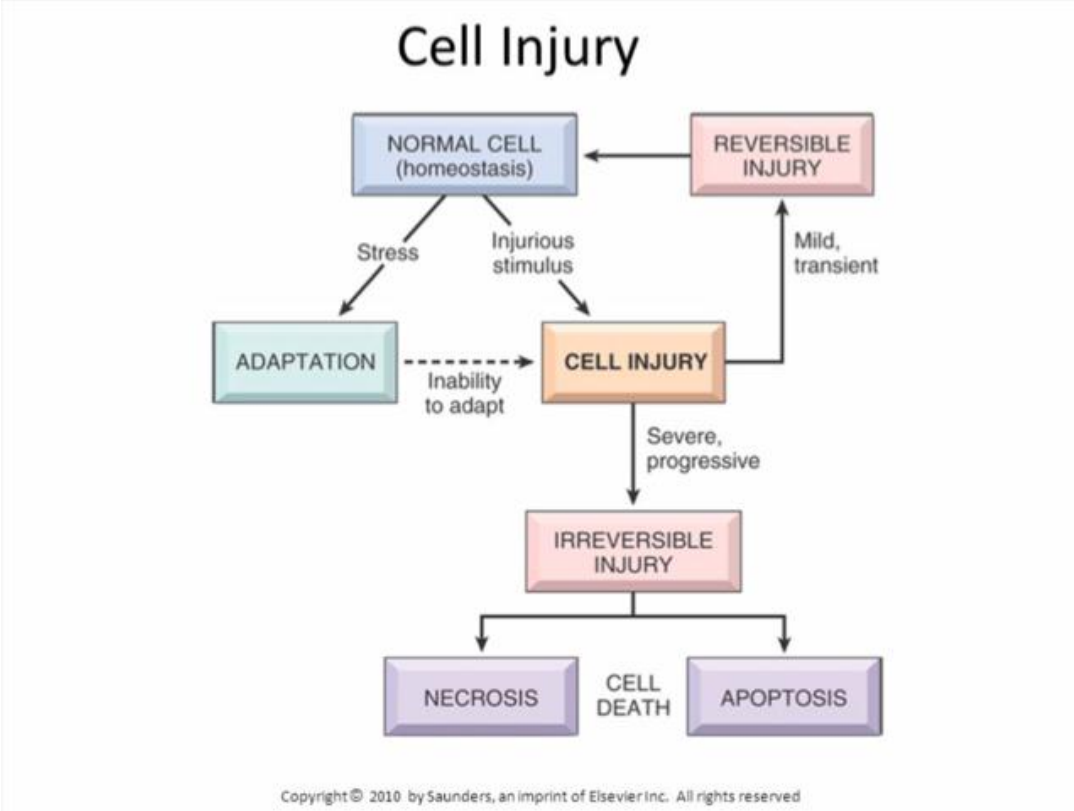
Lecture 1: Cell injury (Cell damage)



Cell injury

An alteration in cell structure or biochemical functioning resulting from some stress that exceeds the ability of the cell to compensate through normal physiologic adaptive mechanisms.

CAUSES OF CELLULAR INJURY

1. Hypoxia

Most common cause of injury

Definition: lack of oxygen leads to the inability of the cell to synthesize sufficient ATP by aerobic oxidation

Major causes of hypoxia:-

i. Ischemia: loss of blood supply, decreased arterial flow or decrease venous outflow e.g., atherosclerosis, thrombus, thromboembolus

ii. Co poisoning

iii. Decreased oxygen-carrying capacity of the blood (example: anemia)

2. Infections

Viruses, bacteria, parasites, and fungi.

3. Immunologic reactions

a. Hypersensitivity reactions

b. Autoimmune diseases

4. Congenital disorders

5. Chemical injury

a. Drugs

b. Poisons (cyanide, mercury, etc.)

c. Pollution

d. Social/lifestyle choices (alcohol, cigarette smoking).

6. Physical forms of injury

a. Trauma (blunt/penetrating/crush injuries, gunshot wounds).

b. Burns

c. Radiation

7. **Nutritional or vitamin imbalance**

a. Inadequate calorie/protein intake

b. Excess caloric intake

c. Vitamin deficiency

8. Aging

Pathogenesis of cell injury

Injury to the normal cell by one or more of the etiologic agents may result in a state of **reversible** or **irreversible** cell injury.

Cellular response to injury depends on several important factors:-

i. The type of injury

ii. The duration of injury

iii. The severity of injury

iv. The type of cell injured

Reversible cell injury

If the ischaemia or hypoxia is of short duration, the effects may be reversible on rapid restoration of circulation**.**

Morphology of reversible cell injury are:-

1. Hydropic change (cloudy swelling, or vacuolar degeneration)
2. Fatty change
3. Hyaline change
4. Mucoid change

Hydropic change:

Means accumulation of water within the cytoplasm of the cell. Other synonyms used are **cloudy** and **vacuolar degeneration** (due to cytoplasmic vacuolation).

The common causes bacterial toxins, chemicals, poisons, burns, high fever, intravenous administration of hypertonic glucose or saline..

Pathogenesis: results from impaired regulation of sodium and potassium at the level of cell membrane. This results in intracellular accumulation of sodium and escape of potassium. This, in turn, is accompanied with rapid flow of water into the cell to maintain iso-osmotic conditions and hence cellular swelling occurs.

The affected organ such as kidney, liver, pancreas, or heart muscle is enlarged due to swelling.

2. Fatty change

The cell has been damaged and is unable to adequately metabolize fat. Small vacuoles of fat accumulate and become dispersed within cytoplasm. It is especially common in the liver (Liver is the commonest site for accumulation of fat because it plays central role in fat metabolism) but may occur in other **non- fatty tissues** like the heart, skeletal muscle, kidneys .Depending on the cause and severity of the lipid accumulation, fatty change is generally reversible. Fatty Change is also known as fatty degeneration, fatty metamorphosis, or fatty steatosis.

3.Hyaline Change

The word 'hyaline' means glassy (hyalos = glass). Hyaline change is a homogenous glassy pink appearance in the histological sections stained with hematoxylin and eosin. It can be due to intracellular accumulation of certain substances as in Russel bodies (multiple myeloma), Mallory bodies (alcoholic liver disease), re-absorption droplets (kidney). Extra cellular hyaline change can be seen in walls of the arterioles in long standing hypertension and diabetes mellitus. This is due to extravasated plasma protein and deposition of basement membrane material.

4. Mucoid Change

Mucus secreted by mucous glands is a combination of proteins complexed with mucopolysaccharides. Mucin, a glycoprotein, is its chief constituent. Mucin is normally produced by epithelial cells of mucous membranes and mucous glands, as well as by some connective tissues.

Intracellular accumulations.

Intracellular accumulation of substances in abnormal amounts can occur within the cytoplasm (especially lysosomes) or nucleus of the cell. Intracellular accumulation of the substance in **mild** degree causes **reversible cell injury** while more **severe** damage results in **irreversible cell injury.**

Such abnormal intracellular accumulations can be divided into 3 groups:

i) **Accumulation of constituents of normal cell metabolism produced in excess** e.g. accumulations of lipids (fatty change, cholesterol deposits), proteins and carbohydrates. In addition, deposits of amyloid and urate .

ii) **Accumulation of abnormal substances produced as a result of abnormal metabolism due to lack of some enzymes** e.g. storage diseases or inborn errors of metabolism.

iii) **Accumulation of pigments** e.g. endogenous pigments under special circumstances, and exogenous pigments due to lack of enzymatic mechanisms to degrade the substances or transport them to other sites.

Proteins

Pathologic accumulation of proteins in the cytoplasm of cells may occur in the following conditions:

i. Protein accumulates in proximal renal tubules in proteinuria

ii. Russell bodies: intracytoplasmic accumulation of immunoglobulins in plasma cells

Glycogen storage diseases

In diabetes mellitus, there is intracellular accumulation of glycogen in different tissues.

Pigments

Pigments are colored substances present in most living beings including humans.

There are 2 broad categories of pigments: endogenous and exogenous.

1- Exogenous pigments

Exogenous pigments are the pigments introduced into the body from outside such as by inhalation, ingestion or inoculation.

i. pigmentation of the lung is secondary to the inhalation of carbon dust

ii. Tattoos

2- Endogenous pigments

Endogenous pigments are either normal constituents of cells or accumulate under special circumstances e.g. melanin and lipofuscin.

i. **Lipofuscin**

yellowish-brown intracellular lipid pigment. Is often found in atrophied cells of old age . Common in the liver and heart

ii. Melanin

• Black-brown pigment

• normally present in the hair, skin, choroid of the eye, meninges and adrenal medulla. Found in melanocytes and substantia nigria

Cellular adaptive responses to injury:-

a. Cellular adaptation is the result of a persistent stress or injury
b. Adaptive responses are potentially reversible once the stress has been removed
c. Some forms of adaptation may precede or progress to malignancy

Atrophy

Definition: decrease in cell size and functional ability

Causes of atrophy:

i. Deceased workload/disuse (immobilization)
ii. Ischemia (atherosclerosis)
iii. Lack of hormonal or neural stimulation
iv. Malnutrition
v. Aging

c. Micro: small shrunken cells with lipofuscin granules

3. **Hypertrophy**

Definition: is an increase in the size of parenchymal cells resulting in enlargement of the organ or tissue, without any change in the number of cells.

Causes

A. Physiologic hypertrophy. Enlarged size of the uterus in pregnancy .

B. Pathologic hypertrophy

1. Hypertrophy of cardiac muscle
2. Hypertrophy of smooth muscle

4. **Hyperplasia**

Definition: is an increase in the number of parenchymal cells resulting in enlargement of the organ or tissue.

Causes

A. Physiologic hyperplasia

1. Hormonal hyperplasia (pregnant uterus, Prostatic hyperplasia in old age.)

B. Pathologic hyperplasia e.g.

i) Endometrial hyperplasia following oestrogen excess.
ii) In wound healing.
iii) Formation of skin warts from hyperplasia of epidermis due to human papilloma virus.

5. **Metaplasia**

Definition: a reversible change of one cell type to another, usually in response to irritation and often reverts back to normal on removal of stimulus. However, if the stimulus persists for a long time, epithelial metaplasia may transform into cancer.

For example, bronchial epithelium undergoes squamous metaplasia in response to the chronic irritation of tobacco smoke.

6. **Dysplasia**

Definition: an abnormal proliferation of cells that is characterized by changes in cell size, shape, and loss of cellular organization. Dysplasia is not cancer but may progress to cancer (preneoplastic lesion)

Examples: cervical dysplasia.

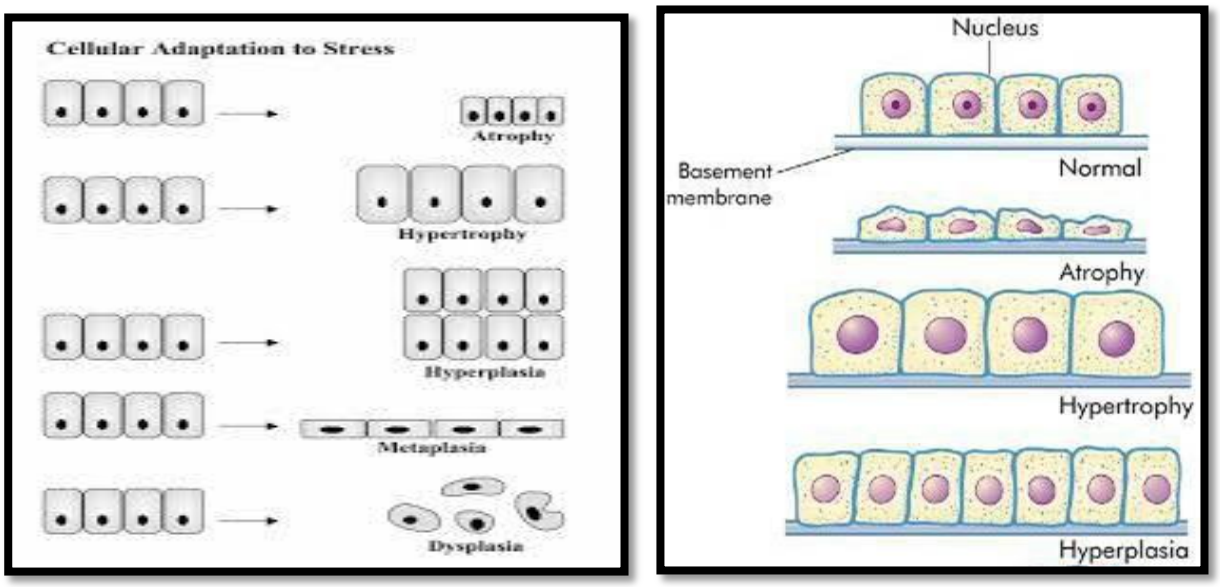


Figure - :Adaptive disorders of growth.

Irreversible cell injury

Persistence of ischemia or hypoxia results in irreversible damage to the structure and function of the cell (cell death).

Cell death is a state of irreversible injury. It may occur in the living body as a local or focal change (i.e. autolysis, necrosis and apoptosis) and the changes that follow it (i.e. gangrene and pathologic calcification), or result in end of the life (somatic death).

a. Severe membrane damage

b. Marked mitochondrial dysfunction.

c. Rupture of the lysosomes

i. Release of lysosomal digestive enzymes into the cytosol

ii. Activation of acid hydrolases followed by autolysis

d. Nuclear changes

1. **Pyknosis**: degeneration and condensation of nuclear chromatin

2. **Karyorrhexis**: nuclear fragmentation

3. **Karyolysis**: dissolution of the nucleus

These pathologic processes involved in cell death are described below

Autolysis

Autolysis (i.e. self-digestion) is disintegration of the cell by its own hydrolytic enzymes liberated from lysosomes. Autolysis can occur in the living body when it is surrounded by inflammatory reaction (vital reaction), but the term is generally used for postmortem change in which there is complete absence of surrounding inflammatory response.

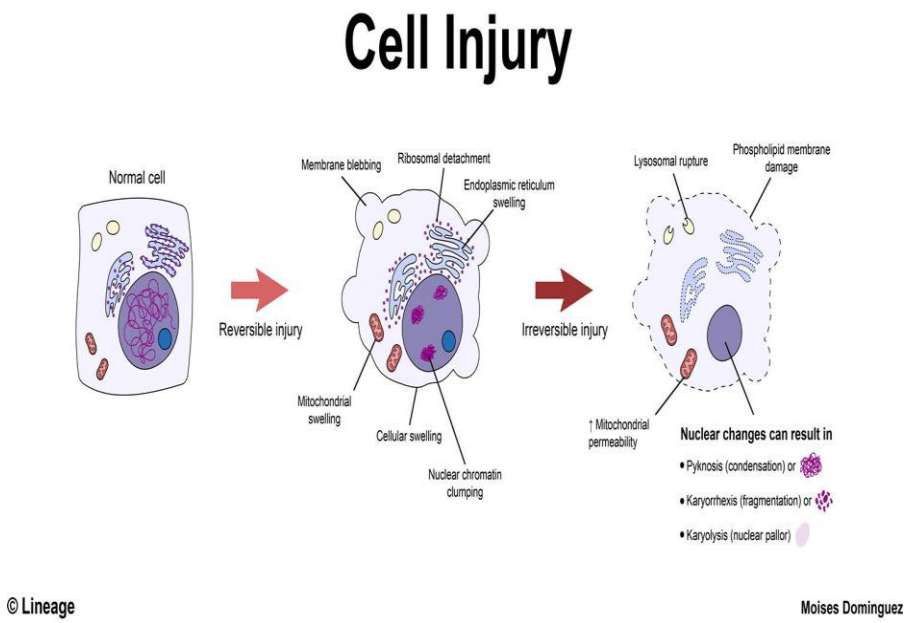


Figure 2- : Cell injury.

Cell death

1- Necrosis

Necrosis is defined as a localized area of death of tissue followed later by degradation of tissue by hydrolytic enzymes liberated from dead cells; it is invariably accompanied by inflammatory reaction.

Necrosis can be caused by various agents such as hypoxia, chemical and physical agents, microbial agents, immunological injury, etc.

Morphologic types of necrosis

Morphologically, there are five types of necrosis: coagulative, liquefaction (colliquative), caseous, fat, and fibrinoid necrosis.

a. Coagulative necrosis

- Most common form of necrosis
- Due to the denaturing and coagulation of proteins within the cytoplasm
- Common in most organs including the **heart**, **liver**, and **kidney**

b. Liquefaction necrosis

- Cellular destruction by hydrolytic enzymes
- Due to autolysis and heterolysis
- Occurs in **abscesses**, **brain infarcts**, and **pancreatic necrosis**

c. Caseous necrosis

- Combination of coagulation and liquefaction necrosis
- Gross: soft, friable, and cheese-like" appearance
- Characteristic of tuberculosis.

d. Fat necrosis

- Caused by the action of lipases on fatty tissue
- Grossly, fat necrosis has a chalky white appearance

e. Fibrinoid necrosis

- Necrotic tissue that histologically resembles fibrin
- Micro: has an eosinophilic (pink) homogeneous appearance

f. Gangrenous necrosis

- term used to describe dead tissue
- Common sites: **lower limbs**, **gallbladder**, **GI tract**, and **testes**

1-Dry gangrene: (microscopic pattern is coagulative necrosis)

This form of gangrene begins in the distal part of a limb due to ischaemia. The typical example is the dry gangrene in the toes and feet of an old patient due to severe atherossclerosis.

2- Wet gangrene: (microscopic pattern is liquefactive necrosis) Wet gangrene occurs in naturally moist tissues and organs such as the bowel, lung, mouth, cervix, diabetic foot.

3-Gas gangrene: It is a special form of wet gangrene caused by gas-forming clostridia (gram-positive anaerobic bacteria) which gain entry into the tissues through open contaminated wounds, especially in the muscles, or as a complication of operation on colon which normally contains clostridia.

2- Apoptosis

- Specialized form of programmed cell death
- Apoptosis is **an active process** regulated by genes and involves RNA and protein synthesis
- Often affects only single cells or small groups of cells
- **Apoptosis is regulated by genes**

i. **bcl-2** (inhibits apoptosis)

ii. **p-53** (stimulates apoptosis)

<u>Physiologic examples of apoptosis</u>

i. Embryogenesis: organogenesis and development

ii. Hormone dependent apoptosis (menstrual cycle)

iii. Thymus: selective death of lymphocytes

<u>Pathologic examples of apoptosis</u>

i. Viral diseases: viral hepatitis.

iii. Cystic fibrosis: duct obstruction and pancreatic atrophy

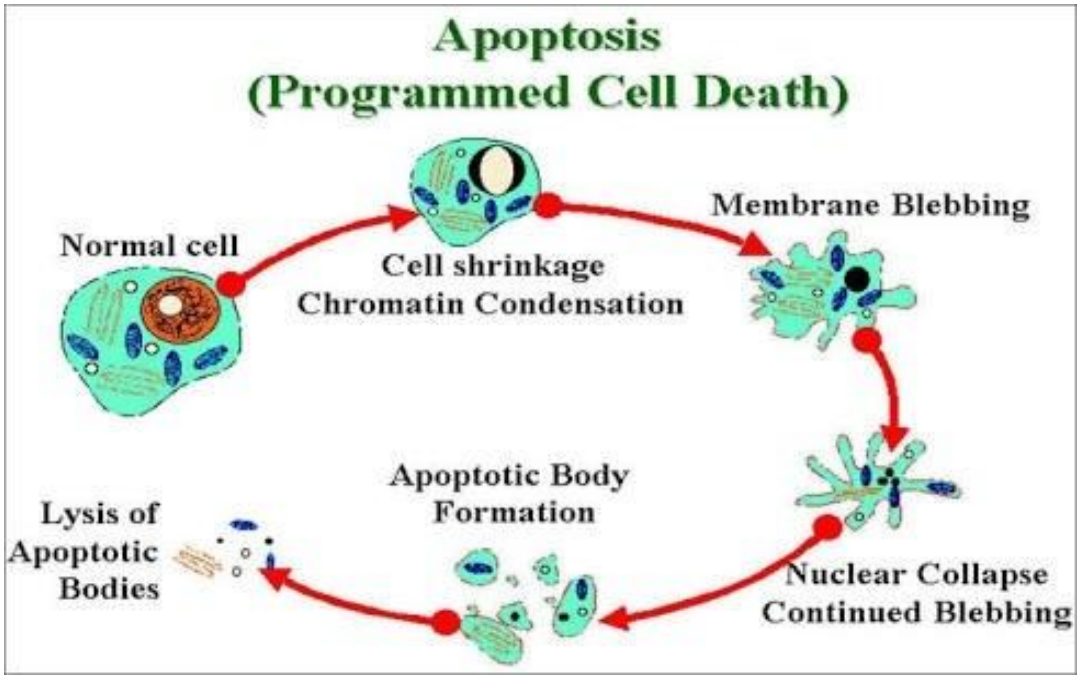


Figure 2-: Apoptosis.

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation (round nucleosome)
Plasma membrane	Disrupted	Intact
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Pathologic	Physiologic and Pathologic

Figure 2- : Differences between Apoptosis and Necrosis.

Lecture: The Respiratory System
(Disorders of The Lungs)

Atelectasis.

Atelectasis is defined as the collapse or closure of the lung resulting in reduced or absent gas exchange. It may affect part or all of one lung . Atelectasis is the collapse of alveoli or lung tissue . It develops when the alveoli become airless from absorption of their air without replacement of the air with breathing.

Atelectasis may be acute or chronic

The most commonly described atelectasis is acute atelectasis, which occurs frequently in the postoperative setting or in people who are immobilized and have a monotonous breathing pattern.

Types of atelectasis:

A- **Obstruction (or resorption) atelectasis**:-

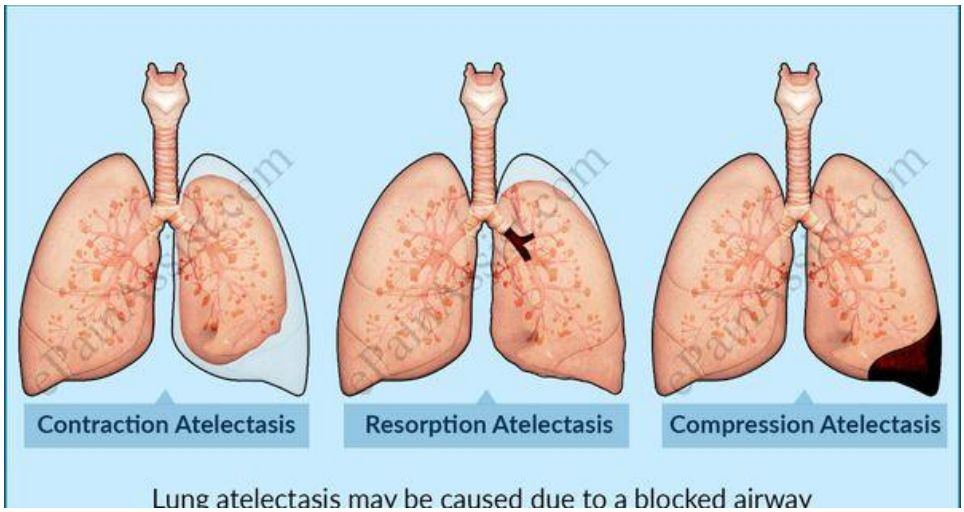
Results from complete obstruction of an airway. It is most often found in bronchial asthma, chronic bronchitis, and with aspiration of foreign bodies; bronchial neoplasms may also cause it.

B- Compression atelectasis:-

Ensues whenever the pleural cavity is partially (or completely) filled by fluid exudate, tumor, blood, or air (pneumothorax) or, in the case of tension pneumothorax, when the entry of air into the pleural cavity causes pulmonary collapse. It is most commonly found in patients with cardiac failure.

C- Contraction atelectasis:-

Occurs when local or generalized fibrotic changes in the lung or pleura prevent full expansion of the lung.



Etiology

- Obstruction of an airway
- Diminished distention of alveoli
- Airway foreign body
- Extrinsic compression on an airway (e.g, compression due to an enlarged vessel)
- Anesthesia
- Bronchospasm and airway inflammation in patients with asthma
- Enlarged lymph nodes that compress the airway
- Masses in the chest that compress the airway or alveoli
- Cardiomegaly or enlarged pulmonary vessels that compress adjacent airways
- Reduced lung volumes due to musculoskeletal or neurologic disorders
- Pain from upper abdominal surgery

Pathophysiology

Reduced alveolar ventilation or any type of blockage. Impedes the passage of air

The trapped alveolar air becomes absorbed into the bloodstream, but outside air cannot replace the absorbed air because of the blockage.

Isolated portion of the lung becomes airless and the alveoli collapse.

Clinical Manifestations

- Cough, sputum production, and low-grade fever.
- Dyspnea, tachycardia
- Tachypnea, pleural pain
- Difficulty breathing in the supine position
- Anxious

Assessment and Diagnostic Findings

- Chest x-ray
- Pulse oximetry
- Physical examination: Decreased breath sounds and crackles are heard over the affected area.

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a severe lung condition. It occurs when fluid fills up the air sacs in lungs. Too much fluid in lungs can lower the amount of oxygen or increase the amount of carbon dioxide in bloodstream. ARDS can prevent organs from getting the oxygen they need to function, and it can eventually cause organ failure.

ARDS is also referred with variety of terms like

- Stiff Lung
- Shock lung
- Wet lung
- Post traumatic lung
- Adult respiratory distress syndrome
- Capillary leak syndrome
- Congestive atelectasis.

Acute respiratory distress syndrome (ARDS) is a sudden and progressive form of acute respiratory failure in which the alveolar capillary membrane becomes damaged and more permeable to intravascular fluid resulting in severe dyspnea and hypoxemia.

ETIOLOGY & RISK FACTORS

1- Direct Lung Injury

– Common causes
  - Aspiration of gastric contents or other substances.
  - Viral/bacterial pneumonia

– Less Common causes
  - Chest trauma
  - Embolism
  - Inhalation of toxic substances
  - Radiation pneumonitis

2- Indirect Lung Injury

– Common causes
  - Sepsis
  - Severe traumatic injury

– Less common causes

- Acute pancreatitis
  - Anaphylaxis
  - intravascular coagulation
  - Multiple blood transfusions
  - Narcotic drug overdose
  - Non-pulmonary systemic diseases
  - Severe head injury
  - Shock

Pathology and Pathophysiology

In normal, healthy lungs there is a small amount of fluid that leaks into the interstitium. The lymphatic system removes this fluid and returns it into the circulation keeping the alveoli dry.

ARDS is a consequence of an alveolar injury which produces diffuse alveolar damage. The injury causes the release of pro-inflammatory cytokine.

Cytokines recruit neutrophils to the lungs, where they become activated and release toxic mediators (eg, reactive oxygen species and proteases) that damage the alveolar epithelium.

Breakdown of the alveolar epithelial barrier allows the air spaces to fill with bloody and debris from degenerating cells. In addition, functional surfactant is lost, resulting in alveolar collapse.

Healthy lungs regulate the movement of fluid to maintain a small amount of interstitial fluid and dry alveoli.

Lung injury interrupts this balance causing excess fluid in both the interstitium and alveoli.

Results of the excess fluid include impaired gas exchange and increased pulmonary arterial pressure.

Three distinct stages (or phases) of the syndrome including:

1 -Exudative stage (0-6 Days)

Accumulation of excessive fluid in the lungs due to exudation (leaking of fluids) and acute injury.

Hypoxemia is usually most severe during this phase of acute injury, as it is injury to the endothelium (lining membrane) and epithelium (surface layer of cells).

Some individuals quickly recover from this first stage; many others progress after about a week into the second stage.

2 -Proliferative stage (7-10 Days)

Connective tissue and other structural elements in the lungs proliferate in response to the initial injury, including development of fibroblasts

Abnormally enlarged air spaces and fibrotic tissue (scarring) are increasingly apparent.

The terms "stiff lung" and "shock lung" frequently used to characterize this stage.

3 -Fibrotic stage (>10-14 Days)

Inflammation resolves.

Oxygenation improves.

Lung function may continue to improve for as long as 6 to 12 months after onset of respiratory failure, depending on the precipitating condition and severity of the initial injury.

Varying levels of pulmonary fibrotic changes are possible.

Clinical Presentation

Development of acute dyspnea and hypoxemia within hours to days of an inciting event

Tachypnea, tachycardia, and the need for a high fraction of inspired oxygen to maintain oxygen saturation.

Febrile or hypothermic.

Sepsis-hypotension and peripheral vasoconstriction with cold extremities.

Diagnostic Evaluation

History of above symptoms

On physical examination

–Auscultation reveals abnormal breath sounds

The first tests done are:

–Arterial blood gas analysis

– Blood tests

–Chest x-ray

– Bronchoscopy

–Sputum cultures and analysis

Other tests are:

– Chest CT Scan

– Echocardiogram

Lecture 5 : The Respiratory System (Disorders of The Lungs)

3-Pulmonary embolism (PE)

Is a blood clot in the lung that occurs when a clot in another part of the body (often the leg or arm) moves through the bloodstream and becomes lodged in the blood vessels of the lung. This restricts blood flow to the lungs, lowers oxygen levels in the lungs and increases blood pressure in the pulmonary arteries.

If a clot develops in a vein and it stays there, it's called a **thrombus**. If the clot detaches from the wall of the vein and travels to another part of your body, it's called an **embolus**.

If PEs are not treated quickly, they can cause heart or lung damage and even death.

Etiology and risk factor

Virtually all pulmonary embolisms develop from thrombi(clots), most of which originate in the deep calf, femoral, popliteal, or iliac veins.

• Other sources of emboli include tumors, fat, amniotic fluid, septic thrombi.

• Major operations, especially hip, knee, abdominal and extensive pelvic procedures predispose the client to thrombus formation because of reduced flow of blood through pelvis.

• Travelling in cramped quarters for a long time or sitting for long periods is also associated with clotting of blood.

The most common sources of embolism are proximal leg deep venous thrombosis (DVTs) or pelvic vein thrombosis.

• The development of thrombosis is classically due to a group of causes named Virchow's triad (alterations in blood flow, factors in the vessel wall and factors affecting the properties of the blood).

Alterations in blood flow: immobilization (after surgery, injury, pregnancy, obesity, cancer

• Factors in the vessel wall: surgery, catheterizations causing direct injury ("endothelial injury")

• Factors affecting the properties of the blood:

- Estrogen-containing hormonal contraception
- Genetic thrombophilia
- Acquired thrombophilia (antiphospholipid syndrome, nephrotic syndrome)
- Cancer

Pathophysiology

- When emboli travel to the lungs, they lodge in the pulmonary vasculature.
- Blood flow is obstructed, leading to decreased perfusion of the section of the lung supplied by the vessel.
- The arterioles constrict, accompanied by a release of histamine, serotonin, catecholamines and prostaglandins.
- These chemical agents result in bronchial and pulmonary artery constriction.
- This vasoconstriction probably plays a major role in the hemodynamic instability that follows pulmonary embolism.
- Pulmonary embolism can lead to right sided heart failure.
- Once the clot lodges, affected blood vessels in the lung collapse.

Symptoms

Symptoms of pulmonary embolism vary, depending on the severity of the clot. Although most people with a pulmonary embolism experience symptom, some will not. The first signs are usually shortness of breath and chest pains. You may cough up bloody sputum. Pulmonary embolism is serious but very treatable. Quick treatment greatly reduces the chance of death.

Symptoms may include:

- Sudden shortness of breath -- whether you've been active or at rest.
- Unexplained sharp pain in your chest, arm, shoulder, neck or jaw. The pain may also be similar to symptoms of a heart attack.
- Cough with or without bloody sputum (mucus).
- Pale or bluish-colored skin.
- Rapid heartbeat (pulse).
- Excessive sweating.
- In some cases, feeling anxious, light-headed or faint.
- Wheezing.

Diagnosis

Pulmonary embolism is commonly detected through the following tests:

Computed tomography (CT) scan.

Blood tests (including the D-dimer test).

Pulmonary angiogram.

Ultrasound of the leg -- helps to identify blood clots in patients who cannot have an X-ray due to dye allergies or who are too sick to leave their hospital room.

Magnetic resonance imaging (MRI) of the legs or lungs.

4- Chronic obstructive pulmonary disease (COPD).

The term **COPD** includes a group of conditions that share one major symptom—dyspnea—and are accompanied by chronic or recurrent obstruction to airflow within the lung.

The most frequent causes of death in patients with COPD.

1- Respiratory insufficiency causing severe hypoxia, respiratory acidosis, and coma

2-Right-sided heart failure

3- Massive collapse of the lungs secondary to pneumothorax from ruptured bullae.

5- Chronic bronchitis:-

Is defined clinically as persistent cough with sputum production for at least3 months of the year, in at least 2 consecutive years.

Clinically there are several forms of chronic bronchitis:

1- **Simple chronic bronchitis**: Patients experience a productive cough but have no evidence of airflow obstruction.

2- **Chronic asthmatic bronchitis**: Some patients may demonstrate severe dyspnea and wheezing in association with inhaled irritants or during respiratory infections due to hyperreactive airways.

3- **Chronic obstructive bronchitis**: Some patients, especially heavy smokers, develop chronic airflow obstruction, usually accompanied by emphysema.

The factors important for the pathogenesis of chronic bronchitis:.

1- Chronic irritation by inhaled substances (cigarette smoking).

2- Infections.

Lecture 6 : The Respiratory System (Disorders of The Lungs)

6-Lung carcinoma:

Is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung. If left untreated, this growth can spread beyond the lung by the process of metastasis into nearby tissue or other parts of the body.

Incidence of lung cancer:

• Lung cancer mainly occurs in older people. About 2 out of 3 people diagnosed with lung cancer are 65 or older.

• About 14% of all new cancers are lung cancers.

• About 224,000 new cases of lung cancer (118,000 in men and 106,000 in women).

Types of Lung carcinoma:

1- Small cell lung cancer (SCLC) – Small Cell Carcinoma

2- Non small cell lung cancer (NSCLC):

a. Squamous Cell Carcinoma
b. Adenocarcinoma
c. Large Cell Carcinoma

1- Small cell lung cancer

- most aggressive form of lung cancer
- Accounts 20% of lung cancer
- tumors have often metastasized to other parts of the body (brain, liver, and bone marrow).

2- Non small cell lung cancer

a- Squamous cell carcinoma

- Slow growing
- makes up 20-30% of all lung cancers
- more common in males
- most occur centrally in the large bronchi
- Uncommon metastasis that is slow effects the liver, adrenal glands and lymph nodes.
- Associated with smoking
- Not easily visualized on x-ray.

b- Adenocarcinoma

- Most common type of Lung cancer
- (30-40% of all lung cancers)
- Common In non-smokers
- Easily seen on a CXR
- Highly metastatic in nature.

c- Large cell carcinomas

- Makes up 15-20% of all lung cancers
- Tends to occur in the outer part (periphery) of lung, invading bronchi or larger airways.
- Metastasis is slow but early metastasis occurs to the kidney, liver organs as well as the adrenal glands.

Etiology

1- Cigarette smoking

- Contains numerous carcinogens
- Up to 90% squamous & small cell CA occur in smokers

2 - Genetic Factors

3- Environmental Hazards:

- Asbestos workers
- Uranium workers
- Exposure to radiation

4- Older age

5- Lung Disease like T.B

6- Diet.

Pathophysiology:

1. Carcinogens like, environmental agents and genetics binds with cell's DNA and damage the cells.
2. Cellular changes and abnormal cell growth occur.
3. Malignant transformation of pulmonary epithelial cells.
4. Abnormal proliferation of the lung cell. These cells grow slowly and covers the bronchi and lobes of the lung.
5. Non-specific inflammatory changes with hypersecretion of mucus and desquamation of the cells.
6. Lesions formation in the lung's tissues involving the bronchi, bronchioles or even alveoli

7. Formation lung carcinoma.

TNM Staging system for Lung Cancer

The most common staging system for lung cancer developed by the International Union Against Cancer (UICC).

T= Tumors: tumor size

N= Node: node involvement

M= Metastasis: general involvement in organs and tissues

1- Tumor size

- Tx – The tumor size is unknown, or cancer cells are only found in sputum.
- T0 – The tumor is present only in the cells lining the airway
- T1 – Tumors less than or equal to 3 cm
- T2- Tumors size is 4-7 cm.
- T3 – Tumors greater than 7 cm
- T4 – tumor that invades structures in the chest such as the heart, major blood vessels near the heart, the trachea, the esophagus.

2- Metastasis

- M0 - The tumor has not spread to distant regions.
- M1:
  - M1a – The tumor has spread to the opposite lung
  - M1b – The tumor has spread to distant regions of the body, such as the brain or bones.

2- Nodal involvement

- N0 – No nodes are involved.
- N1 – The tumor has spread to nearby nodes on the same side of the chest.
- N2 – The tumor has spread to nodes farther away, but on the same side of the chest.
- N3 – The tumor has spread to lymph nodes on the other side of the chest, or has spread to nodes near the collarbone or neck muscles.

Staging

Stage 1

- Tumor is small and localized to lung
- no lymph node involvement
- A-Tumor <3 cm
- B-Tumor >3 cm and invading surrounding local area

Stage 2

- A-Tumor <3cm with invasion of lymph nodes.
- B-Tumor >3 cm involving the bronchus and lymph nodes on the same side of chest.

Stage 3

- A-Tumor spread to the nearby structure and regional lymph nodes
- B-Tumor involving heart, trachea, esophagus, and lymph nodes.

Stage 4: distant metastasis

Sign and Symptoms:

- A cough that gets worse
- Sputum
- Chest pain that is often worse with deep breathing, coughing, or laughing

- Coughing up blood
- Hoarseness
- Weight loss and loss of appetite
- Shortness of breath
- Feeling tired
- Infections such as bronchitis and pneumonia
- Bone pain (like pain in the back or hips)
- Yellowing of the skin and eyes (jaundice), from cancer spread to the liver.

Diagnosis

1- Medical history and physical exam

2- Blood tests:

- A complete blood count (CBC) looks at whether patient blood has normal numbers of different types of blood cells.
- Blood chemistry tests can help spot abnormalities in some of patient organs, such as the liver or kidneys.

3- Chest x-ray: this is often the first test will do to look for any abnormal areas in the lungs.

4- Computed tomography (CT) scan: uses to make detailed cross-sectional images of patient body. This test can show the size, shape, and position of any lung tumors and can help find enlarged lymph nodes.

5- CT-guided needle biopsy: If a suspected area of cancer is deep within patient body, a CT scan can be used to guide a biopsy needle into the suspected area.

6- Bronchoscopy: can help the find some tumors or blockages in the airways.

7- Thoracoscopy: is used to view the lung and the space surrounding the lungs.

Lecture 7 : Oral and Esophageal Disorders

Benign and malignant tumors as also a number of tumor-like lesions and premalignant lesions are encountered in the oral soft tissues

A. TUMOUR-LIKE LESIONS

1- Fibrous Growths. Fibrous growths of the oral soft tissues are very common. These are not true tumors (unlike intraoral fibroma and papilloma), but are instead inflammatory or irritative in origin.

2- Pyogenic Granuloma. This is an elevated, bright red swelling of variable size occurring on the lips, tongue, buccal mucosa and gingiva. It is a vasoproliferative inflammatory lesion. Pregnancy tumor is a variant of pyogenic granuloma.

3- Mucocele. Also called mucous cyst or retention cyst, it is a cystic dilatation of the mucous glands of the oral mucosa. The cyst often ruptures on distension and incites inflammatory reaction due to mucous extravasation.

4- Dermoid Cyst. This tumor-like mass in the floor of the mouth represents a developmental malformation. The cyst is lined by stratified squamous epithelium. The cyst wall contains sebaceous glands, sweat glands, hair follicles and other mature tissues.

B. BENIGN TUMOURS

1- Squamous Papilloma. Papilloma can occur anywhere in the mouth and has the usual papillary or finger-like projections.

2- Haemangioma. Haemangioma can occur anywhere in the mouth; when it occurs on the tongue it may cause macroglossia. It is most commonly capillary type, although cavernous and mixed types may also occur.

3- Lymphangioma. Lymphangioma may develop most commonly on the tongue producing macroglossia; on the lips producing macrocheilia, and on the cheek. Cystic hygroma is a special variety of lymphangioma occurring in children on the lateral side of neck.

4- Fibroma. Although most common benign oral mucous membrane mass is fibroma appearing as a discrete superficial pedunculated mass, it appears to be nonneoplastic in nature. It probably arises as a response physical trauma.

5-Fibromatosis Gingivae. This is a fibrous overgrowth of unknown etiology involving the entire gingiva. Sometimes the fibrous overgrowth is so much that the teeth are covered by fibrous tissue.

MALIGNANT TUMOURS

Squamous Cell (Epidermoid) Carcinoma

There is a definite male preponderance. It can occur anywhere in the mouth but certain sites are more commonly involved. These sites, in descending order of frequency, are: the lips (more commonly lower), tongue, anterior floor of mouth, buccal mucosa in the region of alveolar lingual sulcus, and palate

Haematemesis Of Esophageal Origin

Massive haematemesis (vomiting of blood) may occur due to vascular lesions in the oesophagus. These lesions are as under:

1.Esophageal Varices. Esophageal varices are tortuous, dilated and engorged esophageal veins, seen along the longitudinal axis of esophagus. They occur as a result of elevated pressure in the portal venous system, most commonly in cirrhosis of the liver. Less common causes are: portal vein thrombosis, hepatic vein thrombosis (Budd-Chiari syndrome) and pylephlebitis.

2. Mallory-Weiss Syndrome. In this condition, there is lacerations of mucosa at the gastro-esophageal junction following minor trauma such as by vomiting, retching or vigorous coughing.

3. Rupture Of The Esophagus. Rupture of the oesophagus may occur following trauma, during oesophagoscopy, indirect injury (e.g. due to sudden acceleration and deceleration of the body) and spontaneous rupture (e.g. after overeating, extensive aerophagy etc).

Carcinoma of Esophagus

The tumor occurs more commonly in men over 50 years of age. Prognosis is dismal: with standard methods of therapy (surgical resection and/or irradiation), 70% of the patients die within one year of diagnosis. Five-year survival rate is 5-10%.

Etiology. Although exact etiology of carcinoma of the esophagus is not known, a number of conditions and factors have been implicated as under:

1. Diet and personal habits:

i) Heavy smoking

ii) Alcohol consumption

iii) Intake of foods contaminated with fungus

iv) Nutritional deficiency of vitamins and trace elements.

2. Esophageal disorders:

i) Esophagitis (especially Barrett's esophagus in adenocarcinoma)

ii) Achalasia

iii) Hiatus hernia

iv) Diverticula

v) Plummer-Vinson syndrome.

3. Other factors:

i) Race—more common in the Chinese and Japanese than in Western races; more frequent in blacks than whites.

ii) Genetic factors—predisposition with coeliac disease, epidermolysis bullosa, tylosis.

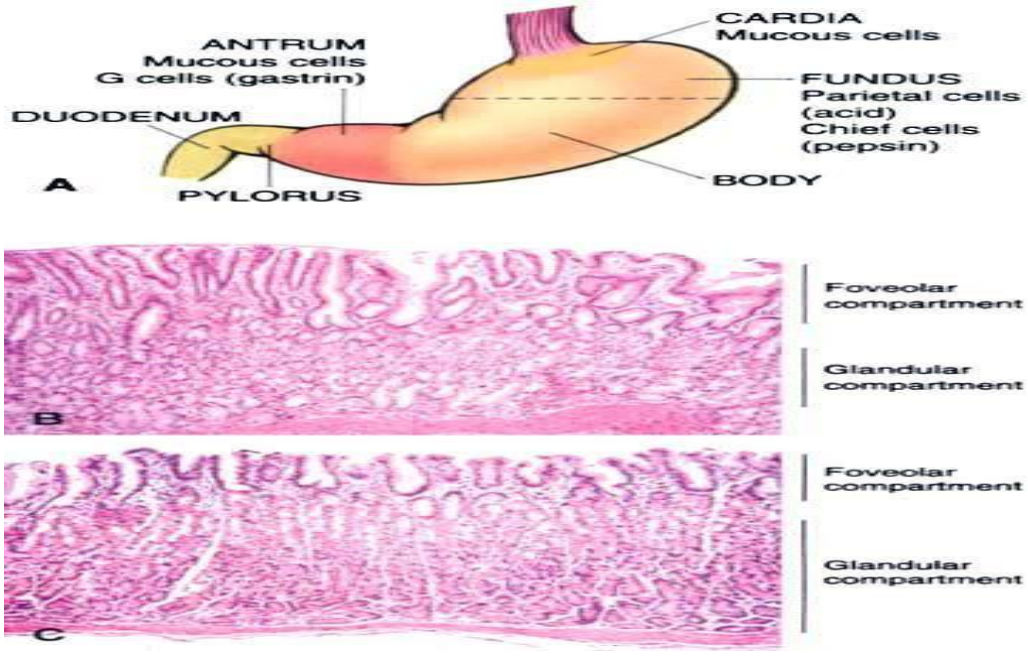
iii) HPV infection—is the recent addition in etiologic factors.

Morphologic Features. Carcinoma of the esophagus is mainly of 2 types—squamous cell (epidermoid) and adenocarcinoma.

Squamous Cell (Epidermoid) Carcinoma. Squamous cell or epidermoid carcinoma comprises 90% of primary esophageal cancers. The disease occurs in 6th to 7th decades of life and is more common in men than women. The sites of predilection are the three areas of esophageal constrictions. Half of the squamous cell carcinomas of esophagus occur in the middle third, followed by lower third, and the upper third of esophagus in that order of frequency.

Adenocarcinoma. Adenocarcinoma of the esophagus constitutes less than 10% of primary esophageal cancer. It occurs predominantly in men in their 4th to 5th decades. The common locations are lower and middle third of the esophagus. These tumors have a strong and definite association with Barrett's esophagus in which there are foci of gastric or intestinal type of epithelium.

Lecture 8 : Gastrointestinal tract Disorders
(Stomach)



Histology:

A-The mucosa: composed of gastric pits (foveolae) & **gastric glands** which are either:

* Mucous secreting in the antrum and cardia

* Glands composed of **chief cells** that secrete pepsin, and **parietal** cells that secrete acid (HCl) and intrinsicfactor (IF).

B- The submucosa

C- The muscular layer

D- The serosa

Gastritis:

It is defined as inflammation of the gastric mucosa.

1- Acute gastritis with **neutrophilic** infiltration.
2- Chronic gastritis with **lymphocytic** infiltration.

Acute gastritis:

Is acute inflammation of the gastric mucosa.

Etiology:

- Heavy use of(non steroidal anti-inflammatory drugs NSAID)
- Excessive alcohol intake
- Heavy smoking
- Uremia
- Severe stress (burn , trauma, surgery)
- Systemic infection (e.g salmonellosis).
- Treatment with chemotherapeutic drugs.

Clinical features:

Epigastric pain, nausea and vomiting, sometimes hematemesis

Grossly:

Congested, edematous surface.

Microscopically:

1- Neutrophils among the surface epithelial cells.
2- Erosion (loss of superficial epithelial cells) resulting in adefective mucosa.
3- Sometimes hemorrhage acute hemorrhagic gastritis.

Chronic gastritis:

Etiological factors:

1- Chronic inflammatory processes (*helicobacter pylori H.P*) which makes the most important factor and present in about 10-80% of cases.
2- Immunological (autoimmune) in association with pernicious anemia which makes about 10% of cases.
3- Toxic e.g alcohol &cigarette smoking.
4- Post surgical e.g reflux of biliary duodenal secretion
5- Motor and mechanical causes including: obstruction,bezoars.
6- Radiation

Pathogenesis of H pylori virulence

1-Flagella, which allow the bacteria to be motile inviscous Mucus
2-Urease, which generates ammonia from endogenous Urea------increase gastric pH around the organisms and protecting the bacteria from the acidic pH of the stomach.
3-Adhesins, which enhance bacterial adherence to surface foveolar cells
4-Toxins, such as that encoded by cytotoxin-associated Gene A (CagA), that may be involved in ulcer or cancer development.

Classification:

1- Type "A" chronic gastritis.
2- Type "B" chronic gastritis.

Type A:

*Is also called **autoimmune** chronic gastritis.
*It can be associated with other autoimmune diseases e.g diabetes, thyroiditis.

* Occur in late adult life.

* The body (**fundus**) mucosa is mostly affected.
* There is a production of antibodies against the **parietal** cells which causes:
    - Decrease the HCL secretion.
    - Decrease in intrinsic factor secretion.
    - Impaired Vit B12 absorption and later on pernicious anemia as a result of the above cause.
    - There is high risk of developing **gastric carcinoma.**

Microscopically:

1- Diffuse **damage of the** acid-producing **mucosa** within the body and fundus which appears markedlythinned, and rugal folds are lost.

2- The inflammatory infiltrate is composed of lymphocytes, macrophages, and plasma cells &neutrophils may be present

3- In contrast with ***H. pylori*** **gastritis,** the inflammatory reaction is deep and centered on the gastric glands.

4- **Parietal and chief cell loss** can be extensive

5- **Intestinal metaplasia** may develop.

Clinical picture:

1- Asymptomatic.
2- Or with epigastric pain.
3- Or pernicious anemia.

Type "B":

* Is called **environmental** type.
* It is more common than type A
* It can arise at any age.
* It involves the **antrum** of the stomach
* The main causative agent is: helicobacter pyloriinfection, it is found in 80% of type B cases.

*Less common causes are: chronic alcohol abuse,cigarette smoking, NSAID.

The importance of type B comes from:

1- It is highly associated with peptic ulcer
2- Associated with gastric carcinoma but less than type A.
3- Association with gastric lymphoma

Microscopically:

1- *H pylori* are concentrated in the mucous layer overlying the epithelial cells
2- Neutrophils also present in the lamina propria ,intraepithelial & even in the lumen of gastric pits (pitabcesses)
3- Chronic inflammatory infiltrate including lymphocyte and plasma cells and macrophages
4- *lymphoid aggregates with germinal centers* frequently present &have the potential to transform to lymphoma
5- Intestinal metaplasia with goblet cells & columner absorptive cells with increased risk of gastric adenocarcinoma.

Characteristics of type B gastritis

Location: Antrum

Inflammatory infiltrate: Neutrophil, subepithelial plasma cells

Acid production: Increased to slightly decreased

Gastrin: Normal to markedly increase

Serology: Antibodies to *H pylori*

Sequelae: Peptic ulcer, gastric adenocarcinoma,lymphoma

Association: Low socioeconomic status, poverty,residence in rural areas

Characteristics of autoimmune gastritis type A:

Location: Body

Inflammatory infiltrate: Lymphocytes, macrophages

Acid production: Decreased

Gastrin: markedly decreased

Serology: Antibodies to parietal cells (H+, intrinsicfactor)

Sequelae: Atrophy, pernicious anemia,adenocarcinoma, carcinoid

Association: Autoimmune disease, thyroiditis, diabetes,Grave's disease

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2- Gastric Ulcer

Acute gastric ulcer:

It means the development of: focal, acutely developing mucosal **defects**.

Causes:

1- Non steroidal anti-inflammatory drugs (NSAID).
2- After severe physiological stress (STRESS ulcer) e.g

-After severe burn (Curling ulcer)
-After head or CNS injury (Cushing ulcer
- After severe trauma e.g (sepsis and major surgery)

Pathogenesis:

1- e.g In patient taking NSAID there will be a decrease in PG secretion which has an important protective effect on the mucosa.
2- Direct stimulation to the vagal nuclei (in head traumas) by increased intracrainial pressure may cause hypersecretion of gastric acid.
3- In severe trauma &burns, systemic acidosis which lowers the mucosal cell PH which are already hypoxic by impaired mucosal blood flow.

Morphologically:
Multiple, small, round-oval, superficial-deep, and may lead to perforation.
Clinical features:
Either asymptomatic or bleeding .

Chronic peptic ulcer:

An *ulcer*: is a defect in the mucosa causing a discontinuity ofthe surface **epithelium** which may extend into the **muscularis mucosae** into the **submucosa**, or **deeper.**
Peptic ulcer: is an ulcer occurring in the areas of the GITthat are exposed to the acid –pepsin secretion as in:

- duodenum **98%** of cases
- stomach
- lower esophagus
- margin of gastroenterostomy
- Meckel diverticulum that have an ectopic gastricmucosa

Epidemiology:

- The ratio of duodenal ulcer/ gastric ulcer = 4/1
- Male/female = 3/1 for duodenal ulcer, 2/1 for gastric ulcer
- There is no racial difference in the incidence
- It is characterized by remission and relapse

Pathogenesis:
Peptic ulcer appears to be produced by an **imbalance** between the gastroduodenal mucosal defense mechanismsand the damaging forces.

Defense forces:

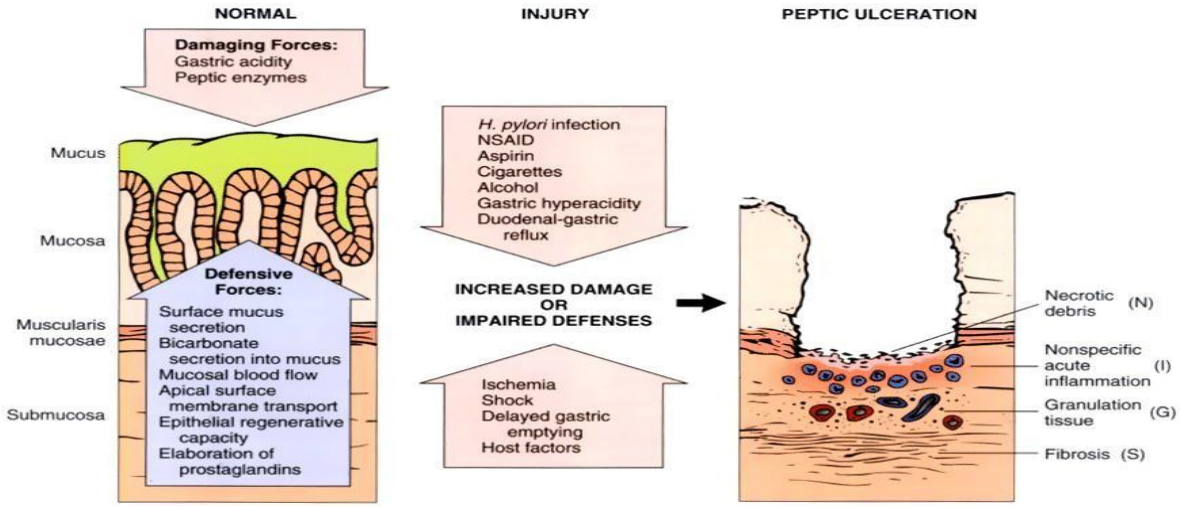
1. Surface mucous layer secreted by the epithelial cells.
2. Bicarbonate secretion into the mucous.
3. Mucosal blood flow
4. Apical surface of the mucosal cells protect against backdiffusion of H ion.
5. Epithelial regenerative capacity
6. Elaboration of prostaglandins from adequate blood flow

Aggressive forces:

1- Gastric acidity (HCl) secretion.2- Peptic enzymes.

3- Other induced cause:

- *H.pylori* infection.
- Aspirin
- NSAIDs
- Cigarette
- Alcohol



*This concludes that **hyperacidity** is **not** the actual cause because only few patients with D.U (duodenal ulcer) and less than few in G.U (gastric ulcer) have hyperacidity

*The most important cause for developing ***GU*** found to be adecrease in the **defense** mechanism

-H.pylori infection is the most important cause &present in70% of GU.

*For ***D.U,* H. pylori** present in 70-90%

- **Genetic** susceptibility play role also that is 20-40% of D.Uhave a +ve family history.

-Blood group (O) has 30% higher risk than other bloodgroups - other **diseases** associated with D.U e.g:

- Alcoholic cirrhosis
- Chronic obstructive pulmonary diseases
- Hyperparathyroidism
- Chronic renal failure
- Hypercalcemia

Morphologically:

1- **site:** G.U usually located at the lesser curvature

D.U at the first 2.5 cm of the duodenum

2- **size:** 2-4 cm, sometimes larger

3- **number:** usually solitary, sometimes two

4- **shape:** round- oval or punched out appearance, the margin of the crater are perpendicular but unlike ulceratedcancers, there is no significant elevation or beading of the edges

5- **Microscopically:**

Four zones could be identified.

- Base &margin have a thin layer of necrotic fibrinoiddebris
- Beneath is a layer of neutrophilic inflammatory cellinfiltration
- In the deeper layers there is a granulation tissueformation.
- The granulation tissue rests on a fibrous tissuesscarring.

Complications:

1- **Healing and scarring:** which lead to contracture, caused by contraction of the fibrous scar- □ *pyloricobstruction especially if the ulcer is located in the prepyloric area□ vomiting, dehydration and hyperkalemic alkalosis.* hour-glass deformity, if theulcer is higher up in the stomach.

2- **Bleeding: occur in 1\3 of patients** &lead to:

- hematemesis and malena
- iron deficiency anemia due to *chronic* loss of smallamounts of blood

3- **Perforation:** leading to escape of the gut content intothe peritoneal cavity□ peritonitis presented with *acute*abdominal pain &is the major cause of death.

4- **Penetration:** of the ulcer into the adjacent structures

e.g small intestine.

5- **Malignant transformation:** occur in less than 1% ofG.U

N.B: D.U ***never*** show a malignant transformation

Gastric carcinoma:

It is one of the most important causes of death from malignant tumors**.**

Geographically:

Common in Japan, china, Chile, Portugal.

Uncommon in USA, U.K, Australia .

Etiology &pathogenesis:

1- Environmental factors

1- Diet

* Nitrites and nitrates used for preservation of food in thepast.
* Smoked food &picked vegetables
* Increased salt intake.
* Lack of fresh fruit and vegetables (antioxidants present may inhibit nitrosation)
* Cigarette smoking.
* Low socioeconomic status

2- *H-pylori* infection.

3- Pernicious anemia.

2- Host factors:

1- Chronic gastritis &intestinal metaplasia.

2- Partial gastrectomy.

3- Gastric adenoma.

3- Genetic

* Increase risk in blood group A
* Family history of gastric carcinoma
* Germline mutation of CDH1 that encode E cadherinespecially in the (diffuse type)
* FAP (familial adenomatous polyposis coli) geneespecially in the intestinal type

4- Ebstein Bar (EB) virus in 10% of gastric carcinoma

Grossly:

* Most of them located at the antrum
* 1-**Exophytic** (fungating) OR

2- **Ulcerative** (excavating) OR

3- **Flat or depressed---diffuse** thickening of the wall without obvious mass (lenities plastica and it look like leather bottle.

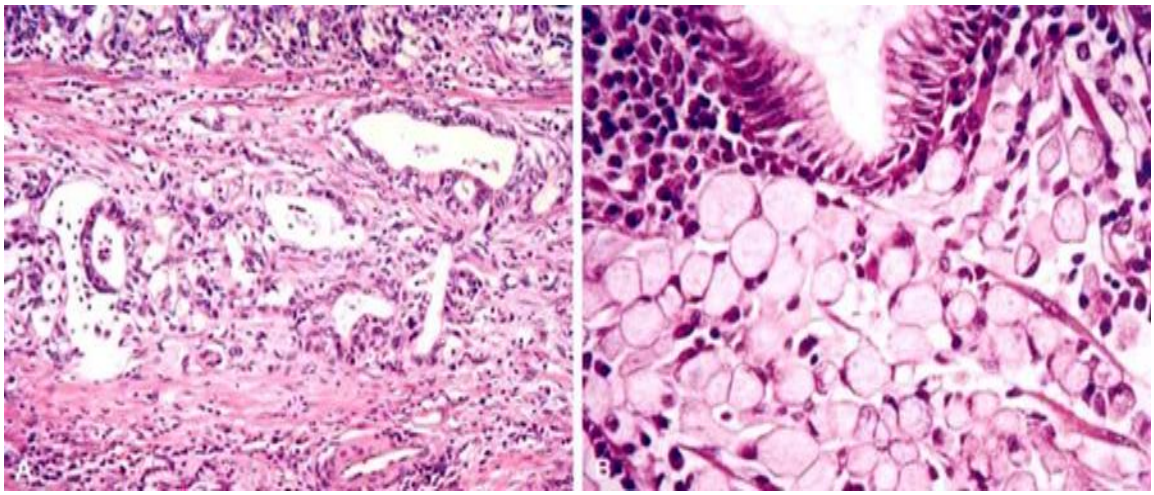
Microscopically:

The type is adenocarcinoma, classified into two types:1- Intestinal type :

- Malignant cells forming neoplastic intestinal glandsresembling those of colonic adenocarcinoma.
  - It is the predominant type in high risk areas
  - Occur in old age group (55) years
  - Better prognosis than other type

2- Diffuse type:

- The tumor is less differentiated
- The cells accumulate intracellular mucin forming **a signet ring**
- No glandular formation
- Occur in a slightly younger age group(48) years
- worse prognosis



Spread:

1- Local spread: to adjacent organs: e.g esophagus,duodenum.
2- Lymphatic spread: to regional lymph nodes
3- Transcoelomic spread: in which the tumor cells shed into the peritoneal cavity and if it get implanted on theovaries it will form the interesting **Krukenberg Tumor**
4- Hematogenous spread: to the liver and lung.

Clinical features:

The most important are:

- Anorexia (loss of appetite)
- Severe weight loss with epigastric pain
- Anemia

Early gastric carcinoma:

Is the carcinoma which is limited to the mucosa orsubmucosa, and it is of good prognosis**.**

Prognosis:

For early gastric ca. the 5-years survival rate is 90-95% For advanced gastric ca. the 5-years survival rate is 15%.

Lecture 9 : Inflammatory Bowel Disease

(Crohn's Disease And Ulcerative Colitis)

Definition. The term 'inflammatory bowel disease (IBD)' is commonly used to include 2 idiopathic bowel diseases having many similarities but the conditions usually have distinctive morphological appearance.

1. Crohn's disease or Regional enteritis is an idiopathic chronic ulcerative IBD, characterised by transmural, non-caseating granulomatous inflammation, affecting most commonly the segment of terminal ileum and/ or colon, though any part of the gastrointestinal tract may be involved.

2. Ulcerative colitis is an idiopathic form of acute and chronic ulceroinflammatory colitis affecting chiefly the mucosa and submucosa of the rectum and descending colon, though sometimes it may involve the entire length of the large bowel.

Both these disorders primarily affect the bowel but may have systemic involvement in the form of polyarthritis, uveitis, ankylosing spondylitis, skin lesions and hepatic involvement. Both diseases can occur at any age but are more frequent in 2nd and 3rd decades of life. Females are affected slightly more often.

Etiopathogenesis. The exact etiology of IBD remains unknown. However, multiple factors are implicated which can be considered under the following 3 groups:

1. Genetic factors. Genetic factors are implicated in the etiopathogenesis of IBD .

2. Immunologic factors. Defective immunologic regulation in IBD has been shown to play significant role in the pathogenesis of IBD.

3. Exogenous factors. Several exogenous and environmental factors has been assigned:

I) Microbial factors, ii) Psychosocial factors, iii) Smoking and iv) Oral contraceptives.

CROHN'S DISEASE. Crohn's disease may involve any portion of the gastrointestinal tract but affects most commonly 15-25 cm of the terminal ileum which may extend into the caecum and sometimes into the ascending colon:

MALABSORPTION SYNDROME

DEFINITION AND CLASSIFICATION

The malabsorption syndrome (MAS) is characterised by impaired intestinal absorption of nutrients especially of fat; some other substances carbohydrates, vitamins and minerals. MAS is subdivided into 2 broad groups:

Primary MAS, which is due to primary deficiency of the absorptive

Mucosal surface and of the associated enzymes.

Secondary MAS, in which mucosal changes result secondary to other factors such as diseases, surgery, trauma and drugs.

CLINICAL FEATURES

1. Steatorrhoea (pale, bulky, foul-smelling stools)
2. Chronic diarrhoea
3. Abdominal distension
4. Barborygmi and flatulence
5. Anorexia
6. Weight loss
7. Muscle wasting
8. Dehydration
9. Hypotension
10. Specific malnutrition and vitamin deficiencies depending upon the cause.

INVESTIGATIONS

I. Laboratory Tests:

1. Tests for fat malabsorption:

I) Faecal analysis for fat content

Ii) Microscopic analysis for faecal fat

Iii) Blood lipid levels after a fatty meal

Iv) Tests based on absorption of radioactive-labelled fat.

2. Tests for protein malabsorption:

I) Bile acid malabsorption

Ii) Radioactive-labelled glycine breath test.

Iii) Prothrombin time (vitamin K deficiency)

Iv) Secretin and other pancreatic tests.

3. Tests for carbohydrate malabsorption:

I) D-xylose tolerance test

Ii) Lactose tolerance test

Iii) Hydrogen breath test

Iv) Bile acid breath test

4. Vitamin B12, malabsorption:

I) Schilling test.

II. Intestinal Mucosal Biopsy:

Mucosal biopsy of small intestine is essential for making the diagnosis of MAS and also evaluation of a patient on follow-up. The availability of endoscopes has enabled easy viewing of affected mucosa directly and taking mucosal biopsy under vision; this has largely replaced the earlier peroral Crosby-Kugler capsule biopsy of small intestine.

HAEMORRHOIDS (PILES)

Haemorrhoids or piles are the varicosities of the haemorrhoidal veins. They are called *'internal piles'* if dilatation is of superior haemorrhoidal plexus covered over by mucous membrane, and *'external piles'* if they involve inferior haemorrhoidal plexus covered over by the skin. They commonly result from increased venous pressure. The possible causes include the following:

1. Portal hypertension

2. Chronic constipation and straining at stool
3. Cardiac failure
4. Venous stasis of pregnancy
5. Hereditary predisposition
6. Tumours of the rectum.

Lecture 10: Hepatic Failure

Hepatic failure may develop from severe acute and fulminant liver Injury with massive necrosis of liver cells *(acute hepatic failure),* or from advanced chronic liver disease *(chronic hepatic failure).*

ETIOLOGY. It includes following:

Acute (fulminant) hepatic failure occurs most frequently in *acute viral hepatitis*. Other causes are hepatotoxic drug reactions (e.g.

Anaesthetic agents, nonsteroidal anti-inflammatory drugs, anti-depressants), carbon tetrachloride poisoning, acute alcoholic hepatitis, mushroom poisoning and pregnancy complicated with eclampsia.

Chronic hepatic failure is most often due to *cirrhosis*. Other causes include chronic active hepatitis, chronic cholestasis (cholestatic jaundice) and Wilson's disease.

Cirrhosis

It represents the irreversible end-stage of several diffuse diseases causing hepatocellular injury and is characterised by the following 4 features:

1. It involves the entire liver.
2. The normal lobular architecture of hepatic parenchyma is disorganised.
3. There is formation of nodules separated from one another by irregular bands of fibrosis.

4. It occurs following hepatocellular necrosis of varying etiology so that there are alternate areas of necrosis and regenerative nodules.

Classification

Cirrhosis can be classified on the basis of morphology and etiology

A. MORPHOLOGIC CLASSIFICATION. There are 3 morphologic types of cirrhosis—micronodular, macronodular and mixed. Each of these forms may have an active and inactive form.

1. Micronodular cirrhosis. In micronodular cirrhosis, the nodules are usually regular and small, *less than 3 mm* in diameter.

2. Macronodular cirrhosis. In this type, the nodules are of variable size and are generally *larger than 3 mm* in diameter. The pattern of involvement is more irregular than in micronodular cirrhosis.

3. Mixed cirrhosis. In mixed type, some parts of the liver show

Micronodular appearance while other parts show macronodular pattern.

B. ETIOLOGIC CLASSIFICATION.

Based on the etiologic agent for cirrhosis.

HEPATIC TUMOURS AND TUMOUR-LIKE LESIONS

Metastatic tumours are much more common than primary tumours and tumour-like lesions.

MALIGNANT HEPATIC TUMOURS

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) or liver cell carcinoma, also trmed as hepatoma, is the most common primary malignant tumour of the liver. The tumour shows marked geographic variations in incidence which is closely related to HBV and HCV infection in the region.

Hepatoblastoma (Embryoma)

Hepatoblastoma is a rare malignant tumour arising from primitive hepatic parenchymal cells. It presents before the age of 2 years as

Progressive abdominal distension with anorexia, failure to thrive, fever and jaundice.

CHOLECYSTITIS

Acute Cholecystitis

In many ways, acute cholecystitis is similar to acute appendicitis. The condition usually begins with obstruction, followed by infection

Later.

Chronic Cholecystitis

Chronic cholecystitis is the commonest type of clinical gallbladder disease. There is almost constant association of chronic cholecystitis with cholelithiasis.

ETIOPATHOGENESIS. The association of chronic cholecystitis with mixed and combined gallstones is virtually always present. However, it is not known what initiates the inflammatory response in the gallbladder wall.

TUMOURS OF BILIARY SYSTEM

MALIGNANT TUMOURS

Carcinoma of the Gallbladder

Primary carcinoma of the gallbladder is more prevalent than other cancers of the extrahepatic biliary tract. Like cholelithiasis and cholecystitis.

Carcinoma of Extrahepatic Bile Ducts and Ampulla of Vater This is an infrequent neoplasm but is more common than the rare benign tumours of the biliary tract. Unlike other diseases of the biliary passages, it is more common in males with peak incidence in 6th decade of life.

ETIOLOGY. There is no association between bile duct carcinoma and gallstones. Bile duct cancers are associated with a number of

Other conditions such as ulcerative colitis, sclerosing cholangitis, parasitic infestations of the bile ducts with *Fasciola hepatica* (liver fluke), *Ascaris lumbricoides* and *Clonorchis sinensis.*

PANCREATITIS

Acute Pancreatitis

Acute pancreatitis is an acute inflammation of the pancreas presenting clinically with 'acute abdomen'. The severe form of the disease associated with macroscopic haemorrhages and fat necrosis in and around the pancreas is termed *acute haemorrhagic pancreatitis* or *acute pancreatic necrosis.* The condition occurs in adults between the age of 40 and 70 years and is commoner in females than in males.

ETIOLOGY. The two leading causes associated with acute pancreatitis are *alcoholism* and *cholelithiasis,* both of which are implicated in more than80% of cases.

COMPLICATIONS. A patient of acute pancreatitis who survives may develop a variety of systemic and local complications.

Systemic complications:

1. Chemical and bacterial peritonitis.
2. Endotoxic shock.
3. Acute renal failure.

Local sequelae:

1. Pancreatic abscess.
2. Pancreatic pseudocyst.
3. Duodenal obstruction.

Chronic Pancreatitis

Chronic pancreatitis or *chronic relapsing pancreatitis* is the progressive destruction of the pancreas due to repeated mild and subclinical attacks of acute pancreatitis. Weight loss and jaundice are often associated. Later manifestations include associated diabetes mellitus and steatorrhoea.

ETIOLOGY. Most cases of chronic pancreatitis are caused by the same factors as for acute pancreatitis. Thus, most commonly, chronic pancreatitis is related to *chronic alcoholism* with protein-rich diet, and less often to *biliary tract disease. Familial hereditary pancreatitis,* though uncommon, is more frequently chronic than the acute form.

Carcinoma of Pancreas

Pancreatic cancer is the term used for cancer of the exocrine pancreas. It is one of the common cancers, particularly in the Western countries and Japan. It is commoner in males than in females and the incidence Japan. It is commoner in males than in females and the incidence increases progressively after the age of 50 years.

ETIOLOGY. Following factors have been implicated in its etiology:

1. Smoking
2. Diet and obesity
3. Chemical carcinogens
4. Diabetes mellitus
5. Chronic pancreatitis
6. *H. Pylori* infection
7. Genetic factors.

Lecture 11: Glomerular Diseases

DEFINITION AND CLASSIFICATION

It is convenient to classify glomerular diseases into 2 broad groups:

I. *Primary glomerulonephritis* in which the glomeruli are the predominant site of involvement.

II. *Secondary glomerular diseases* include certain systemic and hereditary diseases which secondarily affect the glomeruli.

CLINICAL MANIFESTATIONS

The clinical presentation of glomerular disease is quite variable but in general four features—proteinuria, haematuria, hypertension and disturbed excretory function.

A number of clinical syndromes are recognised in glomerular diseases. The following are six major glomerular syndromes commonly found in different glomerular diseases:

I. ACUTE NEPHRITIC SYNDROME. This is the acute onset of haematuria, proteinuria, hypertension, oedema and oliguria .

II. NEPHROTIC SYNDROME Nephrotic syndrome is a constellation of features in different diseases having varying pathogenesis; it is characterised by findings of massive proteinuria, hypoalbuminaemia, oedema, hyperlipidaemia, lipiduria, and hypercoagulability.

III. ACUTE RENAL FAILURE. Acute renal failure (ARF) is characterised by rapid decline in renal function.

IV. CHRONIC RENAL FAILURE. These cases have advanced renal impairment progressing over years and is detected by significant proteinuria, haematuria, hypertension and azotaemia.

V. ASYMPTOMATIC PROTEINURIA. Presence of proteinuria unexpectedly in a patient may be unrelated to renal disease (e.g. Exercise- induced, extreme lordosis and orthostatic proteinuria).

VI. ASYMPTOMATIC HAEMATURIA. Asymptomatic microscopic

Haematuria is common in children and young adolescents and has many diverse causes such as diseases of the glomerulus, renal

Interstitium, calyceal system, ureter, bladder, prostate, urethra, and underlying bleeding disorder, congenital abnormalities of the kidneys or neoplasia.

Iga Nephropathy ***(Synonyms: Berger's Disease, iga GN)***

Iga nephropathy is emerging as the most common form of glomerulopathy worldwide and its incidence has been rising.

ETIOPATHOGENESIS. The etiology of iga nephropathy remains unclear:

I) It is idiopathic in most cases.

Ii) Seen as part of Henoch-Schonlein purpura.

Iii) Association with chronic inflammation in various body systems (e.g. Chronic liver disease, inflammatory bowel disease, interstitial pneumonitis, leprosy, dermatitis herpetiformis, uveitis, ankylosing spondylitis, Sjögren's syndrome, monoclonal iga gammopathy).

Pathogenesis of iga nephropathy is explained on the basis of following mechanisms:

I) iga nephropathy has been considered to arise from *entrapment* of these complexes in the mesangium.

Ii) Activation of *alternate complement pathway.*

Iii) *Increased mucosal secretion of iga.*

Iv) HLA-B35 association *genetically-determined* abnormality.

CLINICAL FEATURES. The disease is common in children and young adults. The clinical picture is usually characterised by recurrent bouts of haematuria that are often precipitated by mucosal infections.

TUMOURS OF KIDNEY

Both benign and malignant tumours occur in the kidney, the latter being more common. These may arise from *renal tubules* (adenoma, adenocarcinoma), *embryonic tissue* (mesoblastic nephroma, Wilms' tumour), *mesenchymal tissue* (angiomyolipoma, medullary interstitial tumour) and from the *epithelium of the renal pelvis* (urothelial carcinoma).

BENIGN TUMOURS

Cortical Adenoma

Cortical tubular adenomas are more common than other benign renal neoplasms.

Oncocytoma

Oncocytoma is a benign epithelial tumour arising from collecting ducts.

Other Benign Tumours

Angiomyolipoma is a hamartoma of the kidney that contains

Differentiated tissue element derived from blood vessels, smooth muscle and fat.

Mesoblastic nephroma is a congenital benign tumour.

Multicystic nephroma is another uncommon tumour of early infancy.

Medullary interstitial cell tumour is a tiny nodule in the medulla

Composed of fibroblast-like cells in hyalinised stroma.

Juxtaglomerular tumour or reninoma is a rare tumour of renal cortex consisting of sheets of epithelioid cells with many small blood vessels.

MALIGNANT TUMOURS

Adenocarcinoma of Kidney

It is now known that the renal cell carcinoma (RCC) is an adenocarcinoma arising from tubular epithelium.

ETIOLOGY AND PATHOGENESIS. Various etiologic factors implicated in the etiology of RCC are as follows:

1. Tobacco.

2. Genetic factors.

3. Cystic diseases of the kidneys.

4. Other risk factors.

Wilms' Tumour *(Synonym: Nephroblastoma)*

Nephroblastoma or Wilms' tumour is an embryonic tumour derived from primitive renal epithelial and mesenchymal components. It is the most common abdominal malignant tumour of young children,

ETIOLOGY AND PATHOGENESIS. Wilms' tumour has following etiologic associations:

1. A defect in *chromosome 11p13*
2. Monozygotic *twins*
3. Association of Wilms' tumour with some *other congenital anomalies*
4. A few *other malignancies* are known to have higher incidence of Wilms' tumour.

Lecture 12: Cervicitis

Some degree of cervical inflammation is present in virtually all multiparous women and some nulliparous women. The normal intact ectocervical stratified epithelium is usually more resistant to infection whereas the endocervical columnar epithelium bears the brunt of the initial inflammation.

Cervicitis may be specific or nonspecific, acute or chronic. *Specific*

Cervicitis may be caused by tuberculosis, syphilis, granuloma inguinale, lymphogranuloma venereum, chlamydia and chancroid.

ACUTE CERVICITIS. Acute cervicitis is usually associated with puerperium or gonococcal infection. Other causes are primary chancre and infection with herpes simplex.

CHRONIC CERVICITIS. The most common organisms responsible for chronic cervicitis are the normal mixed vaginal flora that includes streptococci, enterococci (e.g. *E. Coli*) and staphylococci. Other infecting organisms include gonococci, *Trichomonas vaginalis, Candida albicans* and herpes simplex. Factors predisposing to chronic cervicitis are sexual intercourse, trauma of childbirth, instrumentation and excess or deficiency of oestrogen.

TUMOURS

Cervical Polyps

Cervical polyps are localised benign proliferations of endocervical mucosa though they may protrude through the external os. They are found in 2-5% of adult women and produce irregular vaginal spotting.

Microglandular Hyperplasia

Microglandular hyperplasia is a benign condition of the cervix in which there is closely packed proliferation of endocervical glands without intervening stroma. The condition is caused by progestrin stimulation such as during pregnancy, postpartum period and in women taking oral contraceptives.

ENDOMETRITIS AND MYOMETRITIS

Myometritis is seen less frequently than endometritis and occurs in

Continuation with endometrial infections. Endometritis and myometritis may be acute or chronic.

Acute form generally results from 3 types of causes—puerperal (following full-term delivery, abortion and retained products of conception), intrauterine contraceptive device (IUCD), and extension of gonorrheal infection from the cervix and vagina.

Chronic form is more common and occurs by the same causes which result in acute phase. In addition, *tuberculous endometritis* is an example of specific chronic inflammation, uncommon in the Western countries but not so uncommon in developing countries.

Endometriosis

Endometriosis refers to the presence of endometrial glands and stroma in abnormal locations outside the uterus. Endometriosis and adenomyosis are closely interlinked, so much so that some gynaecologists have termed adenomyosis as *endometriosis interna* and the other category termed as *endometriosis externa* for similar appearance at the extrauterine sites. The chief locations where the abnormal endometrial development may occur are as follows (in descending order of frequency): ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum, laparotomy scars, and infrequently in the umbilicus, vagina, vulva, appendix and hernial sacs.

TUMOURS OF ENDOMETRIUM AND MYOMETRIUM Endometrial Polyps

'Uterine polyp' is clinical term used for a polypoid growth projecting into the uterine lumen and may be composed of benign lesions (e.g. Endometrial or mucous polyp, leiomyomatous polyp and placental polyp), or malignant polypoid tumours (e.g. Endometrial carcinoma, choriocarcinoma and sarcoma).

Endometrial Carcinoma

Carcinoma of the endometrium, commonly called uterine cancer, is the most common pelvic malignancy in females in the United States and Eastern Europe but is uncommon in Asia where cervical cancer continues to be the leading cancer in women. It is primarily a disease of postmenopausal women, the peak incidence at onset being 6th to 7th decades of life and is uncommon below the age of 40 years.

ETIOPATHOGENESIS. The exact etiology of endometrial cancer remains unknown. However, a few factors associated with increased frequency of its development are chronic unopposed oestrogen excess, obesity, diabetes, hypertension and nulliparous state.

Leiomyoma

Leiomyomas or fibromyomas, commonly called *fibroids* by the gynaecologists, are the most common uterine tumours of smooth muscle origin, often admixed with

variable amount of fibrous tissue component. About20% of women above the age of 30 years harbour uterine myomas of varying size. Vast majority of them are benign and cause no symptoms.

Leiomyosarcoma

Leiomyosarcoma is an uncommon malignant tumour as compared to its rather common benign counterpart. The incidence of malignancy in preexisting leiomyoma is less than 0.5% but primary uterine sarcoma is less common than that which arises in the leiomyoma.

Fibrocystic Change

Fibrocystic change is the most common benign breast condition producing vague 'lumpy' breast rather than palpable lump in the breast. Its incidence has been reported to range from 10-20% in adult women, most often between 3rd and 5th decades of life, with dramatic decline in its incidence after menopause suggesting the role of oestrogen in its pathogenesis. It was previously termed *fibrocystic disease* but is currently considered as an exaggerated physiologic phenomena and not a disease.

As such, fibrocystic change of the female breast is a histologic entity characterised by following features:

I) Cystic dilatation of terminal ducts.

Ii) Relative increase in inter- and intralobular fibrous tissue.

Iii) Variable degree of epithelial proliferation in the terminal ducts.

It is important to identify the spectrum of histologic features by core

Needle biopsy or cytologic findings by FNAC in fibrocystic changes since only some subset of changes has an increased risk of development of breast cancer. Presently, the spectrum of histologic changes are divided into two clinicopathologically relevant groups:

A. Nonproliferative Fibrocystic Changes:

Simple Fibrocystic Change

Simple fibrocystic change most commonly includes 2 features—formation of cysts of varying size, and increase in fibrous stroma.

B. Proliferative Fibrocystic Changes;

Epithelial Hyperplasia and Sclerosing Adenosis

Proliferative fibrocystic change in the breasts includes 2 entities: epithelial hyperplasia and sclerosing adenosis.

EPITHELIAL HYPERPLASIA. Epithelial hyperplasia is defined as increase in the layers of epithelial cells over the basement membrane to three or more layers in the ducts *(ductal hyperplasia)* or lobules *(lobular hyperplasia).* The latter condition, lobular hyperplasia, must be distinguished from adenosis in which there is increase in the number of ductules or acini without any change in the number or type of cells lining them.

CARCINOMA OF THE BREAST

Cancer of the breast is among the commonest of human cancers throughout the world. Its incidence varies in different countries but is particularly high in developed countries.

General Features and Classification

Cancer of the breast occurs more often in left breast than the right and is bilateral in about 4% cases.

Carcinoma of the breast arises from the ductal epithelium in 90% cases while the remaining 10% originate from the lobular epithelium. For variable period of time, the tumour cells remain confined within the ducts or period of time, the tumour cells remain confined within the ducts or lobules (non-invasive carcinoma) before they invade the breast stroma (invasive carcinoma). While only 2 types of *non-invasive carcinoma* .

A. NON-INVASIVE *(IN SITU)* BREAST CARCINOMA

Intraductal Carcinoma

Carcinoma *in situ* confined within the larger mammary ducts is called intraductal carcinoma.

Lobular Carcinoma *in Situ*

Lobular carcinoma *in situ* is not a palpable or grossly visible tumour. Patients of *in situ* lobular carcinoma treated with excisional biopsy alone

B. INVASIVE BREAST CARCINOMA

Infiltrating (Invasive) Duct Carcinoma-NOS

Infiltrating duct carcinoma-NOS *(not otherwise specified)* is the classic breast cancer and is the most common histologic pattern

Accounting for70% cases of breast cancer.

Infiltrating (Invasive) Lobular Carcinoma

Invasive lobular carcinoma comprises about 5% of all breast cancers.

Medullary Carcinoma

Medullary carcinoma is a variant of ductal carcinoma and comprises about1% of all breast cancers.

Colloid (Mucinous) Carcinoma

This is an uncommon pattern of breast cancer occurring more frequently in older women and is slow-growing. Colloid carcinoma has better prognosis than the usual infiltrating duct carcinoma.

Other Morphologic Forms

A few other morphologic forms of invasive breast carcinoma having clinical significance have been recognised:

PAPILLARY CARCINOMA. It is a rare variety of infiltrating duct carcinoma in which the stromal invasiodn is in the form of papillary structures.

C. PAGET'S DISEASE OF THE NIPPLE

Paget's disease of the nipple is an eczematoid lesion of the nipple, often associated with an invasive or non-invasive ductal carcinoma of the underlying breast.

Lecture 13: Non-Infectious Inflammatory Dermatoses

1. Dermatitis (Eczema). The pathologic term dermatitis is synonymous with the clinical term eczema. Both refer to inflammatory response to avariety of agents acting on the skin from outside or from within the body such as chemicals and drugs, hypersensitivity to various antigens and haptens etc. Accordingly, clinical types such as contact dermatitis, atopic dermatitis, drug-induced dermatitis, photo-eczematous dermatitis and primary irritant dermatitis are described. Intercellular oedema) that may lead to formation of intraepidermal vesicles or bullae. The vesicles and bullae as well as the oedematous epidermis are permeated by acute inflammatory cells. The upper dermis shows congested blood vessels and mononuclear inflammatory cell infiltrate, especially around the small blood vessels.

Subacute dermatitis may follow acute dermatitis. Spongiosis and

Vesicles are smaller than in acute dermatitis. The epidermis shows moderate acanthosis and varying degree of parakeratosis in the horny layer with formation of surface crusts containing degenerated leucocytes, bacteria and fibrin. The dermis contains perivascular mononuclear infiltrate. The classical example of subacute dermatitis is *nummular dermatitis.*

Chronic dermatitis shows hyperkeratosis, parakeratosis and

Acanthosis with elongation of the rete ridges and broadened dermal papillae. Vesicles are absent but slight spongiosis may be present. The upper dermis shows perivascular chronic inflammatory infiltrate and fibrosis

SCALING DERMATOSES

1. PSORIASIS. Psoriasis is a chronic inflammatory dermatosis that affects about 2% of the population. It usually appears first between the age of 15 and 30 years. The

lesions are characterised by brownish-red papules and plaques which are sharply demarcated and are covered with fine, silvery white scales. As the scales are removed by gentle scrapping, fine bleeding points appear termed *Auspitz sign.*

Tumours and tumour-like lesions may arise from different components of the skin such as surface epidermis, epidermal appendages and dermal tissues. Each of these tissues may give rise to benign and malignant tumours as well as tumour-like lesions.

I. TUMOURS AND CYSTS OF THE EPIDERMIS

D. Malignant Tumours

1. SQUAMOUS CELL CARCINOMA. Squamous cell carcinoma may arise on any part of the skin and mucous membranes lined by

Squamous epithelium but is more likely to occur on sun-exposed parts in older people.

2. BASAL CELL CARCINOMA (RODENT ULCER). Typically, the basal cell carcinoma is a locally invasive, slow-growing tumour of middle- aged that rarely metastasises. It occurs exclusively on hairy skin, the most common location (90%) being the face, usually above a line from the lobe of the ear to the corner of the mouth. Basal cell carcinoma is seen more frequently in white-skinned people and in those who have prolonged exposure to strong sunlight like in those living in Australia and New Zealand.

3. METATYPICAL CARCINOMA (BASOSQUAMOUS CELL CARCINOMA).

Metatypical or basosquamous cell carcinoma is the term used for a

Tumour in which the cell type and arrangement of cells cause difficulty in deciding between basal cell carcinoma and squamous cell carcinoma.

Lecture 14: Bone Tumors

Bone tumours may be primary or metastatic. Since histogenesis of some bone tumours is obscure, the WHO has recommended a widely accepted classification of primary bone tumours based on both histogenesis and histologic criteria.

The diagnosis of any bone lesion is established by a combination of clinical, radiological and pathological examination, supplemented by biochemical and haematological investigations

Wherever necessary. These include: serum levels of calcium, phosphorus, alkaline phosphatase and acid phosphatase. Specific

Investigations like plasma and urinary proteins and the bone marrow examination in case of myeloma, urinary catecholamines in metastatic neuroblastoma and haematologic profile in lymphoma and leukaemic involvement of the bone, are of considerable help.

BONE-FORMING (OSTEOBLASTIC) TUMOURS

Bone-forming or osteoblastic group of bone tumours are characterised by the common property of synthesis of osteoid or bone, or both, directly by the tumour cells (osteogenesis).

Osteoma

An osteoma is a rare benign, slow-growing lesion, regarded by some as a hamartoma rather than a true neoplasm. Osteoma is almost exclusively restricted to flat bones of the skull and face.

Osteoid Osteoma and Osteoblastoma

Osteoid osteoma and osteoblastoma (or giant osteoid osteoma) are closely related benign tumours occurring in children and young adults. Osteoid osteoma is more common than osteoblastoma.

Osteoid osteoma is small (usually less than 1 cm) and painful tumour, located in the cortex of a long bone.

Osteoblastoma, is larger in size (usually more than1 cm), painless, located in the medulla, commonly in the vertebrae,

Ribs, ilium and long bones, and there is absence of reactive bone

Formation.

Osteosarcoma

Osteosarcoma or osteogenic sarcoma is the most common primary malignant tumour of the bone.

Osteosarcomas are classified into 2 main categories:

Central (medullary) and surface (parosteal and perosteal).

Chondrosarcoma

Chondrosarcoma is a malignant tumour of chondroblasts.

Lecture 15: Prostatitis

Acute Prostatitis

Acute focal or diffuse suppurative inflammation of the prostate is not uncommon. It occurs most commonly due to ascent of bacteria

From the urethra, less often by descent from the upper urinary tract or bladder, and occasionally by lymphogenous or haematogenous spread from a distant focus of infection. The infection may occur spontaneously or may be a complication of urethral manipulation such as by catheterisation, cystoscopy, urethral dilatation and surgical procedures on the prostate. The common pathogens are those which cause UTI, most frequently *E. Coli,* and others such as *Klebsiella*, *Proteus, Pseudomonas, Enterobacter*, gonococci, staphylococci and streptococci.

Chronic Prostatitis

Chronic prostatitis is more common and foci of chronic inflammation are frequently present in the prostate of men above 40 years of age.

Chronic prostatitis is of 2 types:

Chronic bacterial prostatitis is caused in much the same way and by the same organisms as the acute prostatitis. It is generally a consequence of recurrent UTI.

Chronic abacterial prostatitis is more common. There is no history of recurrent UTI and culture of urine and prostatic secretions is always negative, though leucocytosis is demonstrable in prostatic secretions.

Granulomatous Prostatitis

Granulomatous prostatitis is a variety of chronic prostatitis, probably caused by leakage of prostatic secretions into the tissue, or could be of autoimmune origin.

Carcinoma Of Prostate

Cancer of the prostate is the second most common form of cancer in males, followed in frequency by lung cancer. It is a disease of men above the age of 50 years and its prevalence increases with increasing age so that more than 50% of men 80 years old have asymptomatic (latent) carcinoma of the prostate. Thus, it is common to classify carcinoma of the prostate into the following 4 types:

1. Latent carcinoma
2. Incidental carcinoma
3. Occult carcinoma
4. Clinical carcinoma

ETIOLOGY. The cause of prostatic cancer remains obscure. However, a few factors have been suspected. These are as under:

1. Endocrinologic factors. Androgens are considered essential for development and maintenance of prostatic epithelium.

2. Racial and geographic influences. There are some racial and

Geographic differences in the incidence of prostatic cancer.

3. Environmental influences. Some common environmental factors and carcinogens have been identified with high risk to development of prostatic cancer. These include high dietary fat, and exposure to polycyclic aromatic hydrocarbons. Flavonoids, antioxidants and selenium may reduce the risk.

4. Nodular hyperplasia. Though nodular prostatic hyperplasia has been suggested by some as precursor for development of prostatic

Cancer, it is considered unlikely. Approximately 15-20% of nodular hyperplastic prostates harbour carcinoma.

5. Heredity. The possibility of genetic basis of prostatic cancer has been suggested by the observations of familial clustering and 2-fold higher frequency in first-degree relatives.

SPREAD. It may spread by following routes:

Direct spread. Direct extension of the tumour occurs into the prostatic capsule and beyond.

Metastases. Distant spread occurs by both lymphatic and haematogenous routes. Haematogenous spread leads most often to characteristic osteoblastic *osseous metastases,* especially to pelvis, and lumbar spine; other sites of metastases are lungs, kidneys, breast and brain. The route of bloodborne metastases may be retrograde spread by prostatic venous plexus or via systemic circulation.

CLINICAL FEATURES. By the time symptoms appear, the carcinoma of prostate is usually palpable on rectal examination as a hard and nodular gland fixed to the surrounding tissues. In such symptomatic cases, clinical features are: urinary obstruction with dysuria, frequency, retention of urine, haematuria, and in 10% of cases pain in the back due to skeletal metastases.

Two serum *tumour markers* employed commonly for diagnosis and
Monitoring the prognosis of prostatic carcinoma are as under:

Prostatic acid phosphatase (PAP) is secreted by prostatic epithelium. Elevation of serum level of PAP is found in cases of prostatic cancer which have extended beyond the capsule or have metastasised.

Prostate-specific antigen (PSA) can be detected by immunohistochemical method in the malignant prostatic epithelium as well as estimated in the serum.

TESTICULAR TUMOURS

Testicular tumours are the cause of about 1% of all cancer deaths. They have *trimodal* age distribution—a peak during infancy, another during late adolescence and early adulthood, and a third peak after 60 years of age.

ETIOLOGIC FACTORS

Exact etiology of testicular germ cell tumours is unknown, but the following factors have been implicated:

1. Cryptorchidism. 30-50 times greater
2. Other developmental disorders e.g. Dysgenetic gonads
3. Genetic factors: High incidence in first-degree family members, twins.
4. Other factors

I) Orchitis

Ii) Trauma

Iii) Carcinogens

CLINICAL FEATURES AND DIAGNOSIS

The usual presenting clinical symptoms of testicular tumours are gradual gonadal enlargement and a dragging sensation in the testis.

SPREAD. Testicular tumours may spread by both lymphatic and
Haematogenous routes:

TUMOUR MARKERS. Two tumour markers widely used in the diagnosis, staging and monitoring the follow-up of patients with testicular tumours are:

Hcg is synthesised by placental syncytio-trophoblast such as in various non-seminomatous germ cell tumours of the testis (e.g. In

Choriocarcinoma, yolk sac tumour and embryonal carcinoma).

AFP is normally synthesised by the foetal liver cells, yolk sac and foetal gut. Its levels are elevated in testicular tumours associated with yolk sac components.

GERM CELL TUMOURS

Germ cell tumours comprise approximately 95% of all testicular tumours and are more frequent before the age of 45 years

Classic Seminoma

Seminoma is the commonest malignant tumour of the testis and corresponds to dysgerminoma in the female.

Spermatocytic Seminoma

It is an uncommon tumour having an incidence of about 5% of all germ cell tumours. Spermatocytic seminoma usually occurs in older patients, generally in 6th decade of life.

Embryonal Carcinoma

Pure embryonal carcinoma constitutes 30% of germ cell tumours but areas of embryonal carcinoma are present in 40% of germ cell tumours.

Yolk Sac Tumour

(Synonyms: Endodermal Sinus Tumour, Orchioblastoma, Infantile Embryonal Carcinoma)

This characteristic tumour is the most common testicular tumour of infants and young children upto the age of 4 years.

Choriocarcinoma

Pure choriocarcinoma is a highly malignant tumour composed of elements consisting of syncytiotrophoblast and cytotrophoblast.

Teratoma

Teratomas are complex tumours composed of tissues derived from more than one of the three germ cell layers—endoderm, mesoderm and ectoderm. Testicular teratomas are more common in infants and children and constitute about 40% of testicular tumours in infants.

Lecture16: Hyperpituitarism

A. Hyperfunction of Anterior Pituitary

Three common syndromes of adenohypophyseal hyperfunction are: gigantism and acromegaly, hyperprolactinaemia and Cushing's syndrome.

GIGANTISM AND ACROMEGALY. Both these clinical syndromes result from sustained excess of growth hormone (GH), most commonly by somatotroph (GH-secreting) adenoma.

HYPERPROLACTINAEMIA. Hyperprolactinaemia is the excessive

Production of prolactin (PRL), most commonly by lactotroph (PRL-secreting) adenoma, also called prolactinoma.

CUSHING'S SYNDROME. Pituitary-dependent Cushing's syndrome results from ACTH excess. Most frequently, it is caused by corticotroph (acthsecreting) adenoma.

B. Hyperfunction of Posterior Pituitary and Hypothalamus

Lesions of posterior pituitary and hypothalamus are uncommon. Two of the syndromes associated with hyperfunction of the posterior pituitary and hypothalamus are: inappropriate release of ADH and precocious puberty.

PRECOCIOUS PUBERTY. A tumour in the region of hypothalamus or the pineal gland may result in premature release of gonadotropins causing the onset of pubertal changes prior to the age of 9 years.

PITUITARY TUMOURS

Tumours of the anterior pituitary are more common than those of the posterior pituitary and hypothalamus. The most common of the

Anterior pituitary tumours are adenomas; primary and metastatic carcinomas being rare. Craniopharyngioma and granular cell tumour (choristoma) are the other benign pituitary tumours found occasionally.

All pituitary tumours, whether benign or malignant, cause symptoms by following 2 ways:

1. Pressure effects
2. Hormonal effects.

Pituitary Adenomas

Adenomas are the most common pituitary tumours. They are conventionally classified according to their H & E staining characteristics of granules into acidophil, basophil and chromophobe adenomas.

THYROIDITIS

Inflammation of the thyroid, thyroiditis, is more often due to non-infectious causes and is classified on the basis of onset and duration of disease into acute, subacute and chronic as under:

I. Acute thyroiditis:

1. Bacterial infection e.g. *Staphylococcus*, *Streptococcus*.
2. Fungal infection e.g. *Aspergillus*, *Histoplasma*, *Pneumocystis*.
3. Radiation injury

II. Subacute thyroiditis:

1. Subacute granulomatous thyroiditis (de Quervain's thyroiditis, giant cell thyroiditis, viral thyroiditis)

2. Subacute lymphocytic (postpartum, silent) thyroiditis

3. Tuberculous thyroiditis

III. Chronic thyroiditis:

1. Autoimmune thyroiditis (Hashimoto's thyroiditis or chronic lymphocytic thyroiditis)

2. Riedel's thyroiditis (or invasive fibrous thyroiditis).

HASHIMOTO'S (AUTOIMMUNE, CHRONIC LYMPHOCYTIC) THYROIDITIS

Hashimoto's thyroiditis, also called diffuse lymphocytic thyroiditis, struma lymphomatosa or goitrous autoimmune thyroiditis, is characterised by 3 principal features:

1. Diffuse goitrous enlargement of the thyroid.
2. Lymphocytic infiltration of the thyroid gland.
3. Occurrence of thyroid autoantibodies.

Hashimoto's thyroiditis occurs more frequently between the age of 30 and 50 years and shows an approximately ten-fold preponderance among females. Though rare in children, about half the cases of adolescent goitre are owing to autoimmune thyroiditis. Hashimoto's thyroiditis is the most common cause of *goitrous hypothyroidism* in regions .

THYROID TUMOURS

FOLLICULAR ADENOMA

Follicular adenoma is the most common benign thyroid tumour occurring more frequently in adult women

THYROID CANCER

Carcinoma of the thyroid gland has 4 major morphologic types with

Distinctly different clinical behaviour and variable prevalence. These are:
Papillary, follicular, medullary and undifferentiated (anaplastic) carcinoma;

ETIOPATHOGENESIS. Most important risk factor implicated in the etiology of thyroid cancer is external radiation, and to a some extent there is role of TSH receptors and iodine excess, while pathogenesis of thyroid cancer is explained on genetic alterations.

1. External radiation. The single most important environmental factor associated with increased risk of developing thyroid carcinoma after many years of exposure to external radiation of high dose.

2. Iodine excess and TSH. In regions where endemic goitre is widespread, addition of iodine to diet has resulted in increase in incidence of papillary cancer.

3. Genetic basis. Familial clustering of thyroid cancer has been observed, especially in medullary carcinoma. Molecular studies reveal that thyroid carcinoma is a multistep process involving genetic alterations but distinct mutations

Papillary Thyroid Carcinoma

Papillary carcinoma is the most common type of thyroid carcinoma, It can occur at all ages including children and young adults but the incidence is higher with advancing age. The tumour is found about three times more frequently in females than in males.

Follicular Thyroid Carcinoma

Follicular carcinoma is the other common type of thyroid cancer

Medullary Thyroid Carcinoma

Medullary carcinoma is a less frequent type derived from parafollicular or Ccells present in the thyroid and comprises about 5% of thyroid carcinomas. It is equally common in men and women.

Anaplastic Carcinoma

Undifferentiated or anaplastic carcinoma of the thyroid comprises less than5% of all thyroid cancers and is one of the most malignant tumour in humans. The tumour is predominantly found in old age (7th-8th decades) and is slightly more common in females than in males

Lecture 17:Nervous system

A large number of pathogens comprising various kinds of bacteria, fungi, viruses, rickettsiae and parasites can cause infections of the nervous system. The micro-organisms may gain entry into the nervous system by one of the following routes:

1. Via blood stream
2. Direct implantation
3. Local extension
4. Along nerve.

In general, resultant lesions are in the form of either diffuse inflammation of the meninges (meningitis) and of brain parenchyma (encephalitis), or combination of both (meningoencephalitis). In addition, other inflammatory lesions of CNS include: brain abscess, epidural abscess, subdural empyema, septic thromboembolism of dural sinuses and encephalomyelitis.

MENINGITIS

Meningitis is inflammatory involvement of the meninges. Meningitis may involve the dura called *pachymeningitis*, or the leptomeninges (pia- arachnoid) termed *leptomeningitis.* The latter is far more common, and unless otherwise specified, meningitis would mean leptomeningitis. Pachymeningitis is invariably an extension

of the inflammation from chronic suppurative otitis media or from fracture of the skull. An *extradural abscess* may form by suppuration between the bone and dura. Further spread of infection may penetrate the dura and form a *subdural abscess.*

Other effects of pachymeningitis are localised or generalised leptomeningitis and *cerebral abscess.* Infectious meningitis is broadly classified into 3 types: acute pyogenic, acute lymphocytic (viral, aseptic) and chronic (bacterial or fungal).

ENCEPHALITIS

Parenchymal infection of brain is termed encephalitis. Encephalitis may be the result of bacterial, viral, fungal and protozoal infections.

Bacterial Encephalitis

Bacterial infection of the brain substance is usually secondary to involvement of the meninges rather than a primary bacterial parenchymal infection. This results in bacterial cerebritis that progresses to form *brain abscess.* However, *tuberculosis* and *neurosyphilis* are the two primary bacterial involvements of the brain parenchyma.

Viral Encephalitis

Most viral infections of the CNS are

The end-result of preceding infection in other tissues and organs.

Most of the viruses reach the nervous system via blood stream before which they enter the body by various routes e.g. Infection of the skin and mucous membrane (in herpes simplex and herpes zoster- varicella), by the alimentary tract (in enteroviruses including polio virus), by arthropod bite (in arbovirus), by transplacental infection (in cytomegalovirus), and through body fluids in AIDS (in HIV infection). Rabies virus travels along the peripheral nerves to reach the CNS. Herpes zoster-varicella is a distinct primary disease (chickenpox) but the virus remains latent for a long time

before it gets reactivated to cause severe hyperalgesia and pain along the distribution of nerve related to acutely inflamed posterior root ganglia (herpes zoster).

CEREBROVASCULAR DISEASES

Cerebrovascular diseases are all those diseases in which one or more of the blood vessels of the brain are involved in the pathologic processes. Various pathologic processes commonly implicated in cerebrovascular diseases are:
Thrombosis, embolism, rupture of a vessel, hypoxia, hypertensive arteriolosclerosis, atherosclerosis, arteritis, trauma, aneurysm and developmental malformations. These processes can result in 2 main types of parenchymal diseases of the brain:

A. Ischaemic brain damage:

A) Generalised reduction in blood flow resulting in *global hypoxic-ischaemic encephalopathy*

B) Local vascular obstruction causing *infarcts.*

B. Intracranial haemorrhage:

A) Haemorrhage in the brain parenchyma *(intracerebral haemorrhage)*

B) Haemorrhage in the subarachnoid space *(subarachnoid haemorrhage).* The *stroke syndrome* is the cardinal feature of cerebrovascular disease. The term stroke is used for sudden and dramatic development of focal neurologic deficit, varying from trivial neurologic disorder to hemiplegia and coma.