanisms:-

- Extra cellular enzymes destroy tissue integrity by digesting structural protein example staph aureus toxin
- Exotoxin can have a binding component that delivers a toxic active component into the cell cytoplasm where alters signaling pathways to cross cell death example
 B. anthracis toxins

BACTERIAL INFECTION IS DIVIDED INTO:

- 1- Acute.
- 2- Chronic.
- Acute Bacterial Infection
- **1.** Catarrhal .affect mucus membrane,e,g Bacillary dysentry.
- 2. Pseudomembranous. Characterized by formation of Pseudomembrane as in diphtheria.
- **3.** Serous . Affect serous cavities and produce serous fluid
- 4. Pyogenic or suppurative .Pus producing . e.g. Abscess

Characterized by production of pus

- Pus is a creamy fluid consist of neutrophil, pus cell (Dead neutrophil) necrotic tissue, bact, & fluid.
- Collection of pus in tissue is called abscess
- M.O stimulate t-lymphocytes to secrete IL I &TNF which stimulate complement, This attract neutrophil which secrete lytic enzyme, destroy tissue & form abscess

Localization of pus leads to abscess formation which appear here as red congested Swelling at the side of the neck





FIGURE 8–7 Pneumococcal pneumonia. Note the intra-alveolar polymorphonuclear exudate and intact alveolar septa.
This is an example of pseudo membranous infection



Pseudo membranous colitis



I - Bacterial infection of the blood

* Classified into:

-Bacteraemia

-Septicaemia

-Pyaemia

-Toxaemia : presence of toxin in blood e.g. D

Diphtheria.



- * Presence of small numbers of bacteria in the blood without multiplication.
- * Patients have subclinical or minor symptoms & lesion.
- * E.g., Strept. viridans in blood after vigorous brushing of teeth with dental sepsis.
- In typhoid fever ,pneumococcal pneumonia,E.coli infection of urinary tract & brucellosis.
- * These bacteria are destroyed rapidly in blood because of antibodies, complement, & circulating macrophages.
- * It is important because it may settle in various parts of the body & cause localized lesion e.g., endocarditis by Strep. Viridans.

SEPTICAEMIA

- *Multiplication of bacteria in the blood of highly pathogenic bacteria e.g., pyogenic cocci, endotoxin producing gram –ve bacilli.
- * Serious infection with profound toxemia in which bacteria have overwhelmed the host defenses.

* It results in serious consequences which may end in death.
Multiple small hemorrhages due to capillary endothelial damage multiple minute metastatic foci of bacterial growth.
Tachycardia. Hypotension. Splenomegaly.shock

PYAEMIA (PUS IN THE BLOOD)

- * Bacteria invade & multiply in a thrombus which then becomes heavily infiltrated by neutrophils & broken down by their digestive enzymes
- * Small fragments of the soften septic thrombus may then break away & be carried off in the blood
- * Results in the developing of pyaemic abscesses in various organs:

Pyaemia (cont)

- 1-In venous circulation as in deep vein thombosis of legs resulting in pyaemic abscesses in lung.
- 2-In arterial circulation as in infective endocarditis resulting in pyaemic abscesses in systemic arterial distribution.
- 3-In portal venous tributary as in acute appendicitis results in portal pyaemia with multiple liver abscess.
- Pyaemic abscess consist of:
- Central zone of necrosis with huge numbers of bacteria surrounded by zone of acutely inflamed hemorrhagic tissue.

Resulting in multiple & wide spread abscesses.

Infection (2)

Dr. Abdulkareem Y. Altaee Associate Professor of Pathology lect 6

> Al Noor University College 2022-2023

Chronic Bacterial infection

Tuberculosis

- Caused by Mycobacterium tuberculosis & Mmycobacterium bovis.Gm +ve bacilli .
- T.B bacilli have a waxy cell wall (mycolic acid) which make them acid and alcohol fast.
- ► It is the single most important infectious cause of death on earth after HIV.
- Poverty , malnutrition, chronic diseases, immunosuppression, over crowding are predisposing factors for T.B Transmission
- (1) Respiratory tract by inhalation ,from open TB lesion.
- (2) Alimentary tract by ingestion of infected milk ,food.
- (3) Skin by inoculation.
- (4) Congenital infection followed by intrauterine through placenta

Pathogenesis of Tuberculosis

- T.B. bacilli produce no exotoxin or endotoxin. The main lesion is due to cell mediated immunity.
- Cell mediated immunity confers resistance to mycobacteria and at the same time result in development of hypersensitivity to mycobacterial antigen which is responsible for granuloma formation and caseation
- Macrophages are the first cells infected by mycobacteria
- T.B. bacilli proliferate inside the macrophage.
- Spread of T.B. bacilli i.e. bacteremia
- In 3 weeks time specifically primed T-lymphocytes T-helper cell are produced in response to tuberculoprotein (through IL-12)
- T-helper cells produce INF-y
- INF-y is the critical mediator that enable the macrophage to control mycobacterial infection.

Pathogenesis of T.B cont.

- INF-y help macrophage to destroy T.B.bacilli by:
 - . formation of phagolyzosome
 - Formation of nitric oxide.
- INF-y also orchestrates formation of the granuloma & caseous necrosis.
- INF-y activate macrophages to form epitheloid cells, some unite to form giant cells resulting in the characteristic picture of T.B. lesion.
- Activated macrophages secrete TNF which attract more monocytes.
- The infection may be terminated at this stage or it may progress in immunosuppressed patients leading to caseous necrosis.

Tissue reaction

- *So the final lesion of TB consist of central area of amorphous, a cellular caseous necrosis, surrounded by macrophages, referred to as epithelioid cells, some macrophages fuse to from multinucleated giant cells, the nuclei of which may be distributed peripherally (Langhans giant cells) these are surrounded by rim of chronic inflammatory cells rich in lymphocytes & at the periphery there is fibrosis.
- It usually affects the lungs but may involve any organ or tissue in the body.



Granuloma of T.B

Spread

Organisms may spread from the site of entry in the usual ways:

- Locally: into adjacent tissues
- lymphatic to regional lymph nodes
- Natural passages e.g. (respiratory, alimentary, urinary & genital tract.)
- Blood veins & arteries) to produce either:
- 1- Miliary tuberculosis with multiple tubercles in numerous organs & tissues.
- 2- Isolated metastatic organ lesions e.g., in kidney, bone, vertebra, joint &epididymis.



FIGURE 8–33 Miliary tuberculosis of the spleen. The cut surface shows numerous gray-white granulomas.

Immunology

- The Lesion of T.B is mainly due to the delayed hypersensitivity reaction type IV to an antigenic protein component of the organism
- This immunity provide the basis for skin test of T.B
- Immunity to T.B. can be induced artificially by intra dermal injection of attenuated mycobacterial strains of bovine type (e.g. BCG vaccine).

Primary tuberculosis

- * It follows initial exposure to TB bacilli in non immunized individuals of any age.
- * Macroscopical: it forms a small sub pleural parenchymal lesion in the mid zone of the lung (Ghon focus) and spread to the hilar lymph nodes. Both lesions are called Primary complex
- * Microscopical: consist of epitheloid granuloma with central caseous necrosis.

*Most of the cases (95%) after treatment heal by fibrosis some may enter into dormant state &few may spread into the body forming progressive primary T.B.

Ghon focus of primary T.B.



Secondary T.B.

- * Either occurs as a reinfection by mycobacterium tuberculous or reactivation of primary infection when there is impairment in the immunity of the patient.
- * Macroscopical: usually occurs at the apex of the lung with minimal lymph node involvement. There is marked damage in the lung parenchyma with cavity formation
- * Microscopical: epitheloid granulomatous with central caseous necrosis & cavity.
- * Healing by fibrosis or may spread forming progressive secondary T.B.

Cavitations of secondary T.B



Clinical Features

- Fever
- Weight loss
- Night sweating
- Cough
- Heamoptysis
- ► I- History.
- II- Clinical Examination.
- III- Investigation include : X- ray, detection of the m.o in the specimen (sputum. urine, in biopsy) by the use of Ziehl-Neelsen staining ,culture or guinea pig inoculation.

Diagnosis

- Biopsy of the infected tissue.
- PCR amplification of T.B. bacilli DNA allows for even more rapid diagnosis.
- * Positive skin test (Mantoux) indicates hypersensitivity to tuberculoprotein but not an active disease.

This is an acid fast stain of Mycobacterium tuberculosis (MTB). Note the red rods--hence the terminology for MTB in histological sections or smears: acid fast bacilli.



Actinomycosis

- * Caused by Actinomyces israellii
- * Virtually anaerobic, gram-positive, long filamentous bacteria.
- * Closely related to mycobacteria with some similarity to fungi.
- It can be found as a commensal m.o. in the mouth , G.I.T., female genital tract

1- Cervicofacial lesion (70%).

2- Abdomial lesion (around iliocecal region or appendix) (15%).

- 3- Pulmonary lesion (10%).
- 4-Subcutaneous lesion (5%).
- **5-** Gynecological infection in female with IUCD

Pathology:

- Infection produces firm masses containing numerous abscesses (honeycomb abscesses) bearing colonies as yellowish granules (sulfur granules) with sinuses & fistulae.
- Chronic granulomatous inflammation with suppuration, bacterial colonies, granulation tissue & thick walled capsule & septae.

Diagnosis:

Yellow granules, gram stain (+Ve), PAS (+Ve).

The colony of actinomycosis at high magnification. The micro organism is filamentous & the filaments project as red specular deposits at the periphery of the colony which is surrounded by neutrophils (mycetoma). Actinomycosis is a chronic granulomatous bacterial infection Note the colony of the micro organism floats in a pool of pus



Spirochetes

- * Are activity motile, Gram negative, unicellular spiral shaped m.o.
- Produce usually interstitial chronic inflammation with perivascular plasma cell & lymphocytic aggregates.
- Syphilis
- * Caused by spirochete treponema pallidum. It is a chronic venereal disease with multiple clinical presentations.

Transmission:

- It needs close physical sexual contact for transmission.
- It penetrates the mucosa through a minor or microscopic abrasion.
- There is transplacental transmission .

Stage of the disease

Primary syphilis: -

- * Lesion (chancre) develops few days or approximately 3 weeks after infection on the glans penis or vulva (90%), anus, lips, fingers & breast in (10%).
- * Chancre is a solitary, slowly enlarging, hard, painless nodule with superficial ulceration associated with enlarged regional lymph nodes.
- Healing occurs in 3-6 weeks either spontaneously or after treatment.

Microscopical picture of primary syphilis

- Ulceration
- Endarteritis
- Periarteritis (infiltration by lymphocytes and plasma cells & macrophages)
- Spirochetes are numerous at the base of the ulcer
- Enlarged lymph node showing reactive hyperplasia& containing spirochetes



Chancre (male or female genitalia)

Lymphadenopathy Rash: palms, soles

Paralytic dementia Aortic aneurysm Aortic insufficiency Tabes dorsalis Gummas (widespread)

Clinical characteristics of the various stages of syphilis.

-13.

Secondary syphilis: -

- Usually develops 1-3 months after infection. It is due to spread & proliferation of the spirochetes within the skin & mucocutaneous tissues.
- Secondary syphilis occurs in approximately 75% of untreated patients.
- * Lesions appear as flat or slightly elevated papules on external genitalia called **condylomata lata**, generalized **macular skin rash**, shallow buccal, lingual & pharyngeal ulceration, and generalized **lymphadenophathy**.
- Healing may occur spontaneously or after treatment.
- Microscopically : same as primary syphilis
- * Some cases progress to tertiary syphilis.

Tertiary syphilis: -

* It appears several years after primary infection (5-30) years.

* Tertiary syphilis has 3 main manifestations:

1-CVS syphilis : (aortic aneurysmal dilatation , aortic , incompetence , aortic regurgitation & coronary ostial narrowing).

2-CNS neurosyphilis : (meningovascular disease, general paralysis, tabes dorsalis, dementia & personality changes).

3-Gumma: formation (firm, rubbery, multiple, nodular masses) most commonly found in the liver (hepar lobatum) ,bones & testes.

Gumma are now very rare because of the use of the effective antibiotics.

* These may occur alone or in combinations.

Histology of gumma:

Granuloma with central coagulative necrosis surrounded by granulation tissue containing numerous chronic inflammatory cells rich in plasma cells with end arteritis obliterans & periarteritis. The endarteritis, which is seen in all stages of syphilis, starts with endothelial hypertrophy & proliferation followed by intimal fibrosis.



FIGURE 8-8 Secondary syphilis in the dermis with perivascular lymphoplasmacytic infiltrate and endothelial proliferation.

The regional L.N. are usually enlarged & may show non specific acute or chronic lymphadenitis, plasma cells infiltration, or focal epitheliod granuloma.



Congenital syphilis

- * It is due to transplacental spread, which occurs most frequently during primary & secondary syphilis, when the spirochetes are most numerous.
- * May cause:
- 1- Stillbirth, neonatal death or disease present in infancy, childhood or even adult life.
- 2- Desquamating skin rash, particularly of the hands , feet , around the mouth & anus.
- 3- Osteochondritis (saddle deformity of the nose).
- 4- Diffuse hepatic fibrosis & interstitial pulmonary fibrosis.

Diagnosis of syphilis:-

- I- History. II- Clinical examination
- III- Investigations include two types of serologcal tests: non-treponemal a.b. test & anti treponema a.b. test:
- 1) VDRL (venereal disease research laboratory) test.
- 2) FTA-ABS (Fluorescent treponemal antibody absorption)Test.

Smear from the ulcer or discharge

- To demonstrate the spirochetes by:
- I- Silver stains e.g. Warthin- Starry stain.
- 2-Dark- Field Examination.
- 3-Immunofluorecence technique.
- PCR test for syphilis.



FIGURE 8–37 *Treponema pallidum* (dark-field microscopy) showing several spirochetes in scrapings from the base of a chancre. (Courtesy of Dr. Paul Southern, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)

Protozoa

I Toxoplasmosis :

- Caused by Toxoplasma gondii.
- It can be either acquired or congenital.
- Toxoplasma gondii infection can result in the formation of pseudocysts, which have the infected cell forming the cyst wall,
- Pseudocysts are seen here in cerebrum in a microglial nodule



1-Acquired toxoplasmosis:

- Results from food contaminated by faeces of pets especially cats, or eating of undercooked meat contaminated by the parasite.
- Most are asymptomatic.
- In symptomatic cases, there is lymphadenitis, esp. of cervical L.N & fever.
- In immune suppressed patient it can cause encephilitis and hepatitis.

Acquired toxoplasmosis:

Pathology.

- The lymph node affected shows:
 - 1- Lymphoid follicle hyperplasia.
 - 2- Microgranuloma.
 - 3- Monocytoid B-cell hyperplasia.

Congenital toxoplasmosis

- Following transplacentral spread from infected but often asymptomic mother.
- It can cause abortion, stillbirth, cerebral necrosis, hydrocephalus or blindness.


HEMODYNAMIC DISORDERS

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oedema

- Approximately 60% of lean body weight is water, of which 2/3 is intracellular, 1/3 extracellular (mainly interstitial)
- only 5% of total body water is plasma
- oedema means increased fluid in the interstitial tissue spaces.

Serous effusions

- means excess fluid in the serous or coelomic cavities e.g.
- Peritoneal cavity→ ascites
- Pleural cavity \rightarrow hydrothorax
- Pericardium→ hydropericardium
- anasarca means severe & generalized oedeme with profound subcutaneous tissue swellings.
- The main ingredient of the fluid is always *water*.
- Exudate----- is a protein-rich edema with a specific gravity of over 1.020.
- Transudate----- is a protein-poor edema with a specific gravity of 1.012.



FIGURE 4–1 Factors affecting fluid balance across capillary walls. Capillary hydrostatic and osmotic forces are normally balanced so that there is no *net* loss or gain of fluid across the capillary bed. However, *increased* hydrostatic pressure or *diminished* plasma osmotic pressure leads to a net accumulation of extravascular fluid (*edema*). As the interstitial fluid pressure increases, tissue lymphatics remove much of the excess volume, eventually returning it to the circulation via the thoracic duct. If the ability of the lymphatics to drain tissue is exceeded, persistent tissue edema results.



FIGURE 4–3 Hyperemia versus congestion. In both cases there is an increased volume and pressure of blood in a given tissue with associated capillary dilation and a potential for fluid extravasation. In hyperemia, increased inflow leads to engorgement with oxygenated blood, resulting in *erythema*. In congestion, diminished outflow leads to a capillary bed swollen with deoxygenated venous blood and resulting in *cyanosis*.

Pathogenesis

- There are 2 opposing factors which govern the movement of the fluid between vascular & interstitial spaces:
- hydrostatic pressure i.e. capillary blood pr.(BP) encouraging the passage of fluid through the capillary wall to the extra vascular compartment =35mmHg.
- oncotic pressure (op) the plasma protein encourages the retention of fluid in the capillaries to maintain osmotic equilibrium, this pr. Is equivalent to 25mmHg.

;Pathophysiology, oedema results from

- 1. Increased hydrostatic pressure,
- 2. Reduced plasma osmotic pressure,
- 3. Lymphatic obstruction.
- 4. Sodium and water retention.
- 5. local effects of inflammatory mediators on vascular permeability
- Oedema may be
 - 1-- localized to a part of the body or 2---generalized.
- 1-acute inflammation: oedema due to local effects of inflammatory mediators---increase vascular permeability.→ accumulation of protein rich fluid (exudates) in the interstitial spaces.
- 3-Venous obstruction → venous congestion increase →↑capill. perm. → transudation of fluid e.g. in the legs during pregnancy due to pressure on the veins by the gravid uterus
 Also after sitting for long periods without moving the legs. Impaired venous out flow e.g. secondary to deep venous thrombosis(DVT) in the lower extremities → oedema restricted to the affected leg

4-lymphatic: due to obstruction of lymphatic drainage e.g. by tumor cells ,trauma ,by radiation or by inflamm. injury e.g. Filariasis →fibrosis of lymphatic vessels & L.N. of the inguinal region → oedema of lower limbs (elephantiasis).

In carcinoma of breast \rightarrow infiltration & obstruction of superficial lymphatics \rightarrow oedema of overlying skin \rightarrow "peau d 'orange"

also after surgery or irradiation of breast cancer \rightarrow sever oedema of the arm.



Generalized edema

- Either due to:
- 1----increased hydrostatic pressure, most commonly in congestive heart failure affecting the right ventriclular cardiac function.
- CHF is associated with reduced renal perfusion →stimulate rennin –angiotensene-aldosteron axis → induce <u>Na+ and water retention</u> by the kidney (secondary hyperaldosteronism).

2----reduced plasma oncotic pressure

- hypoalbuminaemia ,this result from excessive loss f or reduced synthesis of albumin.
- an important cause of albumin loss is **nephrotic syndrome** characterized by a leaky glomerular basement memb.→ excessive loss of protein (albuminurea)→ generalized oedema.
- Pitting oedema can be manifested in oedematous tissues (because the finger pressure will displace the interstitial fluid leaving a finger shaped depression).



Pulmonary oedema

is common clinical problem & frequently follow Left side heart failure & The lungs ...are typically 2-3 times their normal wt

On sectioning frothy & sometimes blood-tinged fluid representing a mixture of air and oedema fluid and extravasated .RBCs

Hyperemia and congestion

 Both terms indicate a local increased volume of blood in a particular tissue

<u>Hyperemia</u>

- It is increase flow of the blood to the area.
- It is an active process, the affected tissue is red, resulting from sympathetic stimulation which causes <u>arteriolar</u> dilatation &local <u>redness</u> produced owing to the engorgement of oxygenated Bd
- e.g. *pathological* as in acute inflammation
- physiological as in exercise

Congestion

- It is a stasis of the deoxygenated blood in the area
- is a passive process, which could be localized or generalized, and the affected tissue is red-blue (cyanosis).
- congestion is a <u>passive</u> dilatation of <u>veins</u> as a result of <u>partial</u> <u>obstruction</u> to the venous return, this will caus<u>e bluish</u> coloration due to accumulation of <u>deoxygenated</u> blood.

Congestion of the liver

- usually follows right sided heart failure →liver moderately enlarged & tender.
- Micro: red cells accumulate in the sinusoids around the central veins surrounded by the peripheral hepatocytes which are better oxygenated because of their proximity to hepatic arterioles so they are less hypoxic &may only develop fatty changes giving it an appearance called "nut meg liver".



Local venous congestion: follows mechanical interference with the venous drainage from an organ

- --- e.g. limbs in DVT caused by venous thrombosis .
- --- compression of a vein by tumor or bandage.
- Local venous congestion will result in localized oedema & ischemic necrosis.

Hemostasis and thrombosis

Normal hemostasis means

- 1. Maintaining blood in a fluid, clot-free state in normal vessels.
- 2. Rapid localized plug at a site of vascular injury.
- Thrombosis, is the pathologic opposite to hemostasis, and it means an inappropriate activation of normal hemostatic process.

Both *hemostasis* and *thrombosis* are ;regulated by

- 1. Vascular wall.
- 2. Platelets.
- 3. Coagulation cascade.

Thrombosis, Virchow triad

 three primary influences predispose to thrombus formation (Virchow triad);

1. Endothelial injury, leading to;

- Exposure of sub-endothelial extracellular matrix.
- Adhesion of platelets
- 2. Stasis or turbulence of blood flow, by causing;
- a. Endothelial injury .
- b. Disruption of laminar flow.
- c. Preventing dilution of activated clotting factors by fresh blood.
- d. Retarding the inflow of clotting factor inhibitors.
- 3. Blood hypercoagulability



Morphology, thrombi may develop anywhere in the CVS

Grossly and microscopically have apparent laminations (lines of Zahn), produced by alternating pale layers of platelets admixed with some fibrin and darker layers containing more red cells.

- Arterial thrombi are usually occlusive, are firmly attached to the wall, and are gray-white and friable.
- Venous thrombi are almost invariably occlusive, are less firmly attached to the wall, and are red.
- Postmortem clots are gelatinous, dark red, usually not attached to the wall, and lack lines of Zahn.
- Mural thrombi, are those attached to the wall of a spacious cavity e.g., cardiac ventricles
- Vegetations, are thrombi formed on heart valves.

These are "lines of Zahn" which are the alternating pale pink bands of platelets with fibrin and red bands of RBC's forming a true thrombus.



Fate of the thrombus, include

.Propagation .1 .Embolization .2 .Dissolution .3 .Organization and re-canalization .4 ;thrombi are significant because .They cause obstruction of vessels .1

2. They are possible sources of emboli.

Embolism

- is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.
- There are many types of emboli;
- 1. Thrombo-emboli.
- 2. Fat.
- 3. Gas (air, nitrogen).
- 4. Atheromatous emboli.
- 5. Tumor fragments.
- 6. Bone marrow.
- 7. Foreign body (bullet).
- The potential effect of embolism is ischemic necrosis (infarction)



This pulmonary thromboembolus is occluding the main pulmonary artery. (gross)



Clinical consequences

include;

- 1. Most pulmonary emboli are silent.
- 2. Sudden death (acute corpulmonale).
- 3. Obstruction of medium-sized arteries may result in pulmonary hemorrhage.
- 4. Obstruction of small end-arterioles result in infarction.
- 5. Multiple emboli over time may cause chronic corpulmonale.



Here is a large wedge hemorrhagic area of infarction produced by a medium-sized thromboembolus to the lung.

Diagnosis: pulmonary infarction (hemorrhagic infarction)

Clinical correlation

- The consequences of a vascular occlusion can range from no or minimal effect, to death of a tissue or even the individual.
- The factors that influence the outcome include;
- 1. Nature of the vascular supply.
- 2. Rate of development of occlusion.
- 3. Vulnerability to hypoxia.
- 4. Oxygen content of blood



 Also called cardio-vascular collapse, is defined as systemic hypo-perfusion caused by reduction either in cardiac output or in the effective circulating blood volume. The end results are;

Shock is categorized into;

- 1. Hypotension.
- 2. Impaired tissue perfusion.
- 3. Cellular hypoxia.

 Initially, cellular injury is reversible, followed in sustained shock by cell death.

Shock is categorized into;

- 1. Cardiogenic.
- 2. Hypovolemic.
- 3. Septic.
- 4. Neurogenic.
- 5. Anaphylactic.

Cardiogenic Shock

Myocardial pump failure: which may be caused by: myocardial infarction, ventricular rupture, arrhythmias, cardiac temponade, pulmonary embolism, open heart surgery.....

Principle mechanism is failure of myocardial pump \rightarrow sudden fall in C.O.

Hypovolemic Shock

result from:

- loss of blood or plasma volume e.g. hemorrhage ,
- fluid loss as in vomiting & diarrhea, burns or trauma.
- Principle mechanism: inadequate blood or plasma volume→ low Cardiac Output

Septic Shock

- is caused by systemic microbial infections (endotoxic shock) & it can occur after gram + bacteria septicemia or even fungal sepsis.
- The toxins produced by these bacteria causes arteriolar vasodilatation & pooling of blood.

Neurogenic shock

• in severe pain following fracture bone.

Anaphylactic shock :

• initiated by type 1 hypersensitivity reaction \rightarrow systemic vasodilatation & \uparrow vascular permeability.

Healing, Repair & Regeneration

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•Healing:

- Replacement of dead cells & damaged ECM by healthy tissue.
- •It include two processes
 - Regeneration of specialized cells (same cells).
 - **Repair**: Replacement by connective tissue characterized by the formation of granulation tissue and its subsequent maturation.

The outcome of the healing is affected by:

- 1-the **nature** of the injury.
- 2-the **severity** of the injury.
- 3-the duration of the injury.

The capacity of regeneration varies between tissues

- •Labile (continuously dividing) cells: epidermis of the skin, GIT epithelium, bone marrow cells.
- •Stable (quiescent) cells: liver, kidney, pancreas, smooth muscle cells.
- •**Permanent** (non dividing) cells: cardiac muscle, skeletal muscle & CNS.

Growth Factors:

- •These are chemical mediators that affect cell growth by binding to specific receptors on the surface or intra-cellular causing
 - •stimulate cellular proliferation.
 - influence cell migration & differentiation.
 - •influence tissue remolding.

Major Growth Factors (GF)

•EGF (epidermal growth factor) & TGF-alpha (transforming GF) •Mitosis of epithelial cells & fibroblasts.

•PDGF (platelet derived GF)

• Fibroblast & S.M. migration & proliferation

•FGF (Fibroblast GF)

Angiogenesis & fibroblast proliferation

•VEGF (Vascular endothelial GF)

Angiogenesis & increase vascular permeability

•TGF-Beta (transforming GF)

•Stimulates fibroblast chemotaxis & collagen deposition

•inhibits degradation of ECM

•Cytokines (e.g. IL-1, TNF)

fibroblast proliferation & collagen synthesis

Extra-cellular Matrix (ECM)

- A major component of all tissue, provides the **backbone & support** of the tissue.
- It consist of
 - Fibrous structure portions
 - •Collagen
 - •Elastin
 - Interstitial matrix
 - •Fibronectin
 - Integrins
 - •Glycosaminoglycans

Repair by Regeneration

- •Replacement injured tissue by **same type of original tissue cells.**
- •Labile & stable cells.
- •It involves two tissue components:
 - •Cellular proliferation.
 - •ECM deposition.

Repair by connective tissue

- Three components
 - •Neovascularization (Angiogenesis)(granulation tissue) formation.
 - Migration & proliferation of fibroblast (fibrosis).
 - •Remodeling (fibrous tissue maturation & organization).

Granulation tissue:

- Proliferation of small new blood vessels & fibroblasts in a loose ECM forming a specialized type of tissue, it is the hallmark of healing.
- Growth factors: FGF & VEGF.

• <u>Fibrosis:</u>

- Fibroblast migration & proliferation.
- ECM deposition.
- Growth factors: PDGF, FGF, TGF-Beta, IL-1 & TNF.

<u>Remodeling:</u>

- Fibrous tissue maturation & organization.
- Metalloproteinases: enzymes produced by many cells & capable of degrading different ECM constituents.


Healing of skin wounds

•1. Healing by primary union

(Primary intention): Clean wound, its edges are approximated e.g. surgical wounds.

•2. Healing by secondary union

(Secondary union): Infected, contaminated wound, large blood clot, edges are widely separated.

Cutaneous wound healing

is generally divided into three overlapping phases

•1- Inflammation.

- •2- Granulation tissue formation and re-epithelialization.
- •3- Wound contraction, extracellular matrix deposition and remodeling.

Steps of wound healing

- •Blood clots on wound surface & fills gap between edges to seal the wound & bind the surfaces together.
- •Acute inflammatory reaction with neutrophils then macrophages that invade the blood clot & gradually digest it as well as secreting GF.
- •Basal epidermal cell proliferation & migration over the wound surface to replace the surface defect.
- •New blood vessels & granulation tissue formation extends from wound edges & gradually replace the blood clot.
- •Fibroblast begin synthesizing ECM proteins esp. collagen that bridges the wound.
- •Continuous cross-linking & remodeling of collagen occurs to increase the tensile strength of the wound.

Skin wounds are classically described to heal by either primary or secondary intention and the distinction is made by the nature and extent of the wound

Healing by first intention:
wounds with clean opposing edges (surgical incision, should form a narrow scar due to small amount of granulation tissue required to fill the gap)

Healing by second intention:wounds with separated edges

- (trauma that requires abundance of granulation tissue for wound closure)
 - Granulation tissue consists of newly formed blood vessels, macrophages, fibroblasts and loose ECM framework
 - As collagen accumulation increases, the granulation tissue scaffolding is converted into a mature scar composed of mature spindle-shaped fibroblasts, dense collagen and elastic fibers.
 - The mature scar does not contain vessels











Photo 1 Malléole interne gauche J 31

Photo 4 Malléole interne gauche J 74



Photo 2 Malléole interne gauche J 41



Photo 5 Malléole interne gauche J 97



Photo 3 Malléole interne gauche J 51



Photo 6 Malléole interne gauche J 111

Wound Healing

Primary Union

(Healing by 1st intention)

- •E.g., surgical wound
- •Narrow incision space resulting in a limited inflammatory reaction
- Granulation tissue invade incision space
- •Limited amount of wound contraction
- •Healing in short time

Secondary Union

(Healing by 2ry intention)

- •E.g. traumatic wound
- •Large tissue defect resulting in a more intense inflammatory reaction
- •Large amount of granulation tissue
- •More amount of wound contraction
- Healing take long time

Factors Known to impair healing

Local Factors

- Infections
- Poor blood supply
- Presence of foreign body
- Ionizing radiation
- Continuous tissue damage
- Mechanical factors
 - Excessive movement
 - Hematoma (localized blood collection)

Systemic Factors

- Nutritional
 - protein lack
 - vitamin C deficiency
 - Zinc deficiency
- Systemic diseases
 - D.M.
 - Renal failure
 - systemic infections
- Corticosteroid treatment
- •Smoking.

Complications of wound healing

1.Infections.

2.Painful scar.

3.Neoplastic changes.

7- Deficient scar formation

- Wound dehiscence
- Ulceration

8- Excessive formation of scar tissue

- •Keloid (excessive collagen deposition
- 9- Contraction



Wound dehiscence







Wound ulceration



Contractu

re

Wound contraction:

•Reduction of wound surface by 1/3 to 1/4 of its original size by contraction of myofibrils of myofibroblasts.



Healing of bone fractures:

- •I. Healing by primary union: rare e.g. in compression fractures.
- •II. Healing by formation of **callus**. Similar to healing by secondary union which includes:
 - Injury----> Fracture----> formation of blood clot
 - Inflammation start----> removal of blood clot
 - Replacement by granulation tissue consisting of capillary and mesenchymal cells (Osteoblast).
 - Formation of collagen fibers and Osteomucin (Osteoid tissue). calcification----> Woven bone. Removal of woven bone and replacement by lamellar bone.



FIG. 3-3 Early repair. There is organization of the hematoma, early primary new bone formation in subperiosteal regions, and cartilage formation in other areas. (Cruess RL, Dumont J: Healing of bone, tendon, and ligament. In Rockwood CA, Green DP (eds): Fractures, p 99. Philadelphia, JB Lippincott, 1975)

Remodeling of bone

•Continous osteoclastic removal and osteoblastic lay down of bone result in remodeling of the bone and correction of any convexity or concavity

Repair of other injured tissues

- •Cartilage-----> Fibrosis.
- •Tendon-----> Fibrosis.
- •Cardiac muscle----- -> Fibrosis.
- •Skeletal muscle:
 - If endomyseal tube **preserved-----> regeneration**.
 - If endomyseal tube damaged-----> organization.

•Peripheral nerves:

- Endoneural tube preserved -----> axon can regenerate
- •Liver cells-----> Regenerate
- Renal tubules -----> Regenerate if the basement membrane preserved.
- •Glomeruli-----> Fibrosis

Thank you

Immunopathology Lecture 9

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INTRODUCTION

- The immune system **protects** the host from invasion by foreign and potentially harmful agents.
- Immune responses can be elicited by a wide range of agents (antigens) including parasites, bacteria, viruses, chemicals, toxins, drugs, and transplanted tissues.
- Immune system is like a **double-edged sword.** Though it is protective in most of the situations, sometimes a defect in the immune system may cause fatal diseases.

Definition

Immunity is resistance (**defense mechanism**) exhibited by host against invasion by any foreign antigen

Types

There are two types

- Innate immunity.
- Adaptive immunity.

Innate (Natural/Native) Immunity

General Features

- **First line** of defense present by birth.
- Provides immediate initial protection against an invading pathogen.
- Does not depend on the prior contact with foreign antigen or microbes.
- Lacks specificity, but highly effective.
- Triggers the adaptive immune response.
- **No memory** is seen.

Major components of innate immunity

1. **Epithelial barriers** :like intact skin that blocks entry of environmental microbes

- 2. **Cellular:** antigen presenting cells (macrophages, Natural killer (NK) cells, Dendritic cells).
- 3. **Humoral:**(palasma proteins of the complement system, and C-reactive protein)

Functions of Innate Immune Response

- **Inflammation** and destruction of invading microbe.
- **Antiviral defense** is mediated by dendritic cells and NK cells.

Specific or adaptive immunity

If the innate immune system <u>fails</u> to provide effective protection against invading microbes, the adaptive immune system is activated.

General Features

- Acquired in nature
- Second line of defense.
- Takes more time to develop and is more powerful than innate immunity.
- **Prior exposure** to antigen is present.
- Capable of recognizing both microbial and nonmicrobial substances.
- Long-lasting protection (Memory)
- specific

It has 2 main components:

- a) Humoral: consisting of antibodies formed by B cells.
- b) **Cellular:** mediated by T cells.
- **Functions of Adaptive Immune Response**
- Antibodies: Protection against <u>extracellular</u> microbes in the blood, mucosal secretions and tissues.
- **T lymphocytes**:
- Defense against viruses, fungi and intracellular bacteria.
- Important immunoregulatory role, orchestrating and regulating the responses of other components of the immune system.



The principal components of innate immunity and adaptive immunity

ORGANS OF IMMUNE SYSTEM

<u>a) Primary lymphoid organs:</u>

- i) Thymus
- ii) Bone marrow

b) Secondary lymphoid organs:

- i) Lymph nodes
- ii) Spleen

iii) MALT (Mucosa-Associated Lymphoid Tissue located in the respiratory tract and GIT).

CELLS OF IMMUNE SYSTEM

- i) Lymphocytes
- ii) Monocytes, macrophages and dendritic cells.
- iii) Mast cells and basophils
- iv) Neutrophils and Eosinophils



Antibody Structure

Diseases of the immune system which are broadly classified into the following 5 groups:

- 1. <u>Hypersensitivity reactions</u> are characterized by *hyperfunction* or inappropriate response of the immune system.
- 2. <u>Autoimmune diseases</u> occur when the immune system *fails to recognize 'self' from 'non-self*'.
- **3.** <u>Immunodeficiency disorders</u> are characterized by *deficient or absent cellular and/or humoral immune functions*.
- **4.** <u>**Possible immune disorders**</u> in which the immunologic mechanisms are suspected in their etiopathogenesis. Classical example of this group is *amyloidosis*.
- **5. Transplantation reaction** has immunological basis (bone marrow, kidney transplantation reaction).

1. Hypersensitivity reactions

Definition: it is a pathological, *hyperfunction*, and injurious immune response to antigen leading to tissue injury, disease or sometimes death in a sensitized individual.

General Features of Hypersensitivity Disorders:

- **Priming or sensitization:** It occurs in **individuals who had previous contact with the antigen** (allergen).
- **Nature of antigens:** It may be **exogenous or endogenous** origin.
 - **Exogenous antigens:** Examples, antigens in dust, pollens, foods, drugs, microbes, chemicals, and few blood products.
 - Endogenous antigens: Self antigens .
- Genetic susceptibility: Hypersensitivity diseases are usually associated with the inheritance of particular susceptibility genes (e.g. HLA genes).

Causes of Hypersensitivity Reactions

- *Autoimmunity: reactions against self antigens*. Normally, the immune system does not react against self-generated antigens. This phenomenon is called self tolerance, implying that the body "tolerates" its own antigens. On occasion, self-tolerance fails, resulting in reactions against the body's own cells and tissues .
- Reactions against microbes
- *Reactions against environmental antigens*. Most healthy people do not react strongly against common environmental substances (e.g., pollens, animal danders, or dust mites), but almost 20% of the population are "allergic" to these substances.

Classification of hypersensitivity reactions

- 1. Type I (immediate) hypersensitivity.
- 2. Type II hypersensitivity (antibody-mediated disorder)
- 3. Type III hypersensitivity (immune complex mediated disorders)
- Type IV hypersensitivity (cell-mediated or delayed type).

TYPE I (IMMEDIATE) HYPERSENSITIVITY REACTIONS

Usually known as **allergic or atopic disorders** and the environmental antigens that elicit these reactions are known as **allergens**.

Definition: Type I hypersensitivity reaction is a type of immunological tissue reaction, which occurs rapidly (within 5-10 minute) after the interaction of antigen (allergen) with a IgE antibody bound to the mast cells in a sensitized person.

Characteristics

- **Immediate** reaction occurring within minutes (5–10 minutes).
- **Antibodies:** Mediated by IgE antibody.
- **Develops after the interaction of an antigen with IgE bodies** bound to **mast cells**.
- Genetic susceptibility: Occurs in genetically susceptible individuals previously sensitized to the antigen.
- Antigens (allergens): Many allergens (e.g. house-dust mite, pollens, animal danders or moulds) in the environment are harmless for majority of individuals. Allergens elicit significant IgE reactions only in genetically predisposed individuals, who are said to be atopic.

Sequence of Events

A. During Initial Exposure to Antigen (Sensitization)

In a genetically susceptible individual, the following events occur:

1. Exposure to sensitizing antigen: Individuals are exposed to environmental allergens and may be introduced by: **1) inhalation, 2) ingestion or 3) injection**.

2. Presentation of the antigen: The **sensitizing antigen (allergen)** is **presented to T cells**. Antigen is captured by the antigen presenting cells and presented to the T cell which then differentiates into **TH2 cell**.

3. Activation of TH2 cells: In genetically susceptible individual, antigens (allergens) activates **TH2 subset of CD4+ helper T cells secrets cytokines (e.g. IL-4, IL-5 and IL-13)**.

4. Production of IgE antibody: IL-4 secreted by TH2 cells stimulates B cells to secrete cytotropic IgE antibodies. IL-5 activates eosinophils and IL-13 stimulates epithelial cells to secrete mucus.

- 5. Sensitization of mast cells by IgE antibody:
- Mast cells are mainly concentrated near blood vessels and nerves and in subepithelial tissues (common sites of type I hypersensitivity).
- Mast cells possess Fc- receptor, which have high affinity for IgE antibodies.
- **IgE** antibodies attach to the Fc-R on the mast cells.



Examples of type I hypersensitivity includes:

Localized hypersensitivity		Systemic hypersensitivity
	Bronchial asthma Hay fever/allergic rhinitis Food allergies Atopic dermatitis Urticaria Angioedema	 Anaphylaxis due to: Antibiotics: Most commonly penicillin (therefore, a test dose should always be given before administration of penicillin to any patient) Bee stings Insect bites

chronic inflammation due to type I hypersensitivity reaction: Nasal mass with edematous stroma with chronic inflammatory cell infiltrate (mainly eosinophils) covered by ciliated columnar epithelium allergic nasal polyp



Bronchial asthma is an example of type I hypersensitivity reaction & is characterized by eosinophilic infiltrate, mucus collection & congestion.





2. <u>ANTIBODY-MEDIATED (TYPE II)</u> HYPERSENSITIVITY REACTIONS

Definition: it is a reaction by antibodies directed toward specific antigens <u>fixed on cell surfaces</u> cause lysis of target cells.

Characteristics:

- Antibodies: IgG (usually) and IgM (rarely).
- Antigen: It may be endogenous or exogenous
- **Endogenous antigens:** It may be normal molecules intrinsic to the cell membrane or extracellular matrix (e.g. autoimmune diseases).
- **Exogenous antigens:** These antigens may get adsorbed on a cell surface or extracellular matrix may cause altered surface antigen (e.g. drug metabolite).

Mechanisms of Injury

Complement-dependent reactions

a. Cell lysis (antibody dependent)

• Antibody (IgM) directed against antigen on the cell membrane activates the complement system, leading to lysis of the cell .

Example: Transfusion reaction, incompatible blood transfusion for either ABO or Rh incompatibility when RBCs from incompatible donor enter the recipient circulation, they become coated with antibodies directed against RBC antigen of the donor and are lysed.

b. Phagocytosis

When circulating cells, such as erythrocytes or platelets, are coated (opsonized) with autoantibodies, with or without complement proteins, the cells become targets for phagocytosis (opsonization) which is phagocytosis of cells coated with antibodies) by macrophages

Example: penicillin attaches to RBCs \rightarrow IgG antibodies are made against penicillin \rightarrow splenic macrophages phagocytose the RBCs (hemolytic anemia).


b- Opsonization of cell by antibody & complement followed by phagocytosis

EXAMPLES OF TYPE II REACTION

Examples of type II reaction are mainly on blood cells and some other body cells and tissues.

1. Antibodies to blood cells e.g.

i) Autoimmune haemolytic anaemia

- ii) Transfusion reactions
- iii) Haemolytic disease of the newborn (erythroblastosis foetalis)
- iv) Idiopathic thrombocytopenic purpura (ITP)
- v) Drug-induced cytotoxic antibodies

2. Antibodies to tissue components e.g.

i) Graves' disease (primary hyperthyroidism),

ii) myasthenia gravis

iii) type 1 diabetes mellitus, islet cell autoantibodies are formed

iv) In *hyperacute rejection reaction*, antibodies are formed against donor antigen.

3. IMMUNE COMPLEX-MEDIATED (TYPE III) HYPERSENSITIVITY REACTIONS

Definition: it is **characterized by formation of immune** (antigen and antibody) **complexes in the circulation** that may **deposited in blood vessels**, **leading to complement activation and acute inflammation**.

The inflammatory cells recruited (neutrophils and monocytes) release lysosomal enzymes that generate toxic free radicals and cause tissue damage.

Characteristics

<u>Antibodies:</u> Complement-fixing antibodies namely IgG, IgM, and occasionally IgA.

Antigen:

- **Exogenous:** Various **foreign proteins**, e.g. foreign serum protein injected (e.g. diphtheria antitoxin, horse anti-thymocyte globulin) or produced by an infectious microbe.
- **Endogenous: Antibody against self-components** (autoimmunity), e.g. nucleoproteins.

Immune complex disease has the following phases:

- Phase I or Immune Complex Formation
- Phase II or Immune Complex Deposition
- Phase III or Immune complex mediated inflammation

EXAMPLES OF TYPE III REACTION

Localized hypersensitivity	Systemic hypersensitivity	1
*Arthus reaction	*SLE	
*Farmer's lung	*Reactive arthritis	
*Hypersensitivity pneumonitis	*Henoch Schonlein purpura	
*Polyarteritis nodosa	*Post streptococcal glomerulonephritis	
	*Serum sickness	
	*Type II lepra reaction	

The deposition of immune complexes in an artery is called vasculitis with circumferential bright pink area of fibrinoid necrosis with protein infiltration & inflammation



4. T Cell–MEDIATED (TYPE IV) HYPERSENSITIVITY REACTIONS

- Type IV hypersensitivity reaction is **mediated by T lymphocytes** including **CD4+ and CD8+ T cells**.
- It develops in response to antigenic exposure in a previously sensitized individual.
- Reaction is delayed by 48 to 72 hours after exposure to antigen. Hence also called as delayed-type hypersensitivity (DTH).
- This hypersensitivity reaction is involved in several **autoimmune diseases** (e.g. rheumatoid arthritis, Hashimoto thyroiditis), pathological **reactions to environmental chemicals** (e.g. poison ivy, nickel) and **persistent microbes (e.g. tuberculosis, leprosy)**.
- **Types:** Two types of Type IV hypersensitivity reaction namely: 1) **Delayed type hypersensitivity reaction** mediated by **CD4+ T cells produce Cytokines**
 - 2) Direct cell toxicity mediated by CD8+ T cells.

AUTOIMMUNE DISEASES Definition:

Immune reactions to <u>self antigens</u> due to the loss of self-tolerance.

Mechanisms(causes)of Autoimmune Diseases

<u>1- Failure of self tolerance</u>

<u>2- Environmental factors</u>

<u>3- Genetic susceptibility</u>



Failure of self tolerance

Failure of tolerance is due to several mechanisms:

1. Failure of activation induced cell death: is due to a defect in Fas-Fas ligand system which leads to failure of apoptosis of <u>self</u> reactive T cells induced by this system with <u>persistence</u> of these cells in the circulation.

2. Break down of T cell anergy:

Anergy is broken when normal cell becomes expressing <u>costimulatory molecules</u> required for T cell activation . (Normally these molecules are not expressed by antigen presenting cells), such induction of expression of costimulatory molecules is due to infection .

- **3. Modification in the structure of self antigen** that allow its recognition as a foreign antigen by T cells.
- e.g. autoimmune hemolytic anemia occurs after use of certain drug because the drug induces change in the surface of RBCs that create an antigen which is recognized as a foreign by T cells which subsequently stimulate B cells to produce autoantibodies against RBCs leading to hemolysis.

4. Molecular Mimicry

- Some infectious agents share the same epitope (shape) with self antigens, so immune response against such microbes produces similar response to the self antigen.
- e.g. polysaccharide coat of streptococci share the same epitope with cardiac glycoprotein so after streptococcal throat infection, antibodies formed against bacteria cross react with antigens in the heart wall leading to carditis (rheumatic heart disease) and damage of endocardium, myocardium and pericardium.

5. Polyclonal lymphocyte activation:

Some clones of anergic (inactivated) lymphocytes become activated by endotoxins of bacteria resulting in autoimmunity.

6. Release of sequestered antigens:

- Any self antigen that is completely sequestered (hidden) from the immune system during development is likely to be recognized as foreign antigen of it is subsequently exposed to the immune system.
 - e.g. spermatozoa and ocular antigens are sequestered self antigens and may be exposed to the immune system after trauma to the testis or eye and recognized as a foreign antigen resulting in autoimmunity.

Environmental factors and Autoimmunity

Role of infections in autoimmunity.

1. Antigenic cross reactivity: this is due to similarity between the microbial antigenic structure and the self antigens. This is also known as **'molecular mimicry'**.

2. Upregulation of co-stimulatory molecules by infectious organisms.

3. Polyclonal B cell activation: caused by EBV and HIV resulting in production of autoantibodies.

4. Alteration of tissue antigens: infections may alter tissue self antigens so that they activate T cells and loose the property of self tolerance.

Examples of Autoimmune Diseases

Organ specific autoimmune disorders

- Type I diabetes mellitus
- Pernicious anemia
- Gravis disease
- Hypothyroidism
- Autoimmune hepatitis and primary biliary cirrhosis

Multisystem autoimmune diseases

- Rheumatoid arthritis
- Systemic lupus erythematosus (SLE)
- Polyarteritis nodosa
- Auto immune hemolytic anemia

TRANSPLANTATION REACTION

- **Types of rejection**
- (1) Superacute rejection:
- Time: within minutes or hours after transplantation.
- **Causes:** these are major incompatibility with high levels of humoral antibodies.

Morphology:

- a. thrombotic occlusion of the capillaries
- b. Fibrinoid necrosis occurs in arterial walls.
- c. Infarction
- d. Neutrophils infiltrating

Superacute rejection



- (A) Capillaritis (Masson trichrome). Presence of polynuclear leukocytes in the peritubular capillaries attracted by chemotaxis.
- (B) Interstitial hemorrhage (H&E).
- (C) Thrombotic microangiopathy with cortical necrosis (PAS).

(2) Acute rejection

Time: Within days to weeks in the untreated recipient. Or may appear suddenly months or even years later, when immunosuppression has been employed.

Types:

a. Acute cellular rejection: diffuse mononuclear cell infiltrating that may invade the tubules, causing focal tubular necrosis, and edema as well as mild interstitial hemorrhage.

b. Acute rejection vasculits (humoral rejection): necrotizing vasculitis with endothelial necrosis, neutrophils infiltration, deposition of immunoglobulins



Acute humoral rejection. Transmural arteritis (fibrinoid necrosis of the vascular wall) (H&E).

(3) Chronic rejection Time: months—years

Morphology: Vascular changes consist of dense intimal fibrosis;Interstitial fibrosis, tubular atrophy, shrinkage of the renal parenchyma;Mononuclear cell infiltrates containing large numbers of plasma cell and numerous eosinophils

GENETIC DISORDERS

LEC. 10

Assist. Prof. Dr. Abdulkareem Y. Altaee al-Noor University College 2022-2023

Genetic disorders

- Genetic disorders occur when a mutation (a harmful change to a gene) affects your genes or when you have the wrong amount of genetic material. Genes are made of DNA (deoxyribonucleic acid), which contain instructions for cell functioning and the characteristics that make you unique.
- You receive half your genes from each biological parent and may inherit a gene mutation from one parent or both. Some cause symptoms at birth, while others develop over time.

Quick Review: What is a chromosome?

 A chromosome is a DNA molecule that is tightly coiled around proteins called histones, which support its structure, to form a thread-like structures.



What Are Mutations?

- Changes in the nucleotide sequence of DNA
- May occur in somatic cells (aren't passed to offspring)
- May occur in gametes (eggs & sperm) and be passed to offspring

Types of Mutations Chromosome Mutations

- May Involve:
 - Changing the structure of a chromosome
 - The loss or gain of part of a chromosome
- Five types exist:
 - Deletion
 - Inversion
 - Translocation
 - Nondisjunction
 - Duplication





Due to breakage A piece of a chromosome is lost



Inversion

- Chromosome segment breaks off
- Segment flips around backwards
- Segment reattaches



Duplication

Occurs when a gene sequence is repeated

Duplication mutation



Translocation

Involves two chromosomes that are NOT homologous
Part of one chromosome is transferred to another chromosome



Genetic disorders can be:

- Chromosomal: This type affects the structures that hold your genes/DNA within each cell (chromosomes). With these conditions, people are missing or have duplicated chromosome material.
- Complex (multifactorial): These disorders stem from a combination of gene mutations and other factors. They include chemical exposure, diet, certain medications and tobacco or alcohol use.
- Single-gene (monogenic): This group of conditions occurs from a single gene mutation.

What are common genetic disorders?

There are many types. They include:

1-Chromosomal disorders	2-Monogenic disorders	3-Multifactorial disorders
 Down syndrome (Trisomy 21). FragileX syndrome. Klinefelter syndrome. Turner syndrome. others 	 Cystic fibrosis. Duchenne muscular dystrophy. Sickle cell disease. others . 	 Late-onset Alzheimer's disease Autism spectrum disorder, in most cases. Cancer, in most cases. Coronary artery disease. Diabetes Spina bifida. Isolated congenital heart defects others .

1-Chromosomal disorders

- Defect either in the number or structure of chromosome
- Failure of chromosomes to separate during meiosis
- Causes gamete to have too many or too few chromosomes
- Disorders:
 - Down Syndrome three 21st chromosomes
 - Turner Syndrome single X chromosome
 - Klinefelter's Syndrome XXY chromosomes

Down Syndrome

Down syndrome (DS or DNS), also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is typically associated with physical growth delays, characteristic facial features and mild to moderate intellectual disability.



2-Monogenic disorders

single gene inheritance disorders

- Single gene inheritance is also called Mendelian or monogenetic inheritance. Changes or
- mutations that occur in the DNA sequence of a single gene cause this type of inheritance.
- There are thousands of known single-gene disorders.
- Example like Single cell disease
- It could be autosomal dominant (Only one parent affected)
 OR it could be autosomal recessive (both parents affected)

Point Mutation

- Change of a single nucleotide
- Includes the deletion, insertion, or substitution of ONE nucleotide in a gene
 Sickle Cell disease is the result of one nucleotide substitution



3-Multifactorial disorders



Spina

What are the causes of genetic disorders?

- □ Chemical exposure.
- Radiation exposure.
- Smoking.
- □ UV exposure from the sun.

DIAGNOSIS AND TESTS

- If you have a family history of a genetic disorder, you may wish to consider genetic counseling to see if genetic testing is appropriate for you.
- Lab tests can typically show whether you have gene mutations responsible for that condition.
- In many cases, carrying the mutation does not always mean you'll end up with it.
- Genetic counselors can explain your risk and if there are steps you can take to protect your health.

If there's a family history, DNA testing for genetic disorders can be an important part of starting a family.

Options include:

- **Carrier testing:** This blood test shows whether you or your partner carry a mutation linked to genetic disorders. This is recommended for everyone considering pregnancy, even if there is no family history.
- Prenatal screening: This testing usually involves blood testing from a pregnant woman that tells a person how likely it is that an unborn child could have a common chromosome condition.
- **Prenatal diagnostic testing:** You can find out whether your unborn child faces a higher risk for certain genetic disorders. Prenatal testing uses a sample of fluid from the womb (amniocentesis).
- Newborn screening: This test uses a sample of your newborn baby's blood and is performed on all babies born in Ohio. Detecting genetic disorders early in life can help your child receive timely care if needed.
NEOPLASIA LECT. 11

Al-Noor University College Prof. Dr. Abudulkarim Altaie 2022-2023

Objectives

- 1. Definition of Neoplasia
- Nomenclature.
- Examples of Benign and malignant tumors
- **Classification of tumors**
- Carcinogenesis

Definition

A neoplasm is : abnormal mass of tissue which grows in an uncoordinated manner even after cessation of the stimuli which evoked the change.

Neoplastic Proliferation:

Benign

 Localized, non-invasive.

 Malignant (Cancer)

 Spreading, Invasive.



Examples of Nomenclature

Benign tumor of the thyroid is called(adenoma) Note the normallooking (welldifferentiated), colloid-filled thyroid follicles



Nomenclature

Benign Tumors

Encapsulated
 Well defined



Nomenclature Cont.

Cancers are classified by the type of cell that the tumor resembles and is therefore presumed to be the origin of the tumor. These types include:

Carcinoma:

Cancers derived from epithelial cells. the breast, prostate, lung, pancreas, and colon.



- Malignant tumor arise from epithelial tissue
 - Adenocarcinoma malignant tumor of glandular cells .
 - Squamous cell carcinoma malignant tumor of squamous cells.

Sarcoma Malignant tumor arising from connective tissue (i.e. bone, cartilage, fat, nerve) develop from cells originating in mesenchymal cells outside the bone marrow.

Malignant tumor (adenocarcinoma) of the colon. The cancerous glands are irregular in shape and size and do not resemble the normal colonic glands. The malignant glands have invaded the muscular layer of the colon





This sarcoma has many mitoses. A very large abnormal mitotic figure is seen at the right.

 Lymphoma and leukemia: These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.

 Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively. Hamartoma – Benign tumour which is made up of mature but disorganised cells of tissues indigenous to the particular organ eg Hamartoma of lung consist of mature cartilage , mature smooth muscles and epithelium.

Choristoma – Ectopic islands of normal tissues. This is hetrotopia not a true tumour.

DIFFERENCE IN BENIGN AND MALIGNANT TUMOURS

CHARECTERISTI CS	BENIGN	MALIGNANT
Surface	Smooth	Irregular
Rate of growth	Slow and Expensile	Erratic
Capsule	Well capsulated	Invasive
Size	Small or Large sometimes very Large.	Small to large
Course	Rarelly fatal	Usually fatal if untreated

Microscopic features	BENIGN	MALIGNANT
Differentiation	Well differentiated	Lack of differentiation
Cytological features	Cells similar to normal	Marked variation in shape and size of cells
Mitosis	Normal	Increased abnormal
Necrosis	unusual	Necrosis and haemorrhage common
Metastasis	Absent	Present



Differentiation

Extent to which parenchymal cells resembles to normal cells .

Neoplastic Cells Well differentiated resembling the mature normal cells of the tissues of origin.

Poorly differentiated undifferentiated tumours

> **Primitive appearing** unspecialised cells.

The presence of mitoses, however, does not necessarily indicate that a tumor is malignant or that the tissue is neoplastic.

More important feature of malignancy are atypical, bizarre mitotic figures, sometimes producing tripolar, quadripolar, or multipolar forms of mitosis.



Dysplasia is a term that literally means disordered growth.
 Characterized by loss in the uniformity of the individual cells as well as a loss in their architectural orientation .

Features of dysplasia

- Pleomorphism ,
- Hyperchromatic nuclei with a
- High nuclear-cytoplasmic ratio.
- The architecture of the tissue disordered.
- Mitotic figures are more abundant than usual .

WHAT IS Ca Insitu

When dysplastic changes are marked and involve the entire thickness of the epithelium but remains confined by the basement membrane, it is considered a preinvasive neoplasm or carcinoma in situ



Carcinoma in situ. This low – power view shows that the entire thickness of the epithelium is replaced by atypical dysplastic cells. **The basement membrane is intact**. B, A high-power view of another region shows marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface.



CLASSIFICATION OF TUMORS

TISSUE OF ORIGIN	BENIGN	MALIGNANT
Connective Tissue and masenchymal origin		
	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteosarcoma

EPITHELIAL TUMOURS	BENIGN	MALIGNANT
Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
Basal cell of skin		Basal cell ca.
Glands and ducts		
	Adenoma	Adenocarcinoma
	Papilloma	Papillary ca.
	Cystadenoma	Cystadeno ca.
Respiratory passage		Bronchogenic ca.

Neuroectoderm	NEVUS	Malignant Melanoma
Renal Epithelium	Renal Tubular Adenoma	RCC
Liver Cell	Liver Cell Adenoma	HCC
Urinary Tract epithelium	Transitional Cell Papilloma	тсс
Placental Epithelium	Hydatidiform Mole	Choriocarcinoma
Testicular Epithelium		Seminoma
		Embryonal Ca







Lipoma; composed of adult adipocytes.



Osteoma formed bundles of compact bone





Chondroma formed of chondrocytes in a hyaline matrix



Squamous cell carcinoma: malignant ulcer of the scalp

Bronchogenic carcinoma,



Squamous cell carcinoma arising on top of squamous metaplasia of bronchial epithelium



Cervical squamous cell carcinoma. Note the disorderly growth of the malignant squamous epithelial cells forming large nests with pink keratin in the centers.

BASAL CELL CARCINOMA





BCC: Groups of neoplastic basaloid cells infiltrating the dermis. The cells at periphery show palisade. The groups of cells are surrounded by clear zone due to fixation artifact (characteristic for BCC).



BCC: peripheral cells are arranged in a palisade with artificial artifact in the stroma



Malignant melanoma of the skin is much larger and more irregular than a benign nevus.

Epidemiology of MALIGNANCY

Epidemiologic studies established the relation of -

- Smoking and lung cancer.
- Implicated in cancer of the mouth, pharynx, larynx, esophagus, pancreas, bladder, and most significantly about 90% of lung cancer deaths.

OTHER FACTORS

Obesity is associated with approximately 14% of cancer deaths in men and 20% in women. Environmental, Racial (possibly hereditary), Cultural influences to the occurrence of specific neoplasms.
What is carcinogen and role of carcinogen in CANCER.

- Carcinogens substances known to cause cancer or produces an increase in incidence of cancer in animals or humans
 - Cause of most cancers is unknown
 - Most cancers are probably multifactorial in origin
 - Known carcinogenic agents constitute a small percentage of cases
 - Unidentified 'environmental' agents probably play a role in 95% of cancers

CARCINOGENIC AGENTS

Chemical carcinogenesis

Radiation carcinogenesis.

Microbial carcinogenesis.

Definition of Carcinogenesis and Carcinogen.

- Carcinogenesis / Oncogenesis / Tumorigenesis means *mechanism of induction of tumours* (pathogenesis of cancer).
- Agents which can *induce tumours are called* carcinogens (etiology of cancer).



Etiology and pathogenesis of cancer can be discussed under following 3 headings:
1. Chemical carcinogens and Chemical Carcinogenesis.

2. Physical carcinogens and Physical Carcinogenesis.

3. Biologic carcinogens and Viral Oncogenesis.

Chemical Carcinogens:

 Depending upon the mode of action of carcinogenic chemicals, they are divided into 2 broad groups: CHEMICAL CARCINOGENS

A. INITIATORS

1. DIRECT-ACTING CARCINOGENS These carcinogens don't require any metabolic conversion to become carcinogenic. They directly damage the DNA causing mutations

2. INDIRECT-ACTING CARCINOGENS

These are chemical Substances which require prior metabolic activation before becoming potent 'ultimate' carcinogens.

B.PROMOTERS

Lack the intrinsic carcinogenic potential but their application subsequent to initiator exposure helps the initiated cell to proliferate further.



Viral & Microbial Carcinogenesis Viruses

DNA Oncogenic Viruses such as:

- Human Papilloma Viruses (HPV).
 - sexually transmitted

RNA Oncogenic viruses Human T-Cell Leukemia Virus type 1 (HTLV-1)

Viral & Microbial Carcinogenesis Helicobacter Pylori

- Bacteria infecting stomach implicated in:
 - peptic ulcers
 - gastric carcinoma
 - marginal zone lymphomas (mucosaassociated B-cell lymphomas (MALTomas))

The best and strongest evidence links Helicobacter pylori infection with the onset of mucosa-associated B-cell lymphomas (MALTomas) of the stomach, which are also known as marginal zone lymphomas.

METHODS OF DIAGNOSIS OF CANCER

. 1 . Histologic examination (paraffinembedded fixed sections, stained by **&**E). **2**. Cytologic smears (Papanicolaou): examination of already shed cancer cells in body secretions. **3**. Fine-needle aspiration: cytologic examination of aspirated tumor cells from palpable masses.

4. IMMUNOCYTOCHEMISTRY

Detection of surface markers or cell products by monoclonal antibodies.

It can be used for detection of cytokeratin, vimentin, desmin, calcitonin, neuron-specific enolase, prostate specific antigen, products of tumor suppressor genes (*p*53), and oncogenes (*c-erb B2*), etc ...

Environmental and Nutritional Pathology **Lect. 12** Assist. Professor Dr. Abdul Kareem Younis **Alnoor University College** 2022-2023

Environmental Diseases Conditions caused by exposure to :-

1- Diseases caused by exposure to Air pollutants.

2-physical injury.

3- chemical injury.

4- Diseases due to nutritional deficiency

Outline of the lectures :-

A- Environmental pollution :-

1- Air pollution.

- 2- Metals as Environment pollution.
- **3-** Industrial and agricultural exposure.(pnemocoiniosis)
- 4- Effects of tobacco
- 5- Effects of alcohol.
- **B- Injury by therapeutic drugs**
- **C- Injury by physical agents**
 - 1- Mechanical trauma.
 - 2- thermal injury.
 - **3-** Electrical injury
 - 4- Injury by ionizing radiation.

D- Nutritional diseases (malnutrition, vitamin deficiency, obesity, diet and cancer)

Air pollution

- Ozone
 - Good + high in the atmosphere
 - Product of UV radiation action on oxygen
 - Accumulates in the ozone layer 10-30 miles above the earth
 - Absorbs most of the dangerous UV radiation emitted by the sun

Air pollution







airway disease (e.g. asthma)

AIR POLLUTION

- Carbon monoxide
 - Colorless, tasteless, odorless
 - Produced in car exhaust and burning of wood
 and fossil fuels
 - Hemoglobin has a 200x higher affinity for carbon monoxide than oxygen, resulting in impaired peripheral oxygen delivery
 - May cause acute or chronic toxicity

Metal pollution

Lead Intoxication

.

- Historically found in house paint and gasoline
- Most current exposures in children occur due to flaking lead paint and contaminated soil
- Interferes with calcium
 metabolism
 and bone

remodeling

yrin

METAL POLUTION

Lead

- Absorbed into CNS, bone, and developing teeth
- Symptoms:
 - Neurotoxicity
 - Adults: Peripheral neuropathy
 - Children: Loss of IQ, behavior problems

Inhibited fracture healing

 Delayed mineralization of cartilage



"Lead lines": Increased radiodensity of epiphyses due to impaired cartilage remodeling

IMPORTANT:

can see these lines in gums





Pneumoconioses

- non-neoplastic lung reaction to inhalation of mineral, inorganic and organic dusts
- 4 major <u>coal dust, silica, asbestos, beryllium</u> it depend on.
- **Concentration.**
- size and shape of particles (<u>1-5μm</u>)
- chemical character of dust
- concurrent smoking

Tobacco

- Causes 90% of lung cancers
- Can cause lung cancer in non-smokers as secondhand smoke"
- Causes more than 5 million deaths annually from:
 - Cardiovascular disease
 - Cancer
 - Chronic respiratory problems
- Smoking while pregnant increases the risk of:
 - Preterm birth
 - Intrauterine growth restriction
 - Spontaneous abortion









Alcohol

- Acute effects
 - CNS depressant
 - Low levels: Disordered motor and intellectual behavior
 - High levels: Depression of cortical neurons and medullary centers may cause respiratory arrest
 - Gastritis
 - Fat accumulation in the liver (steatosis)



Alcohol

Medical College

- Chronic effects
 - Alcoholic hepatitis and cirrhosis
 - Gastrointestinal bleeding due to portal hypertension, ulcers
 - Thiamine deficiency
 - Peripheral neuropathy
 - Wernicke-Korsakoff syndrome not uncommon
 - Encephalopathy
 - Cardiomyopathy
 - Pancreatitis



Alcohol

- Effects in pregnancy
 - First trimester is particularly vulnerable period
 - Fetal alcohol syndrome:
 - Microcephaly
 - Growth retardation
 - Facial abnormalities
 - Mental deficiencies



Injury by therapeutic agents

- adverse drug reactions extremely common in practice of medicine
- most frequently antibiotics, antineoplastic agents, immunosuppressive drugs
- adverse reaction predictable (dose-dependent) digitalis, streptomycin, <u>unpredictable</u>
 idiosyncrasy massive necrosis of the liver after paracetamol

- Poison: Difficult to define because it depends on dosage ("the dose makes the poison")
 - "All substances are poisons; the right dosage differentiates a poison from a remedy." –

Analgetics

<u>aspirin</u> (acetylsalicylic acid)

- overdose - intoxication - respiratory alkalosis, metabolic acidosis, Reye syndrome (?)

- chronic toxicity - erosive gastritis, ulcers

<u>acetaminophen</u> - very large doses - hepatotoxicity

Exogenous estrogens and oral contraceptives

- ► 1. HRT in postmenopause to prevent osteoporosis
- 2. <u>oral contraception</u>
- unopposed E therapy increases risk of endometrial ca, the risk is eliminated with adding progesterone
- very low increase of risk of breast ca
- not increased risk of thrombembolism
- elevation of HDL, decrease of LDL, 40-50% decrease of risk of ischemic heart disease.

- Mechanical trauma
 - Car accidents, stabbings, shootings, falls, beatings, etc



Epidermis

Dermis

Muscle

- Thermal injury
 - Superficial (firstdegree): Epidermis only
 - Partial thickness (second-degree): Epidermis and Distering dermis
 - Full thickness (third- and fourth
 - degree): Subcutaneous tissue, muscle





Superficial (first degree) burn













Full thickness (third degree) burn



- Electrical injury
 - Two injury types:
 - Burns
 - Arrhythmias (ventricular fibrillation)
 - Severity depends on current (amperage), duration, and path of the current
 - Household current (120 or 220 VAC) is enough to kill



Hyperthermia

<u>heat cramps</u> - due to loss of electrolytes (sweating)
 <u>heat exhaustion</u> - sudden onset, collapse, hypovolemia
 <u>heat stroke</u> - high temperature + high humidity - rise of core body temperature; in severe cases 50% mortality - peripheral vasodilatation, shock, necrosis of muscles, DIC

Hypothermia

- local reactions
- ► <u>freezing of cells</u> crystallinization of water within cells, high salt concentrations
- <u>circulatory changes</u> vasoconstriction, increased permeability, edema, hyperviscosity of blood - ischemia (e.g. gangrene of toes)



Nutritional diseases Protein-energy malnutrition

most frequent and most important

range of clinical syndromes, 2 main forms - marasmus & kwashiorkor

Marasmus

- deficiency of energy (calories) due to starving growth retardation - arrest, loss of muscle mass, serum albumin is normal, subcutaneous fat is used as a fuel - extremities are emaciated
- anemia, immune deficiency (namely cellular immunity)

Kwashiorkor

deficiency of proteins, mainly animal

- most common in Africa children, who have been weaned too early (arrival of another child) and fed by exclusively carbohydrate diet
- kwashiorkor is more severe than marasmus loss of visceral proteins - <u>hypoalbuminemia</u> - generalized edema, ascites
- skin lesions, hair changes, fatty liver, defects of immunity, secondary infections, anemia


A, Marasmus. Note:

1.The loss of muscle2.subcutaneous fat;3.the head appears to be too large for the emaciated body

B, Kwashiorkor.
1.Infant shows generalized edema.
2.Puffiness of the face
3.Hand and legs.

Vitamin deficiencies

 vitamin deficiency - <u>primary</u> (diet) or <u>secondary</u> (malabsorption, metabolic disorders, liver diseases)
 oversupply can be harmful as well !!!

Vitamin A

- retinol_and related substances
- important for vision (visual pigment) and differentiation of some types of epithelial cells (mucus-secreting)
- main sources: liver, fish, milk, eggs, butter
- ► in 3rd world is hypovit. A frequent cause of blindness

changes:

- impaired vision in reduced light
- squamous metaplasia
- decreased resistance to infections



Vitamin A deficiency: its major consequences in the eye and in the production of keratinizing metaplasia of specialized epithelial surfaces, and its possible role in epithelial metaplasia. Not depicted are night blindness and immune deficiency.

Vitamin D

maintenance of normal plasma Ca and P levels, important for normal development and mineralization of bones
Lead To

(Ricket, Osteomalacia)

two sources:

<u>endogenous</u> synthesis in the skin (UV light) from 7-dehydrocholesterol
 - 80% of needed amount

<u>exogenous</u> - dietary sources (deep-sea fish, plants, grains)



Figure 8-21

Rickets. Note bowing of legs due to the formation of poorly mineralized bones.

Vitamin K required <u>cofactor for synthesis of clotting factors</u> VII, IX, X

Vitamin B12 (cyanocobalamine)

- deficiency in <u>strict vegetarians</u> or in <u>chronic atrophic gastritis</u> pernicious anemia (lack of synthesis of intrinsic factor in gastric mucosa due to autoimmune inflammation
- in deficiency <u>megaloblastic anemia</u> (decreased number of RBC, increased size; hypersegmentation of neutrophilic leucocytes) and <u>demyelinization of spinal cord and peripheral nerves</u>

Vitamin C (ascorbic acid)

- fruits and vegetables <u>not synthesized endogenously</u>
- involved in <u>metabolism of collagen and basic</u> intercellular matrix - involvement of vessel walls increased fragility - bleeding
- deficiency in adults scurvy
- deficiency in children Möller-Barlow disease subperiostal hematomas



Figure 8-22

Major consequences of vitamin C deficiency caused by impaired formation of collagen. They include bleeding tendency because of po vascular support, inadequate formation of osteoid matrix, and impaired wound healing.

Obesity

- ► <u>20% of world population</u>
- disorder of energetic balance food derived energy chronically exceeds energy expenditure, excess calories are stored as fat
- some genetic predispositions (multifactorial disease)
- ► Results
- <u>hypertension</u>
- ► <u>DM type II</u>
- hypercholesterolemia AS MI
- ► more frequent <u>malignant tumors</u> colon ca, breast ca, gallbladder ca, endometrial ca
- respiratory insuficiency in chronic bronchitis pulmonary hypertension cor pulmonale
- cholelithiasis (gallstones).

Diet and cancer

- not completely clear no clear evidence, that diet can cause or prevent from ca
- most frequently accused:
- red meat, animal fat, cholesterol, refined sugar, chemical additives
- assumption of WHO 1/3 of all ca nutrition
- oral cavity, pharynx, esophagus alcohol, smoking of cigarettes
- <u>colorectal ca</u> increased intake of fat, reduced intake of fibers
- <u>liver ca</u> aphlatoxin (nuts, grains) cirrhosis hepatocellular ca
- <u>breast ca</u> fat intake (in USA 10% of females increasing incidence)

Cardiovascular Disease

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Vascular Pathology

- Arteriosclerosis Means:
- hardening of the arteries
- 1 Atherosclerosis.
- 2 Monckeberg medial calcific sclerosis.
- 3 Arteiolosclerosis:
- 'The most common arteries involved in descending order:

Aorta

-Coronary

- -Popliteal
- -Internal carotid
- -Vessels of circle of Willis

Natural history and main consequences of Atherosclerosis

- The lesion is divided into 6 types:
- 1- fat dots
- 2- fatty streak
- **3- intermediate**
- 4- atheroma
- **5- fibroatheroma**
- 6- complicated atheroma

Risk factors of Atherosclerosis including: age, gender(male), obesity smoking, DM, lack of exercise, hypertension, hyperlipidaemia, type A personality (impatient, workaholic)

Sequence of cellular interactions in atherosclerosis Evolution of arterial wall changes in response to injury hypothesis



Complications:

1. Rupture, ulceration, and erosion of the surface>thrombosis

- 2. Hemorrhage in to plaque.
- 3. Thrombosis
- 4. Atheroembolism
- 5. Aneurysm



<u>Ischemic Heart Disease</u>

- Hypoxemia (diminished transport of oxygen by the blood) less deleterious than ischemia
- Also called coronary artery disease (CAD) or coronary heart disease

- IHD =Syndromes

late manifestations of coronary atherosclerosis

Cause => 90% of cases, coronary atherosclerotic arterial obstruction

Ischemic Heart Disease

- 75% stenosis = symptomatic ischemia induced by exercise
- 90% stenosis = symptomatic even at rest

Pathogenesis

- ↓ coronary perfusion relative to myocardial demand
- Role of Acute Plaque Change
 - (Erosion/ulceration, Hemorrhage into the atheroma, Rupture/fissuring, Thrombosis)
- Role of Inflammation
 - T cell, Macrophages (MMPs), CRP
- Role of Coronary Thrombus
 - The most dreaded complication
- Role of Vasoconstriction (VC)
 - Platelet & Endothelial factors, VC substances



<u>Ischemic Heart Disease</u>

- Angina Pectoris

- Chest discomfort = prolonged, recurrent, different qualities
- Cause = transient myocardial ischemia(seconds to minutes)
- Patterns
 - Stable = 75% vessel block, transient (<15 minutes), aggravated by exertion, relived by rest & Nitroglycerin (VD)</p>
 - Prinzmetal = coronary spasm, episodic, Typical EKG change ST elevation, Relived by VD but not rest
 - Unstable = 90% vessel block or Acute plaque change (superimposed thrombus), prolonged (>15 min.), not relived by rest, VD, Pre-infarction Angina



<u>Transmural</u>

Full thickness

Superimposed thrombus in atherosclerosis

Focal damage



<u>Sub-endocardial</u>

Inner 1/3 to half of ventricular wall

Decreased circulating blood volume(shock, Hypotension, Lysed thrombus) Circumferential



<u>Ischemic Heart Disease</u>

► <mark>M</mark>

Pathogenesis

- Coronary vessel occlusion
 - Atherosclerosis with thrombus = MC cause (90% cases)
 - ► Others = vasospasm (10%)
- Most important mechanism = dynamic changes in the plaque (rather than plaque size),
- Plaque disruption
 PLTS aggregation
 thrombus and VC (happens in minutes)
- Irreversible changes = after 30 minutes of ischemia
 - ► ATP < 10% of normal
- Mechanism of cell death = necrosis (Coagulative)



<u>Ischemic Heart Disease</u>

MI = Clinical

- Silent MI = DM, Elderly, Cardiac transplantation recipients,
- **Typical features** = Rapid, weak pulse and sweating profusely (diaphoretic), Dyspnea, chest pain

Lab=

- Diagnostic
 - **Best markers = Troponins (T & I), both sensitive and cardio specific**
 - ► Next best CK-MB
- Predictive
 - ► CRP->3mg/l highest risk

VASCULITIS

- Vasculitis : vessel wall inflammation.
- * Causes & pathogenesis
- I- Direct microbiological infection: eg. Pseudomonas, Aspergillus
- **II Immune-mediated:**
- 1) Immune complex deposition
- 2) Antineutrophil cytoplasmic antibodies
- 3) Antiendothelial cell antibodies
- 4) Autoreactive T cells

III-Others

(Physical and chemical injury, including radiation, mechanical trauma, and toxins)

Immune Complex-Associated Vasculitis

Autoantibody production and formation of immune complexes that deposit in vessels, eg.

1. SLE

- 2. Drug hypersensitivity vasculitis (penicillin)
- 3. Vasculitis secondary to infections (hepatitis B).

Giant Cell Arteritis

- The most common form of vasculitis in elderly (> 50yrs).
- Chronic, typically granulomatous inflammation of large to small size arteries.
- Most common arteries involved are: (temporal, vertebral, ophthalmic, aorta "giant cell aortitis")
- Pathogenesis:
- T cell mediated immune response to an as-yet uncharacterized vessel wall antigen that drive subsequent Pro-inflammatory cytokines release (especially TNF)
- Anti-endothelial cell antibodies & anti-smooth muscle ab found in 2/3 of cases.

Clinical features

- Temporal artery: headache & pain in artery course
- Ophthalmic artery: diplopia, loss of vision Temporal artery, giant cell arteritis
- Morphology: segemental involvement of vessel



- Giant cells arteritis:

- Granulomatous inflammation within the inner media with multinucleate giant cells
- Fragmentation of the internal elastic laminas

INFECTIVE ENDOCARDITIS .

Classification

- Acute, occurs in previously normal heart valve, caused by highly virulent microbe (eg. S aureus)
- Subacute, occurs in a previously abnormal valve, caused by low virulent microbe (eg. S viridans)
- * Both types are points along a spectrum and a clear delineation between them does not always exist

. Characterized by:

- Microbial infection of the heart valves or the mural endocardium
- Formation of friable vegetations (thrombotic debris & organism)
- Destruction of the underlying cardiac tissues
- . Causes:
- Bacteria (most cases) inclduing: S. viridans, S. aureus, enterococci,
- **Etiology and pathogenesis**
- Predisposing cardiac conditions
 - . Rheumatic heart disease
 - . Myxomatous mitral valve
 - . Degenerative calcific valve
 - . Bicuspid aortic valve

- . Artificial valves
- Host factors
- . Neutropenia
- . Immunodeficiency
- . Malignancy
- . Diabetes mellitus
- . Intravenous drug and alcohol abuse

Morphology

Single or multiple friable, bulky and destructive vegetations
 containing *inflammatory cells, fibrin, and microbes on the heart valves* Aortic and mitral valves are most commonly involved



Infective bacterial endomcarditis

A. large friable vegetations.

B. congenitally bicuspid aortic valve with extensive cuspal destruction and ring abscess

Hypertensive vascular disease

- Multifactorial disorder, (genetic & environmental)
- Defined as: sustained elevation of blood pressure above 140/90 mmHg

Types

- Essential (idiopathic) 95%
- Secondary 5% to .
 - renal disease .
 - endocrine abnormality .
 - cardiovascular disorder .neurogenic cause

CONGENITAL HEART DISEASES

- Most common types of heart diseases among children
- Occur in about 1% of live births, higher incidence in prematures and stillborns
- Etiology and pathogenesis
- I. Most are developmental anomalies during gestational 3-8 weeks
- **II. Multiple factors account for most cases:**
- **1.** Genes involved have been identified in only a minority of conditions, trisomy 21 is the most common
- 2. In utero rubella and syphilitic infections of the fetus

Clinical Features

Right to left shunt

Left to right shunt

- **Flow obstruction Shunt : is an abnormal communication between chambers or blood vessels.**
- Right to left shunt
- -Cyanosis is early, examples: .
- **Tetralogy of Fallot**.
- Transposition of the great arteries.
- Tricuspid atresia.
- **Tetralogy of Fallot TETRA:**
- 1) VSD
- 2) Subpulmonary stenosis
- 3) Aorta overrides the VSD
- 4) **Right ventricular hypertrophy**



Cardiovascular Diseases-2

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Principles of Cardiac dysfunction

- Failure of the pump : Damaged muscle contracts or relaxes weakly or inadequately.
- An obstruction to flow : This overworks the chamber behind obstruction.
- **Regurgitation flow:** Some of the output from each contraction is refluxed back—volume workload to ventricles.
- Disorders of cardiac conduction
- Disruption of the continuity of the circulatory system.

Hypertensive vascular disease:

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It is a multifactorial disorder defined as sustained elevation of blood pressure above 140/90 mmHg. According to this criterion about 25% of populations are regarded as hypertensives. There are two types:

- 1. Essential (idiopathic) in 95% of cases.
- 2. Secondary due to some underlying cause :
 - a. Renal (glomerulonephritis, renal artery stenosis and polycystic kidney diseases.
 - Endocrine (adrenocortical, pheochromocytoma, hyper and hypothyroidism).
 - c. Cardiovascular (coarctation of aorta and polyarteritisnodosa).
 - d. Neurogenic (psychogenic, increase intracranial pressure).

Morphology, there are two changes:

I. Hyaline arteriosclerosis.

- a. Occur in elderly patients particularly those with mild hypertension and diabetes.
- b. The lesion probably reflect EC injury with plasma leakage into arteriolar walls and ECM synthesis from SMCs.
- c. Microscopically there is diffuse pink hyaline thickening.

2. Hyperplastic arteriolosclerosis :

- a. Characteristic of malignant hypertension.
- b. There is concentric laminated (onion skin) thickening


Vascular pathology in hypertension. A, Hyaline arteriolosclerosis. The arteriolar wall is hyalinized and the lumen is markedly narrowed. B, Hyperplastic arteriolosclerosis (onion-skinning) causing luminal obliteration (arrow), with secondary ischemic changes, manifest by

Aneurysms:

It is a localized dilatation of the vessel or heart wall. We have two types:

- 1. True,
- 2. False.

Causes, include:

- 1. Atherosclerosis.
- 2. Congenital.
- 3. Trauma.
- 4. Infection.
- 5. Inflammation.

Morphologically: there are 2 types

- **1.**Saccular.
- **2.**Fusiform.



Types and sites of Aneurysm

Berry Aneurysms,

Are secular congenital of unknown etiology seen in smaller arteries of the brain especially in the circle of Willis:

- 1. Cigarette smoking and hypertension are considered as predisposing factors.
- 2. Although the aneurysms" are labeled as congenital, they are not present at birth but develop over time owing to the underlying defect in the medial.
- 3. Morphologically, they measure few millimeters to up to 3cm. There is lack of intimal elastic tissue and muscle fibers in the wall, which are replaced by hyalinized tissue.
- 4. Rupture of the aneurysm leads to subarachnoid hemorrhage, most frequent at the fifth decade and slightly more common in female.



Berry aneurysm. A saccular aneurysm (*arrow*) arises from the posterior cerebral artery.

Veins and Lymphatics:

<u>Varicose Veins</u>:

Abnormally dilated, tortous veins produced by prolonged increased intraluminal pressure and loss of vessel wall support. The superficial veins of the legs are the main sites of involvement. People at risk are:

- 1. Occupations with long period of standings.
- 2. People older than 50 years.
- 3. Obese individuals.
- 4. Women with multiple pregnancies.
- 5. Familial tendency (wall weakness).

Morphology, the dilated veins are tortous, elongated and scarred, with thrombosis.

Clinical course,

leg edema with stasis dermatitis. No embolism. Apart from legs, varices occur also at the lower end of esophagus and ano-rectum (hemorrhoids).



Tumors of Vessels:

Benign tumors and tumor-like conditions:

Ex. Hemangiomas; Capillary. Cavernous are the most common.



Hemangiomas. A, Hemangioma of the tongue. B, Histology of juvenile capillary hemangioma. C, Histology of cavernous hemangioma. D, Pyogenic granuloma of the lip. (A and D, Courtesy of Dr. John Sexton, Beth Israel Hospital, Boston, Massachusetts. B, Courtesy of Dr. Christopher D.M. Fletcher, Brigham and Women's Hospital, Boston, Massachusetts. C, Courtesy of Dr. Thomas Rogers, University of Texas Southwestern Medical School, Dallas, Texas.)

Cardiac (heart) Failure:

• A state that develops when the heart fails to maintain an adequate cardiac output to meet the demands of the body.

Left sided heart failure

- Progressive damming of the blood within the pulmonary circulation and the consequences of diminished peripheral BP and flow.
- Causes :
- IHD
- Systemic HTN,
- MI,
- valvular disease,
- Non ischemic myocardial disease.

Left sided heart failure: Morphology

Lungs:

- Pressure in the pulmonary veins are transmitted retrograde to the capillaries and arteries.
- Pulmonary congestion and oedema.
- Heavy wet lungs.

Pulmonary changes:

- A perivascular and interstitial transudate, particularly in the interlobular septa.
- Progressive oedematous widening of alveolar spaces.
- Accumulation of oedema fluid in the alveolar spaces.
- Siderophages or heart failure cells.



Clinical manifestation:

- **Dyspnoea (breathlessness):**
- Exaggeration of the normal breathlessness that follows exertion.
- **Orthopnea:**
- Dyspnoea on lying down that is relieved by sitting or standing.
- Paroxysmal noctural dyspnea:
- An extension of orthopnea with attacks of extreme dyspnoea bordering on suffocation, usually occurring at night.
- ► Cough

Right sided heart failure.

- Usually as a consequences of left sided heart failure.
- *Cor pulmonale:* chronic severe PHT due to increased resistance within the pulmonary circulation.
- Other causes : multiple pulmonary emboli, valvular diseases.
 - HEART:
 - Hypertrophy and dilation are generally confined to right ventricle and atrium.
 - ► LIVER AND PORTAL SYSTEM:
 - Passive Congestive hepatomegaly

(Nutmeg liver)

- Centrilobular necrosis along with the sinusoidal congestion in case of severe central congestion.
- Cardiac sclerosis or cardiac cirrhosis.
- ► Congestive splenomegaly (300 500gm).
- Ascites: accumulation of transudate in the peritoneal cavity.



Heart failure

LHF

- Pulmonary congestion and oedema.
- Cough
- Dyspnoea
- Orthopnea
- PND

RHF

- Absence of respiratory symptoms/insignificant.
- Systemic (and portal) venous congestive syndrome.
- Hepatosplenomegaly
- Peripheral oedema
- Pleural effusion
- Ascites.

Congenital Heart Disease

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• Most common type of heart disease

among children

- a) $\sim 1\%$ of live births
- **b)** most causes unknown
 - i) $\sim 10\%$ genetic
 - e.g., trisomy 21 (Down syndrome)
 - congenital defect in parent or sibling is greatest factor

Types:

- a) L to R shunt
- **b) R** to **L** shunt

c) obstructions

1.- <u>L to R shunts</u>

- a) ASD, VSD, PDA
 - i) \uparrow pulmonary blood flow (ASD)
 - NO cyanosis
- **b**) \uparrow RV pressures and Vol. (VSD,PDA) i) hypertrophy

 - ii) ↑ PVR (vasoconstriction)
 - to prevent edema

- c) Over time $PVR \uparrow$ to that of SVR
 - i) reverses shunt (cyanosis)

2.- <u>R to L shunt</u>

- a) ↓ pulmonary blood flowi) Cyanosis "blueness" of skin
- **b**) examples:
 - i) tetralogy of Fallotii) great vessel transposition
 - iii) tricuspid atresia

c) long standing cyanosis is associated with "clubbing" of the tips of the fingers and toes





Left to Right Shunts



i) VSD most common

close spontaneously (50%)
ii) ASD usually not symptomatic before 30 yrs

Right to Left Shunts

• <u>Tetralogy of Fallot</u>

a) Most common form of cyanoticcongenital heart disease

Defects:

a) VSD
b) Pulmonary artery stenosis
i) determines clinical outcome
c) aorta that overrides VSD

Tetralogy of Fallot



Heart with Defects Found with Tetralogy of Fallot



Obsttructive Congenital Anomalies

Coarctation of the Aorta

Narrowing

Males 2:1 vs. female
 a) females with Turners frequently have coarctation

• 2 types:

- a) infantile (with PDA; poor outcome)
 - symptoms early in life
 - cyanosis of lower body
- b) adult (without PDA)
 - i) most children asymptomatic until late in life
- ii) hypertension in upper extremities iii) hypotension in lower extremities LV hypertrophy



Rheumatic Fever and Heart Disease

• <u>*RF*</u> is acute inflammation

a) within weeks following group A streptococcal pharyngitis

i) cross reaction of Ab directed at M proteins of Strep.

proteins

with glycoprotein Ag in heart, etc.

b) acute carditis (RF) may develop to chronic <u>**RHD**</u>

c) consequence of RF is chronic valvular deformities (fibrosis)

- mitral and aortic
 - mainly mitral stenosis
 - permanent

Pathology:

- a) RF → focal inflammatory lesions
 i) "Aschoff" bodies pathognomonic for RF
 - swollen eosinophilic collegen
 - found is any layer of the heart ("pancarditis"
 - in pericardium → fibrinous or serofibrinous exudate
 - ii) "Anitschkow" cells
 - swollen activated macrophages and/or plasma cells





b) RHD - chronic i) organized acute inflammation - fibrosis \rightarrow ii) leaflet thickening iii) commissure fusion (stenosis) - "buttonhole" or "fishmouth" stenoses iv) cord fusion / thickening V) Aschoff bodies replaced with fibrous scar

Stenotic mitral Valve seen from left atrium. Both commissures are fused; the cusps Are severely thickened. The left atrium is huge. The valve is both incompetent and stenotic



Opened stenotic mitral valve showing thickening distorted cusps, adherent commissures with calcification and thrombus deposition, and thickening, fusion and shortening of chordae tendinae



- <u>Clinical (major criteria):</u>
 - a) migratory polyarthritis
 i) large joints
 b) carditis
 c) s.c. nodules
 - d) erythema marginatum
 - e) Chorea movements (CNS) (Sydenham Chorea) ("St. Vitus Dance")
- Minor criteria
 - Fever
 - ArthralgiaHigh ESR



Infective Endocarditis

- Most cases are bacterial
- Classification based on clinical grounds a) acute i) destructive (necrotic, ulcerative) valvular infections ii) Friable, bulky, vegetation contiaing fibrin, inflammatory cells and m.o. iii) highly virulent (S. aureus) iv) frequently of healthy valve $v \sim 50\%$ lethal: days to weeks - despite antibiotics/surgery



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b) Subacute

i) low virulence (causative organisms) ii) \uparrow recovery with antibiotic Tx iii) vegetative growths show signs of healing iv) colonizing a previously abnormal heart valves. v) Splenomegaly is common. vi) The aortic and mitral values are the most common sites of infection

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Anemia

Is a reduction in circulating erythrocyte mass. A diagnosis of anemia is made by demonstrating a reduction in hemoglobin, hematocrit (HCT), or red blood cell (RBC) count. Anemia leads to decreased oxygen transport by the blood and ultimately to tissue hypoxia.

The symptoms of iron deficiency are those of anemia in general.

With advanced disease, a smooth and glistening tongue (atrophic glossitis) and inflammation at the corners of the mouth (angular stomatitis) may be encountered, as well as a spoon shaped deformity of the fingernails (koilonychia).

Treatment of iron deficiency :

Correcting the source of chronic blood loss and oral or parenteral iron supplementation.

Clinical Classification of Anemias is by Morphology or Pathophysiology

Anemias are classified by morphology or pathophysiology.

The morphologic classification of anemia is based on erythrocyte appearance, as determined by automated blood counters and microscopic evaluation of a blood smear. RBC size is reflected in the mean corpuscular volume (MCV), which allows division of anemias into three groups:

- 1. Microcytic (decreased MCV)
- 2. Normocytic (normal MCV),
- 3. Macrocytic (increased MCV).

Anemias may also be classified as normochromic (RBCs with a normal content of hemoglobin) or hypochromic (RBCs with a reduced content of hemoglobin).



Iron Deficiency Anemia

Iron deficiency interferes with normal heme (hemoglobin) synthesis and leads to impaired erythropoiesis and anemia. Iron deficiency is the most common cause of anemia worldwide.

Anemia of Lead Poisoning

 Lead poisoning results in anemia by interfering with several enzymes involved in heme synthesis



Thalassemia

Are anaemias that result from defective globin chain synthesis. Ineffective haematopoiesis results from precipitation of abnormal hemoglobins within newly formed RBCs and increased erythrocyte fragility, features that lead to erythrocyte destruction in the marrow.



Thalassemia are generally classified according to the affected globin chain. The two most clinically significant forms involve deficits of α and β chains.

Sickle cell disease

In sickle cell disease, an abnormal hemoglobin, namely hemoglobin S, transforms the erythrocyte into a sickle shape upon deoxygenation.



Megaloplastic anemia

Are caused by impaired DNA synthesis usually because of deficiency in Vit B12 or folic acid.


Bleeding Tendency Causes

Thrombocytopenia

Thrombocytopenia is defined as a platelet count under 150,000/ μ l. The lower the platelet count, the greater the risk of traumatic and perioperative bleeding. Patients with fewer than 10,000 platelets/ μ l are at an increased risk of spontaneous hemorrhage

Causes of Thrombocytopenia

1.decresed platelet production

- a . Aplastic anaemia .
- b . Megaloblastic anaemia (decrease Vit . B12 or / and decrease folic acid) .
- c . Bone marrow infiltration by neoplasms .
- d . Cytotoxic drugs (Dose Dependant) .
- e . lonizing radiation (Dose Dependant) .
- f. Drugs ; cause thrombocytopenia in some recipients : Metheprim , Phenylbutazone , Gold compounds .

g . Alcohol .

2. Increased destruction of platelets

Usually it occurs after sensitivity to many drug through type-2 hypersensitivity reaction (IgG dependent)

Hemophilia

Hemophilia A (Factor VIII Deficiency)

PATHOGENESIS: Hemophilia A is the most common sex-linked inherited bleeding disorder (1 per 5,000 to 10,000 males). Causative mutations in the very large factor VIII gene at the tip of the long arm of the X chromosome (Xq28)

Hemophilia B

PATHOGENESIS: Hemophilia B is an X-linked heritable disorder of factor IX deficiency.

At 1 in 20,000 male births, hemophilia B is four times less com mon than hemophilia A and accounts for 15% of all cases of hemophilia.

Factor IX is a vitamin K-dependent protein that is made in the liver. Many different mutations.

Diseases of WBCs

Principal Causes of Neutrophilia

- Primarily bacterial
- Immunological Inflammatory
- **Neoplasia**
- Hemorrhage
- Drugs i.e. Glucocorticoids

Decreased Production

- Irradiation
- Drug-induced (long- and short-term)
- Viral infections
- Others

Leukemia and lymphoma

Malignant leukocytes originate from either myeloid cells or lymphoid cells. Malignant proliferations of myeloid cells are derived from bone marrow cells and manifest as myelodysplastic syndromes, myeloproliferative diseases, or acute myelogenous leukaemia.

By contrast, malignant lymphocytes can arise in any compartment that contains lymphoid (lymphoma)

Lymphomas

Lymphomas are malignant proliferations of lymphocytes or lymphoblasts.

B-and T-cell lymphomas are further categorized as derived from immature (precursor) cells or from mature (peripheral) effector cells.



GIT, Liver, Pancreas, and Gallbladder Diseases Lect 15

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The Esophagus

 A muscular tube extend from the epiglottis to the gastro-esophageal junction

Histology of esophagus

- 1.Mucosa: nonkeratinised stratified squamous epithelium.
- 2.Submucosa
- 3..Muscular layer
- 4.Adventitia



Esophageal varieces

- Dilatation of the veins of the submucus plexus at the lower end of the esophagus due to portal hypertention.
- The are liable to rupture causing fatal bleeding



Reflux esophagitis

Inflammation and ulceration at the lower part of the esophagus due to reflux of the acid gastric juice .

Causes of Reflux esophagitis

- 1.Hiatus hernia
- 2.Persistant vomiting
- 3.Increased intra-abdominal pressure e.g. pregnancy, obesity etc.

Pathology of reflux esophagitis

- Macroscopically: The lower part of the esophageal mucosa show patchy ulceration, inflammation and in chronic cases fibrosis and stricture
- Microscopically: Chronic inflammation and fibrosis



Acute gastritis

- Acute inflammation of the gastric mucosa
- Etiology: drugs,alcohol,bacterial toxins
- Bacterial infection is not important
- Macro: the mucosa red oedematous with focal

haemorrhages, ulceration, perforation

 Micro:Congestion and acute inflammation



Chronic gastritis

- Chronic inflammatory changes of gastric mucosa with variable degree of loss of specialised glandular epithelium, metaplasia that may lead to achlorhydria and loss of intrinsic factor which lead to pernicious anaemia.
- It is usually associated with chronic gastric ulcer and gastric cancer

Etiology (cont)

Etiology:

- I. It is considered as organ specific autoimmune disease. Due to presence of autoantibody in the serum against cell membrane of parietal cells and against intrinsic factor. It has familial tendency and associated with other autoimmune diseases e.g thyroiditis
- 2.H.pylori (Helicobacterium pylori)
- 3.Drugs, alcohol smoking

Pathology of chronic

- Sastrivise opically: There is little correlation between gross, microscopic appearance and symptom of the patient
- So the classification of chronic gastritis depends on the microscopical appearance

Pathology of chronic gastritis (cont)

- Microscopically: there are three types:
- 1. Chronic superfecial gastritis. characterised by:
- Normal thickness of the mucosa
- The inflammatory changes is limmited to the superfectial zone only
- 2. Chronic atrophic gastritis:
- Follow chronic superfecial gastritis.
- The inflammatory changes involve the entire thickness of the mucosa
- The thickness of the mucosa reduced
- There is atrophy of the specialised cells(chief &parietal cells) which are replaced my mucus secreating cells(pseudopyloric metaplasia)
- Intestinal metaplasia:presence of goblet cells,paneth cells and prominent striated border

Pathology of chronic gastritis (cont)

Gastric atrophy:

- Thickness of mucosa markedly reduced
- Complete atrophy of specialised cells
- Intestinal metaplasia, cystic changes and presence of lymphoid follicles

Peptic ulcer

Digestion of the mucosa of the affected part (stomach,esophagus,meckles diverticulum) by acid and pepsin

Etiology of peptic ulcer

- 1. Acid and pepsin secreation
- 2. Infection by H-pylori
- 3. Alteration of mucus secreation
- 4. Others: dietary genetics, vascular trauma, gastritis, smoking, psychsomatic etc.



Types of gastric ulcer

- According to the duration, degree of penetration and degree of healing, peptic ulcer is divided in to:
- 1.Acute peptic ulcer.
- 2.Chronic peptic ulcer

Acute gastric ulcer

- Gross: small multiple 1-2 cm , affect any part of the stomach, involve mucosa and submucosa and heal without fibrosis
- Rarly it may perforate and bleed

Chronic gastric ulcer

- Microscopically:
- the surface is covered by fibrinoid materials.
- Layer of granulation tissue
- Layer of fibrous tissue
- Interruption of muscular layer
- Endarteritis of affected vessels
- Usually single rarely two ,The lesser curvature is most commonly arrected.
- Large in size up to 5 cm rounded or oval , its surface is covered by necrotic materials
- the induration involve the entire thickness of the wall of the stomach, it may be adherant to surrounding organ and may form fistulla.



Complications of chronic gastric ulcer

- 1. Heamorrhage; leading to hematemesis and Malena. Chronic oozing lead to anemia
- 2. **Perforation:** result in passage of food, gastric juice , bacteria to peritoneal cavity leading to peritonitis
- 3. Fibrosis: fibrosis lead to pyloric obstruction , hour glass stomach
- 4. Malignant changes: Rare .=/less 1%

Duodenal ulcer

- Usually affect the first part of the duodenum
- Grossly and microscopically the same as chronic gastric ulcer
- The complications are similar except that malignant changes is extremely rare

Anat ony

Shape:	Pear shaped
Size:	7-10cm x 3cm
Capacity:	30-50 ml.
Parts:	Fundus, Body, Nec
Cystic duct:	3-4 cm long
CBD:	8 cm long
	6 mm in diameter

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k

Functions of GB:

Storage & conc. of bile
 Acidification of Bile



Gallstones

Types of gallstone

- Cholesterol stones (80%)
- Pigment stones (20%)

Epidemiology

- Fat, Fair, Female, Fertile, Fourty inaccurate, but reminder of the typical patient
- F:M = 2:1
- 10% of British women in their 40s have gallstones
- Genetic predisposition ask about family history

Pathogenesis

- Cholesterol
 - Imbalance between bile salts/lecithin and cholesterol allows cholesterol to precipitate out of solution and form stones
- Pigment
 - Occur due to excess of circulating bile pigment (e.g. Heamolytic anaemia)

Other Factors

- Stasis (e.g. Pregnancy)
- Ileal dysfunction (prevents re-absorption of bile salts)
- Obesity and hypercholesterolaemia

Infective Factor

cholesterol stones: composed of cholesterol



solitary, smooth surface oval/round shape pale-yellow coloured

Pigment stones: consist of Ca-bilirubinate

Black /Dark brown



Associated with raised bilirubin production-haemolysis

Small, multiple, soft putty-like-masses.

EFFECTS AND COMPLICATIONS OF GALLSTONES

In the gall bladder

silent stone Ac. Cholecystitis Chr. Cholecystitis Gangrene

In the bile duct:

obstructive jaundice cholangitis Acute pancreatitis

In the intestine:

Acute intestinal obstruction [gallstone ileus]

perforation empyema mucocele carcinoma

CHOLECYSTITIS:

It is an inflammatory condition of the gall bladder.

- 1. Acute
- 2. Chronic

(a) Secondary chronic cholecystitis(b) Primary chronic cholecystitis

CUTE CHOLECYSTITIS: 90% associated calculi

PATHOLOGY

- . Obstruction or stasis
- . Chemical irritation
- . Bacterial Infection



Pathology

 GB is shrunken, contracted,small, nonfunctioning, fibrotic with thickened GB wall

Mucosa proliferates into Lumen → ROKITANSKY ASHCHOFF SINUSES Muscular wall replaced by Fibrotic tissue

Chronic Cholecystitis

Chronically Inflammed Thickened Gallbladder which is NONFunctioning NONdistending



- Microscopic :
 - Reactive proliferation of mucosa
 - Inflammation (lymphocytes, plasma cells, and macrophages in the mucosa and in the subserosal fibrous tissue). May be minimal.



- Prominent outpouching of the mucosal epithelium through the wall (Rokitansky Aschoff sinuses)
- Marked subepithelial and subserosal fibrosis
- +-Superimposed acute inflammation
- +-Extensive calcification within the wall
 →porcelain gall bladder →increase risk of cancer





Fig. 16.21 Histology of chronic cholecystitis. A thickened gall bladder with diffuse chronic inflammatory infiltration and Rokitansky-Aschoff sinuses (arrowed).

Pancreas Pathology

Microscopic Anatomy of the Pancreas



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PANCREAS DISEASES

- Congenital
- Inflammatory
 - Acute
 - Chronic
- Cysts

Neoplasms Congenital

Agenesis (very rare)

Pancreas Divisum (failure of 2 ducts to fuse) (common)

Annular Pancreas (pancreas encircles duodenum) (rare)

Ectopic Pancreas (very common)

PATHOLOGY OF THE PANCREAS

Major clinical problem of the pancreas

Pancreatitis

- Inflammation of the pancreas associated with acinar cell injury = pancreatitis General pathogenesis: Acinar cell injury releases pancreatic enzymes that autodigest the parenchyma
- Occurs along a spectrum of severity (ranging from mild/self-limited to severe/life threatening) and a spectrum of duration

(quick transient attack to chronic irreversible loss of function)

 Mechanism: autodigestion by inappropriately activated pancreatic enzymes

Two major forms of pancreatitis

Acute pancreatitis

 By definition, the gland can return to normal if the underlying cause is removed

Chronic pancreatitis

 By definition, there is irreversible destruction of predominately the exocrine pancreatic parenchyma

Acute pancreatitis: Reversible damage Chronic pancreatitis: Permanent damage

Acute Pancreatitis

Relatively common

- Annual incidence in Western countries is 10-20 cases/100,000 people
- 80% of cases in Western countries are associated with:

Duct obstruction from tumor, medications (thiazide diuretics), infections

- Biliary tract disease such as gallstones
 - Male to female ratio = 1:3
- Alcoholism
 - Male to female ratio = 6:1
- Less common causes

Acute pancreatitis caused by biliary tract disease is female-dominant, while alcohol-related pancreatitis is male-dominant. Summary of different ways you can get pancreatitis. Nothing added.






Chronic Pancreatitis

body do when damaged? Answer: Make a

scar (fibrosis)

- Repeated bouts of pancreatitis
- Loss of pancreatic parenchyma and replacement by fibrosis
 - Relative sparing of the Islets of Langerhans until the late stages
- Resultant irreversible impairment of pancreatic exocrine function
 Due to lack of release of Not sure why this

nzvmes

- Malabsorption ∠
- Steatorrhea <
- Most common cause: long-term alcohol abuse

From Robbins: 65% of chronic pancreatitis in the US is from chronic alcohol abuse







Pancreatic Adenocarcinoma

- Often considered a disease of the elderly
 - 80% occur between the ages of 60 80
- Risk Factors
 - <u>Smoking</u>
 - The strongest environmental factor
 - Doubles the risk of developing pancreatic cancer (impact is significant due to large number of people who smoke)
 - Chronic pancreatitis

Pancreatic Adenocarcinoma Clinical Features

Often remains silent until it impinges on some other structure

- Pain is often one of the first symptoms 4
- Obstructive jaundice is common < Due to increased bilinubin
 Weight loss, anorexia, generalized malaise and weakness
 Disease course is usually brief and progressive
 Fewer than 20% are resectable at the time of diagnosis

Pancreatic Cancer

Macroscopic Features

- 60% occur in the HOP
 - 15% body
 - 5% tail
 - 20% diffusely involves the pancreas
- Gross exam:
 - Hard, stellate, gray-white, poorly defined



- Carcinoma in the HOP often leads to obstruction
- Carcinoma of the body and tail may remain silent for a longer period of time

ead of the

none as

- Infiltrative nature often leads to extension into retroperitoneal space and lymphovascular invasion
- Metastasis to liver is common
 And to the supraclavicular nodes on the side and the periumbilical region (Gol)

Microscopic Findings

- 2 features highly characteristic of pancreatic ductal adenocarcinoma
 - Highly infiltrative
 - Elicits an intense non-neoplastic host response comprised of fibroblasts, chronic inflammatory cells, and matrix "desmoplastic



sible exam



Liver Pathology

- Largest internal organ
- Weighs about 1400-1800 gram
- Located on right side under ribcage
- Ability to regenerate
- Has over 500 vital functions
- Involved in many digestive, vascular and metabolic activities





Patterns of Hepatic Injury

 When exposed to any injurious stimuli, the hepatocytes undergo certain changes.

 Irrespective of the cause, 5 general responses are seen. These changes may exist alone or in combination depending upon the etiology.

- 1) Degeneration & Intracellular accumulation
- 2) Necrosis & Apoptosis
- 3) Inflammation
- 4) Regeneration
- 5) Fibrosis

Liver diseases pathogenesis is characterized by two main mechanisms:

- the direct hepatocytes affection:
- a) dystrophy,
- b) necrosis;
- autoimmune injury of hepatocytes by autoantibodies, which are formed in response to hepatocytes antigens structure changed.
- Liver affection by any of the above described etiologic factors may lead to such state, when the liver becomes not capable to execute its functions and to provide the homeostasis. That state is called the liver insufficiency.
- It may be total, when all functions are suppressed;
- or partial, when only some functions suffer, e.g., the bile-forming one.

Causes of Hepatocyte Injury

Various forms of hepatocyte injury:

- Infectious
 - Viral Hepatitis Most common form of injury viral hepatitis
 - Others...
- Autoimmune Hepatitis
- Toxic/Drug Induced Injury

 Alcohol
- Metabolic Injury
 - Non-Alcholic Fatty Liver Disease (NAFLD) Epidemic of metabolic syndrome, obesity. This is a growing topic.
- Intracellular Depositions
 - Hemochromatosis
 - Alpha-1-antitrypsin
 - Wilson Disease

ACUTE VIRAL HEPATITIS

+/-

- INCUBATION PERIOD Depends on the particular hepatotropic virus.
- CLINICAL FEATURES Malaise, Anorexia, Nausea. pyrexia, upper abdominal pain.
- jaundice, +/- dark urine and pale stool.
- tender hepatomegaly.
- **BLOOD TESTS** Those of "hepatocellular" jaundice.
- viral markers.
- ACUTE HEPATITIS VIRUSES A, B, C, E, AND DELTA AGENT
- ACUTE INFECTION MAY CAUSE JAUNDICE OR SUBCLINICAL
- OTHER VIRUS CAUSING LIVER DAMAGE, INCLUDE EPSTEIN-BARR VIRUS, HERPES
 SIMPLEX VIRUS AND CMV
- VIRUS TRANSMITTED BY ORAL(A,E) OR BLOOD BORN ROUTE" B,C".
- BLOOD BORNE VIRUS CAN CAUSE CHROMIC INFECTION (B,C) AND ARE ASSOCIATED WITH CIRRHOSIS AND HEPATOCELLULAR CARCINOMA HCC.

POSSIBLE OUTCOME OF VIRAL HEPATITIS

RESOLUTION -

- FULMINANT HEPATITIS
- 1% Or less. (HAV & HBV)
- Massive liver necrosis (panacinar necrosis).
- And death from liver failure
- CHRONIC HEPATITIS
- 5 10% But much higher in HCV.
- Some types do not progress to chronicity.
- CIRRHOSIS
- +/- Hepatocellular carcinoma.

CHRONIC HEPATITIS

- Chronic hepatitis is an inflammation of the liver continuing without improvement for at least 6 months.
- Is a clinico-pathological syndrome, not a single disease.
- has several causes.
- Is characterized by varying degrees of inflammation, necrosis and usually fibrosis.
- It may or may nor be associated with cirrhosis (cirrhosis may already be established at the time of diagnosis).



Chronic hepatitis with lobular activity. Clumps of inflammatory cells, some of them associated with hepatocyte loss, extend

Alcoholic liver disease

3 forms of alcoholic liver injury

- Hepatocellular steatosis Fatty change
- Alcoholic hepatitis (steatohepatitis)
- Steatofibrosis cirrhosis

Mechanism include:

- Toxic effects of acetaldehyde (the metabolite of alcohol)
- Oxidative stress
- Impaired carbohydrate and fat metabolism
- Stimulation of collagen synthesis



Cirrhosis

Etiology: triad

- 1. necrosis
- 2. regenerating nodules
- 3. fibrosis
- Categories: Major^{. disruption} of architecture of the liver
 - Alcoholic (#1 cause in western world) Post necrotic
 - Minor
 - Wilson's disease
 - Haemochromatosis
 - Biliary
 - Chronic hepatic congestion
 - **Budd-Chiari syndrome**
 - uncommon condition Induced by thrombotic or nonthrombotic obstruction to hepatic venous outflow
 - Cardiac
 - Right sided heart failure
 - Tricuspid insufficiency



Cirrhosis Healthy Fatt

Cirrhosis



