Amyloidosis

- Amyloid
  - Fibril proteins (95%)
    - AL
    - AA
    - Others
      - ATTR
      - AB_2M
      - AB
      - AH
      - Amyloid of Hormone precursor proteins
      - Amyloid of prion proteins
      - Hereditofamilial
  - Non fibril components (5%)
    - Amyloid-P-Component
    - Apolipoprotein-E
    - Sulphated Glucosaminoglycans (GAGs)
    - α_1 antichymotrypsin
    - Protein-X
    - Others

Pathogenesis

	AL	AA
Stimulus	Plasma cell dyscrasias, B-cell lymphoma, Multiple myeloma, Idiopathic	Chronic infection, Chronic non inf. inflammation, Cancer, Familial mediterranean fever
	↓	↓
	Monoclonal B-cell proliferation	Activation of macrophage → IL-1, IL-6 (Cytokines)
	↓	↓
Soluble precursor proteins	Excess Ig production (Intact λ & κ light chains)	SAA production ↑↑ in liver
	↓	↓
Partial degradation	Macrophage	Reticuloendothelial cells
	Urinary excretion of Bence-Jones proteins	
Non fibril components	GAGs, ApoE, AP	
Insoluble fibril proteins	AL amyloid	AA amyloid

Amyloid enhancing factors → Reticuloendothelial cells

Classification

Category	Associated diseases	Biochemical type	Organ involved
Systemic			
- Primary	Plasma cell dyscrasias	AL	Kidney, Skin, Nerve, Bowel, Heart
- Secondary	Chronic inflammation	AA	Kidney, Adrenal, Spleen, liver
- Hemodialysis associated	Renal failure	AB_2M	Synovium, Joints, Tendon sheaths
- Hereditofamilial			
- Hereditary polyneuropathies	-	ATTR	Peripheral and autonomic nerve, Heart
- Familial mediterranean fever	-	AA	Kidney, Adrenal, Spleen, liver
- Others more			Systemic amyloidosis
Local			
- Senile cardiac	Senility	ATTR	Heart

- Senile cerebral	Alzheimer's disease & transmissible encephalopathies	Aβ, Aβ₁₋₄₂	cerebral vessels, plaque neurofibrillary tangles
- Endocrine	Medullary carcinoma Type-2 diabetes mellitus	Procalcitonin Proinsulin	Thyroid Islets of Langerhans
- Tumor formation	Lungs, Skin, Thyroid	AL	Associated anatomical structures

2. Shock

Classification

- Hypovolaemic shock
  - Acute Haemorrhage
  - Acute pancreatitis
  - Excessive use of diuretics
  - Burns
  - Dehydration due to vomiting and diarrhoea
- Cardiogenic shock
  - Deficient emptying
    - Myocardial infarction
    - Cardiomyopathies
    - Rupture of Heart / Ventricle / Papillary muscles
    - Cardiac arrhythmias
  - Deficient filling
    - Cardiac tamponade due to Haemopericardium
  - Obstruction in outflow
    - Ball valve thrombus
    - Pulmonary embolism
    - Tension pneumothorax
    - Dissecting aortic aneurysm
- Septic shock
  - Gram +ve septic shock (Exotoxic shock)
  - Gram -ve septic shock (Endotoxic shock)
- Other types
  - Traumatic shock
    - Severe injury
    - Surgical loss of blood
    - Obstetric bleeding
  - Neurogenic
    - High cervical spinal cord injury
    - Excessive administration of spinal anaesthesia
    - Severe head injury
  - Hypoadrenal shock.
    - Administration of high doses of glucocorticoids
    - Secondary adrenal insufficiencies.

I am a student of

Pathogenesis

- Hypovolaemic shock → ↓ Effective circulating blood volume
- Septic shock → ↓ Effective circulating blood volume
- Cardiogenic shock → ↓ Cardiac output

↓ Effective circulating blood volume → ↓ Venous return → ↓ Cardiac output

- Other types

↓ Blood flow

↓ Supply of oxygen

↓

Anoxia

↓

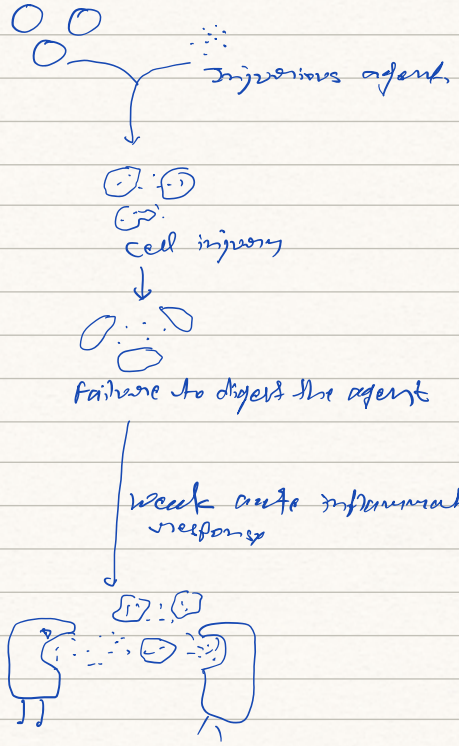
Inflammatory mediators

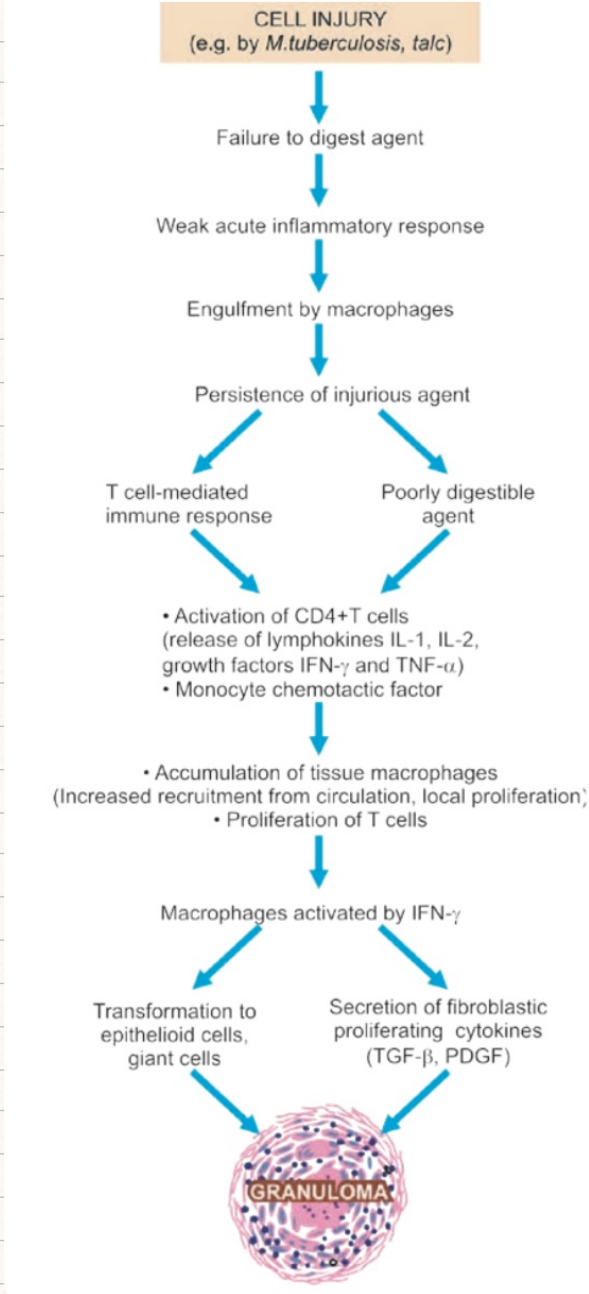
↓

Shock.

3. Granulomatous inflammation

Pathogenesis





- Tissue macrophage ↑↑
  - Recruitment from circulation
  - Proliferation
- T-cells ↑↑
  - Proliferation

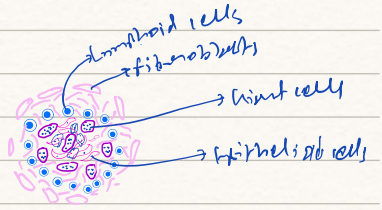
IFN-γ → Activation

Activated macrophage

- Transformation → Epithelioid cells → Giant cells
- Secretion (cytokines)
  - TNF-β
  - PDGF
  → fibroblast proliferation

in granuloma

- Epithelioid cells
- Giant cells
- Lymphocytes
- Necrosis
- Fibrosis



Granuloma

4. Gangrene

Ischaemia → Inflammation → Coagulative necrosis

virulent bacterial infection → massive necrotising inflammation

Coagulative necrosis + massive necrotising inflammation → Necrosis + Putrefaction → Gangrene

TABLE 3.5: Contrasting Features of Dry and Wet Gangrene.

	Feature	Dry Gangrene	Wet Gangrene
1.	*Site*	Commonly limbs	More common in bowel
2.	*Mechanisms*	Arterial occlusion	More commonly venous obstruction, less often arterial occlusion
3.	*Macroscopy*	Organ dry, shrunken and black	Part moist, soft, swollen, rotten and dark
4.	*Putrefaction*	Limited due to very little blood supply	Marked due to stuffing of organ with blood
5.	*Line of demarcation*	Present at the junction between healthy and gangrenous part	No clear line of demarcation
6.	*Bacteria*	Bacteria fail to survive	Numerous present
7.	*Prognosis*	Generally better due to little septicaemia	Generally poor due to profound toxaemia

5. Pathological calcification

⇒ Deposition of calcium salts in the tissues other than osteoid and enamel.

⇒ 2 types
- Dystrophic calcification
  - In dead & degenerated tissues
  - Normal
    - Calcium metabolism
    - Serum calcium level
- Metastatic calcification
  - In normal tissues
  - Deranged calcium metabolism
  - Hypercalcaemia

⇒ pathogenesis of both is different

Dystrophic calcification

- Sites
  - Dead tissues
    - Caseous necrosis
    - Liquefaction necrosis
    - Fat necrosis
    - Gamma gandy bodies (in spleen – Haemosiderin + Ca^{2+} deposits)
    - Infarcts
    - Thrombi
    - Hematoma in the vicinity of bones
    - Dead parasites
    - Congenital toxoplasmosis involving the CNS
  - Degenerated tissues
    - Dense old scars
    - Atheromas

- Monckeberg sclerosis
- Stroma of tumours
- Psammoma bodies
- Calcinosis cutis
- Wall of cyst
- Senile degenerative changes

TABLE 3.6: Differences between Dystrophic and Metastatic Calcification.

	Feature	Dystrophic Calcification	Metastatic Calcification
1.	*Definition*	Deposits of calcium salts in dead and degenerated tissues	Deposits of calcium salts in normal tissues
2.	*Calcium metabolism*	Normal	Deranged
3.	*Serum calcium level*	Normal	Hypercalcaemia
4.	*Reversibility*	Generally irreversible	Reversible upon correction of metabolic disorder
5.	*Causes*	Necrosis (caseous, liquefactive, fat), infarcts, thrombi, haematomas, dead parasites, old scars, atheromas, Mönckeberg's sclerosis, certain tumours, cysts, calcinosis cutis	Hyperparathyroidism (due to adenoma, hyperplasia, CRF), bony destructive lesions (e.g. myeloma, metastatic carcinoma), prolonged immobilisation, hypervitaminosis D, milk-alkali syndrome, hypercalcaemia of infancy
6.	*Pathogenesis*	Increased binding of phosphates with necrotic and degenerative tissue, which in turn binds to calcium forming calcium phosphate precipitates	Increased precipitates of calcium phosphate due to hypercalcaemia at certain sites e.g. in lungs, stomach, blood vessels and cornea

- Pathogenesis
  - Not clear
  - Necrotic/degenerative tissue → Denatured proteins → Binds with phosphate → React with calcium → Calcium phosphate precipitates
  - Stages — Initiation – Calcium phosphate aggregates — Intracellularly – In mitochondria; Extracellularly – In vesicles
    - Propagation – Crystal formation
- Irreversible.

Metastatic calcification

- Causes — Excessive mobilisation of calcium from the bone
  - Hyperparathyroidism
  - Bony destructive lesions
  - Prolong immobilisation
- Excessive absorption of calcium from gut
  - Hypervitaminosis-D
  - Milk-alkali syndrome
  - Hypercalcaemia in infancy
- Sites — Kidney; Liver; Lungs; Cornea; Blood vessels; Synovium
- Pathogenesis
  - Underlying metabolic derangement → Phosphate binds with calcium → Calcium phosphate precipitate → Accumulation
- Reversible upon correction of metabolic disorder

6. Classification of Leprosy

- 2 types
  - Lepromatous leprosy – 'Low resistance' → Polar
  - Tuberculoid leprosy – 'High resistance' → Polar
- 5 clinicopathologic groups (Modified Ridley and Jopling's classification)
  - TT (Tuberculoid polar) – High resistance
  - BT (Borderline Tuberculoid)
  - BB (Mid Borderline) - Dimorphic
  - BL (Borderline lepromatous)

- LL (Lepromatous polar) – Low resistance.

TABLE 6.5: Differences between Lepromatous and Tuberculoid Leprosy.

Feature	Lepromatous Leprosy	Tuberculoid Leprosy
1. *Skin lesions*	Symmetrical, multiple, hypopigmented, erythematous, maculopapular or nodular (leonine facies).	Asymmetrical, single or a few lesions, hypopigmented and erythematous macular.
2. *Nerve involvement*	Present but sensory disturbance is less severe.	Present with distinct sensory disturbance.
3. *Histopathology*	Collection of foamy macrophages or lepra cells in the dermis separated from epidermis by a 'clear zone'.	Hard tubercle similar to granulomatous lesion, eroding the basal layer of epidermis; no clear zone.
4. *Bacteriology*	Lepra cells highly positive for lepra bacilli seen as 'globi' or 'cigarettes-in-pack' appearance.	Lepra bacilli few, seen in destroyed nerves as granular or beaded forms.
5. *Immunity*	Suppressed (low resistance).	Good immune response (high resistance).
6. *Lepromin test*	Negative	Positive

7. Leukaemoid reaction

- Reactive excessive leucocytosis
- Resembles like leukaemia in a person who does not have leukaemia.
- Clinical features of leukaemia are absent
  - Splenomegaly
  - Haemorrhages
  - Lymphadenopathies
- Underlying causes are obvious.
- 2 types
  - Myeloid – more common
  - Lymphoid

Myeloid leukaemoid reaction

- Commonly involves granulocyte series

Causes

- Infections
  - Staphylococcal pneumonia
  - Disseminated tuberculosis
  - Diphtheria
  - Sepsis
  - Meningitis
  - Plague
  - Endocarditis
  - Infected abortions
- Intoxications
  - Eclampsia
  - Mercury poisoning
  - Severe burns
- Malignant disorders
  - Multiple myeloma
  - Myelofibrosis
  - Hodgkins disease.
  - Bone metastasis
- Severe haemorrhage and severe haemolysis

Lymphoid leukaemoid reaction

Causes

- Infections
  - Infectious mononucleosis
  - Cytomegalovirus infections.
  - Infectious lymphocytosis
  - Pertussis
  - Measles
  - Chickenpox
  - Tuberculosis
- Malignant disorders – Rare.

8. Inflammatory Bowel Disease (Crohns disease & ulcerative colitis)

Crohns disease/Regional enteritis

- Idiopathic chronic ulcerative IBD
- Non caseating granulomatous inflammation (Transmural)
- Involves terminal ileum & colon

Ulcerative colitis
- Acute/Chronic ulcero-inflammatory colitis
- Involves rectum ± descending colon (Mucosa → Submucosa)

- Common in 10-30 yrs of age
- Systemic involvement
  - Polyarthritis
  - Ankylosing spondilitis
  - Uveitis
  - Skin lesions
  - Liver

Etiopathogenesis / Causes
- Genetic factors → 3-20 times higher incidence in first degree relatives
  - → 50% chance in monozygotic twins.
  - → gene association with IBD — 5q
    6p
    12p
    14q
    16q → CARD-15 → Mutation → Loss of function → 50 times higher chance of Crohn's disease
  - → HLA studies — HLA-DRB1 → Ulcerative colitis
    - HLA-DQ1 → Crohn's disease.
    - HLA-DR7
- Immunologic factors
  - Defective regulation of immune suppression → CD_4 +ve cells → Secrete inflammation inhibitory cytokines (IL-10, TGF-β)
    - Defective → ✗
  - Transgenic mouse experimental model studies
    - Deletion of inflammation inhibitory cytokines (IL-2, IL-10, TGF-β) or their receptors
    - Deletion of T cell recognition molecules (T cell antigen receptors)
    - Interference with epithelial barrier function (Deletion of MDR gene)
    - Type of inflammatory cells
      - Activated CD_4 +ve cells — Activate and recruit inflammatory cells
        - TH_1 → Secrete proinflammatory cytokines (IFN-γ, TNF, IL-12) - Crohn's dis
        - TH_2 → Induce superficial mucosal inflammation (IL-4, 5, 13) - Ulcer. Colitis
- Exogenous factors
  - Microbial
  - Psychosocial
  - Smoking - Crohn's disease
  - Oral contraceptives

- Back-wash ileitis - Backflow of colonic contents into the terminal ileum (In 10% cases of Ulcer. colitis.)

Complications
- Crohn's disease
  - Malabsorption
  - Fistula formation
  - Stricture formation
  - Development of malignancy
- Ulcerative colitis
  - Toxic megacolon (fulminant colitis)
    - Thin walled colon
    - Perforation → Faecal peritonitis
  - Perianal fistula
  - Carcinoma (may occur in disease of more than 10 years)
  - No stricture formation.

9. Primary pulmonary tuberculosis

⇒ Infection of an individual who has not been previously infected or immunised is called primary tuberculosis / Ghon's complex / primary complex / childhood tuberculosis.

- Primary complex → Lesion of portal of entry + Draining lymphatic vessels & nodes
  - 3 components
    - Primary component
      - 1-2 cm solitary area
      - Located peripherally
      - More often in upper part of lower lobe subpleurally
    - Lymphatic vessel component
      - Phagocytes containing bacilli
      - May develop miliary tubercles along the path of hilar lymphnodes.
    - Lymph node component
      - Enlarged hilar & tracheobronchial lymph nodes
      - Caseous necrosis

⇒ Fate of primary tuberculosis

⇒ Do not progress → Heal by fibrosis → calcification / ossification

⇒ Progressive primary tuberculosis

Lung → caseous necrosis disseminated → Same lung / other lung
Airway bronchi

⇒ Progressive miliary tuberculosis

Erosion in a blood vessel → spread to other organs

- Liver
- Spleen
- Brain
- Kidney
- Bone marrow

⇒ Progressive secondary tuberculosis - more common in children

Lowered resistance / Increased hypersensitivity → Reactivation of dormant bacilli

10. Haemochromatosis

- Iron storage disorder (Excessive accumulation of iron in parenchymal cells)
- Tissue damage and functional insufficiency of organs
  - Liver
  - Pancreas
  - Heart
  - Pituitary gland
- Triad of features
  - Micronodular pigment cirrhosis
  - Diabetes mellitus + Skin pigmentation → Bronze-diabetes
- Males >> females
  - Physiological loss of iron delays symptoms
- 2 forms
  - Primary / Genetic / Idiopathic haemochromatosis
    - Autosomal recessive disorder
    - Overexpression of HFE gene (6p chromosome)
    - Mutation in HFE gene → complexes with transferrin receptors on intestinal epithelial cells
  - Secondary / Acquired haemochromatosis:

- Excessive absorption of dietary iron
- Cross iron overload
- Arising secondary to other diseases
  - Thallassemia
  - Sideroblast anaemia
  - Alcoholic cirrhosis
  - Multiple transfusion

- Etiopathogenesis
  - Normally
    - Daily iron intestinal mucosal absorption of iron
      - male → 1 mg
      - female → 1.5 mg
    - Body iron content → 3-4 gm
    - Serum iron concentration → 125 µg/dl
    - Serum transferrin saturation ≅ 30%.
  - iron absorption goes up to 4 mg/day
  - Primary/Idiopathic/Genetic haemochromatosis
    - Genetic basis
    - Defect at
      - Intestinal mucosal level
      - Post absorption excretion level
    - Iron deposited in cytoplasm of parenchymal cells of
      - Liver
      - Spleen
      - Bones
      - Pancreas
      - Endocrine glands.
    - Tissue injury results from
      - Iron-laden lysosomes of parenchymal cells.
      - Lipid peroxidation of cell organelles by excess iron.
  - Secondary/Acquired haemochromatosis
    - Accumulation of iron due to
      - Ineffective erythropoiesis
      - Defective haemoglobin synthesis
      - Alcohol consumption (Iron absorption ↑↑)
      - Multiple blood transfusions
      - Bantu siderosis
        - Bantu tribe of south africa → Home-brews prepared in iron vessels
    - Increased iron storage in
      - Liver
      - Reticuloendothelial system.
    - Generally magnitude of iron is insufficient to cause tissue damage.
  - Clinical features
    - Major clinical manifestations
      - Skin pigmentation
      - Diabetes mellitus
      - Cardiac and hepatic dysfunction
      - Arthropathy
      - Hypogonadism
    - Bronze pigmentation - 90% of cases
    - Demonstration is possible by measurement of
      - Serum iron
      - Percent saturation of transferrin
      - Serum ferritin concentration
      - Estimation of chelating iron stores
      - Liver biopsy.

- Hepatocarcinoma is a late complication

11. **Portal hypertension**

- Increase in portal venous pressure due to obstruction to portal blood flow
- Classification
  1) Intrahepatic
     - Cirrhosis of liver
     - Metastatic tumours
     - Hepatic veno-occlusive disease
     - Budd-Chiari syndrome
     - Diffuse granulomatous disease
     - Extensive fatty change.
  2) Posthepatic
     - Budd-Chiari syndrome
     - Hepatic veno-occlusive disease
     - Congestive cardiac failure
     - Constrictive pericarditis
  3) Prehepatic
     - Absence of portal vein
     - Thrombosis in portal vein
     - Neoplastic obstruction of portal vein
     - Myelofibrosis
- Major sequelae of portal hypertension
  1) Ascites
     - Accumulation of excessive volume of fluid within peritoneal cavity.
     - Factors
       - Systemic factors
         - Decreased plasma colloid osmotic pressure
         - Hyperaldosteronism
         - Impaired renal excretion
       - Local factors
         - Increased portal pressure
         - Increased hepatic lymph formation.
  2) Varices
     - Collateral channels on porto-systemic shunts
     - Principle sites
       - Oesophageal varices
       - Haemorrhoids
       - Caput medusae.
       - Retroperitoneal anastomoses
         - Veins of Retzius
         - Veins of Sappey
  3) Splenomegaly
  4) Hepatic encephalopathy

12. **Osteogenic Sarcoma/ Osteosarcoma**

- Most common primary malignant tumour of bone
- Formation of osteoid/bone by sarcoma cells.
- 2 categories.

(1) Central (medullary) osteosarcoma
- Arises centrally in the metaphysis
- ↓
- Extends longitudinally
- ↓
- Expands laterally
- ↓
- Lifts the periosteum breaking through cortex

Grow in surrounding tissues
- Sunburst pattern
- Presence of Codmans triangle.
- Pain, tenderness and swelling
- Metastasize rapidly by haematogenous route
- Histological variants
  - Telangiectatic osteosarcoma
  - Small cell osteosarcoma
  - Fibrohistiolytic osteosarcoma
  - Anaplastic osteosarcoma
  - Well differentiated osteosarcoma
- Types -

Primary medullary osteosarcoma
- more common
- Etiology
  - Genetic basis - mutation at Retinoblastoma locus (13th chromosome)
  - Period of active bone growth
  - Environmental influence

Secondary medullary osteosarcoma
- more aggressive behaviour than Primary
- Develops following pre-existing bone diseases
  - Paget's disease
  - Fibrous dysplasia
  - Multiple osteochondromas
  - Chronic osteomyelitis
  - Infarcts
  - Fracture of bone

2) Surface osteosarcoma
- 5% of total osteosarcoma cases
- On the surface of bone
- Grow slowly / Poor prognosis
- 2 types

i) Parosteal / Juxta-cortical osteosarcoma
- Arise from metaphysis on external surface of bone
- Lower end of femur, upper end of humerus

ii) Periosteal osteosarcoma
- Arises b/w cortex and underlying periosteum
- Diaphysis of the tibia and femur.

13. Osteoclastoma / Giant Cell Tumor
- Multinucleate osteoclast type Giant cell
- Aggressive bone tumor - Benign / Low grade malignant
- 20-40 yrs - age
- Molecular analysis - mononuclear neoplastic cell
- Express RANK ligand - Stimulate the development of surrounding non-neoplastic osteoclast type cells
- Clinical course
  - Arises in epiphysis and involves metaphysis of long bone
  - Distal femur and proximal tibia
  - Pain
  - Solitary tumors
  - Purely lytic and eccentric

- Overlying cortex is destroyed
- Bulging soft tissue mass with a thin shell of reactive bone
- Map of GCTs occurs after simple curettage
- ~2% spread to the lungs

14. **One-Stage Prothrombin Time (PT)**

- Measures extrinsic system factors VII and other factors
- Test sample

Tissue thromboplastin + Calcium ↓ Coagulation

↑ Time ⇒ Prothrombin Time

Normal = 10-14 seconds

- Causes of prolonged PT
  - Administration of oral anticoagulants
  - Liver disease
  - Vit-K deficiency
  - Disseminated intravascular coagulation

15. **Grave's disease**

- Basedow's disease / Exophthalmic goitre / Diffuse toxic goitre
- Triad of features
  - Thyrotoxicosis
  - Opthalmopathy
  - Dermopathy
- 30-40 yrs
- Woman - 5 times

Etiopathogenesis

- Immunological similarities with Hashimoto's thyroiditis
  - Genetic association
    - HLA-DR_3
    - CTLA-4
    - PTPN-22
  - Autoimmune disease association
    - Organ specific immune diseases
    - Both may be pnt in same family
    - Both may be pnt in same patient
  - Other factors
    - female > Male
    - Smoking
    - Emotional stress
  - Autoantibodies
    - Against TSH-receptor autoantigens
      - TSI (Thyroid Stimulating Immunoglobulin) - Binds with TSH receptor
      - TGI (Thyroid Growth-stimulating Immunoglobulin) - Proliferation of follicular epithelium
      - TBII (Thyroid Binding Inhibitor Immunoglobulin) - Inhibitors to binding of TSH to TSH receptor
- Intrathyroidal Helper T-cells stimulates B-cell to secrete antibodies.
- Infiltrative opthalmopathy
  - Autoimmune origin
  - Lymphocytic infiltration around ocular muscles
  - Circulating antibodies against muscle antigen

- Iodine administration
  - Accumulation of colloid in follicular cells
  - Decrease in vascularity

Clinical features
- Thyrotoxicosis
- Opthalmopathy
- Dermopathy – Pretibial myxoedema
- Ocular abnormalities
  - Lid lag
  - Upper lid retraction
  - Proptosis
  - Stare

16. Obesity

- Dietary imbalance and overnutrition
- An excess of adipose tissue that impacts health risk [A body weight of 20% excess of ideal body weight
- BMI > 30

Etiology
- Overeating
- Inactivity and sedentary life style
- Genetic predisposition
- Diet derived from carbohydrate and lipid, others than protein rich diet.
- Secondary obesity – underlying diseases

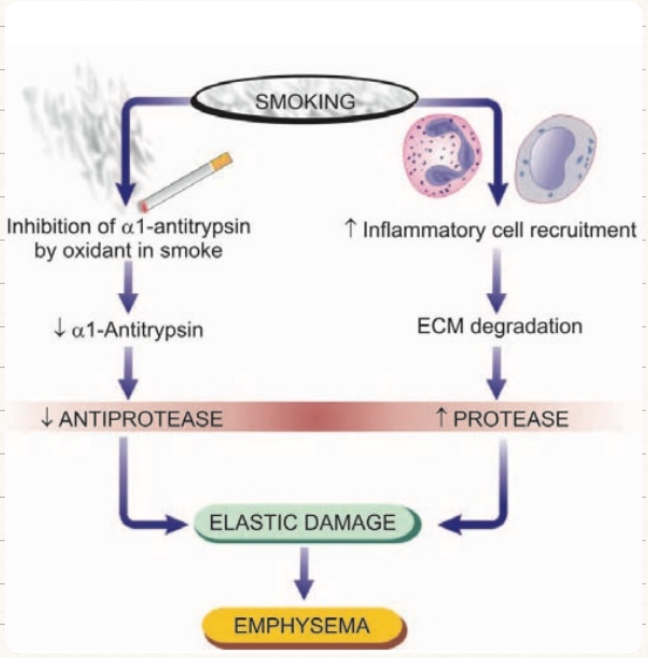
Pathogenesis
- Adipocytes
  - Lipid /fat storing cells
  - Int in vascular and stromal compartment
  - Release endocrine regulating molecule
    - Leptins – Energy regulating hormone
    - Cytokines – IL-6, TNF-α
    - Insulin sensitivity regulatory agents
      - RBP-4
      - Adiponectin
      - Resistin
    - Plasminogen activator inhibitors
    - Angiotensinogen
- Adipocytes → Number ↑, Size ↑ → Adipose tissue ↑
- Familial
- Genes – Ob — Leptin; db — Leptin receptor

Sequelae
- Hyperinsulinaemia
- Type-2 DM
- Hypertension
- Hyperlipoproteinaemia
- Hyperuricaemia (Pickwickian syndrome)
- Atherosclerosis
- NAFLD (Non Alcoholic fatty liver disease)

- Osteoarthritis
- Cholelithiasis
- Cancer

17. **Pathogenesis of emphysema**

- Commonest forms of COPD = Chronic bronchitis + Pulmonary emphysema
  - ↳ Doesn't always lead to each others ↲
  - Smoking → Both condition associates
  - Air pollutants
- Destruction of the alveolar walls
  - Not linked to bronchial change
  - Related to deficiency of serum α_1-antitrypsin
  - Protease-Antiprotease hypothesis



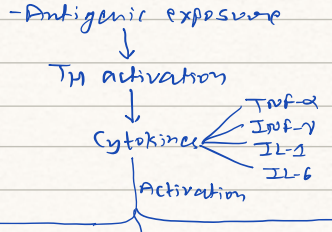
- Protease-Antiprotease Hypothesis
  - α_1-AT / α_1 protease inhibitor
    - Glycoprotein
    - Synthesis in liver
    - 15q
    - Inhibits proteases (Mainly elastases)
      - Derived from neutrophils
      - Digest the lung parenchyma
    - Alleles
      - Pi MM
      - Pi ZZ
      - Pi null null
      - Pi SS
  - Most common abnormal phenotype is homozygous PiZZ
    - Glu → Lys
    - Polymerisation of α_1-AT
    - Can't be released from liver
    - Hepatic cirrhosis
    - α_1-AT. deficiency
      - Emphysema
        - Non smokers
        - Smokers – 15 years earlier than non-smokers
- Liver
  - Obstructive jaundice
  - Cirrhosis
  - Hepatoma
- Mechanism of alveolar wall destruction
  - Protease/Elastase activity ↑
  - Antiprotease/Antielastase activity ↓
- Smoking promotes emphysema
  - Oxidants in cigarette inhibits α_1-A.T.
  - Smokers have upto 10 times more phagocytes and neutrophils in their lungs than non-smokers

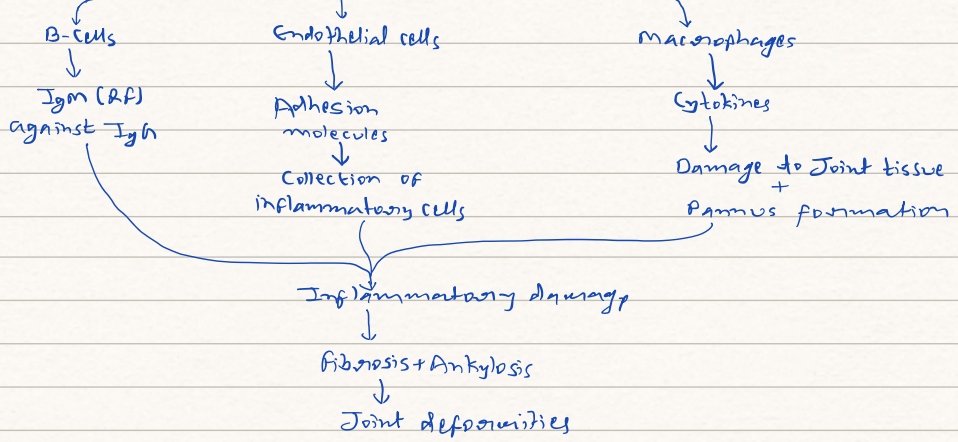
18. **Rheumatoid arthritis**

- Inflammatory arthritis of peripheral joints with symmetrical distribution.
- Systemic manifestations
  - Haematologic abnormalities
  - Pulmonary "
  - Neurological "

- Cardiovascular "

- 20-40 yrs
- Female → 3-5 times
- HLA-DR1, HLA-DR4
- Beginning symptoms
  - fatigue
  - weakness
  - Joint stiffness
  - Vague arthralgia
  - myalgia
  - Pain
  - Swelling of joint
- Commonly involved joints
  - Hand
  - Wrist
  - Feet
- 20%. patients develop rheumatoid nodules
- 80%. cases are seropositive for rheumatoid factor (RF)
- Radiological abnormalities
  - Narrowing of joints
  - Ulnar deviation of fingers
  - Radial deviation of wrist
- Laboratory findings
  - Normocytic-normochromic anaemia
  - Elevated ESR
  - Mild Leucocytosis
  - Hypergammaglobulinaemia
- Etiopathogenesis
  - Immunologic derangements.
    - Circulating RF of IgM/IgG class against Fc-portion of autologous IgG
    - Presence of IgG-RF complex
    - Presence of other autoantibodies
      - Anti Nuclear factor (ANF)
      - Against collagen type-II
      - Against cytoskeleton
    - Antigenicity of proteoglycans of human articular cartilage.
    - Presence of IgG and IgM in synovial fluid
    - Association with amyloidosis
    - Activation of CMI
  - Triggers events
    - Existence of an infectious agent
      - Mycoplasma
      - Epstein-Barr virus (EBV)
      - CMV
      - Rubella
    - Role of HLA-DR1 and HLA-DR4
    - Events



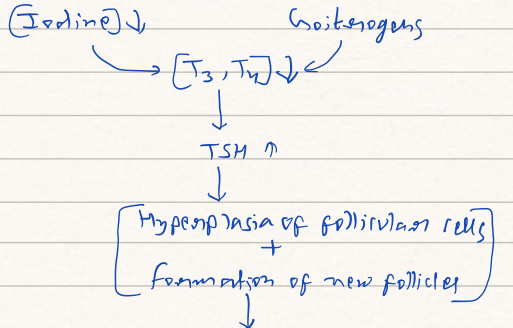


- Variant forms
  - Juvenile RA — < 16 yrs; RF is rarely +ve
  - Felty's syndrome — Splenomegaly; Hypersplenism
  - Ankylosing spondylitis — HLA-B27 association; Spine and sacroiliac joint

19. Colloid / Simple non toxic / Diffuse goitre
- Diffuse enlargement of thyroid gland
- Hypothyroidism ⟶ Euthyroidism (most of cases)
- [TSH] ↑
- Common in females
- Appears in — Puberty; Adolescence
- May regress or progress to nodular goitre.

Etiology
- Occurs in 2 forms
  - Endemic goitre
    - >10% population in a geographical area
    - Due to — Low iodine intake; Goitrogens — Drugs used in treatment of hyperthyroidism; Cabbage, Cauliflower, turnip
  - Sporadic / Non-endemic goitre
    - Less common
    - Causal influence
      - Suboptimal iodine intake
      - Genetic factors
      - Dietary goitrogens
      - Hereditary dyshormonogenesis – Defective synthesis of thyroid hormones
      - Errors in iodine metabolism

Pathogenesis



[Cyclic hyperplasia + Involution]
↓
Simple goitre
↓
[Repeated hyperplasia + Involution] → Growth + fibrosis
↓
Nodular goitre

20. **Acute pyelonephritis**

- Acute suppurative inflammation of kidney caused by pyogenic bacteria

Etiopathogenesis

- Lower UTI is most common cause
- Common pathogenic organisms
  - E. coli (90%) > Enterobacter > Klebsiella > Pseudomonas > Proteus
- 2 routes
  - Ascending infection
    - Most common
    - Faecal contamination of urethral orifice
    - Common in females of reproductive age
      - Attributions
        - Shorter urethra
        - Hormonal influence – Bacterial adherence to the mucosa
        - Absence of prostatic secretions
        - Urethral trauma during sex
          - Honeymoon pyelitis
    - Susceptibility increases with
      - D.M.
      - Pregnancy
      - U.T. Obstruction
      - Instrumentation
    - Bacteriuria
    - Urethritis
    - Cystitis
    - Bacteria → Renal pelvis → Renal cortex (vesicoureteral reflex)
  - Haematogenous infection
    - Less common
    - Blood-borne spread of infection
    - Occurs more often in patients with
      - Obstructive lesion in U.T.
      - Immunosuppressed patients

Clinical features

- Chills
- Fever
- Loin pain
- Lumbar tenderness
- Dysuria
- >100000 bacteria/ml of urine

- Pyuria cells and pyuria cast in urinary sediment

Complications
- Papillary necrosis
- Pyonephrosis
- Perinephric abscess

21. Nodular Hyperplasia
- BPH (Benign Nodular Hyperplasia) / BEP (Benign Enlargement of Prostate)
- Frequent above the age of 50
- >80 yrs - Incidence increases upto 75-80%
- Surgical treatment - 5-10% of total cases

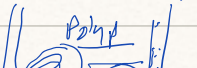
Etiopathology
- Causes
  - Endocrinological ✱
  - Racial
  - Inflammation
  - Arteriosclerosis
- As age advances
  - Androgens ↓ → Periurethral outer prostate is responsive to androgens
    - ↳ Involvement in Carcinoma
  - Oestrogen ↑ → Involvement in BEP
    - → Periurethral inner prostate is responsive to oestrogen
- Synergistic stimulation of prostate
  - ↳ Oestrogen sensitize the prostate to the growth effect of androgen (Testosterone → Dihydro testosterone)

Clinical features
- Urethral obstruction
- Bladder
  - Hypertrophy
  - Cystitis
- Ureter - Hydroureter
- Kidney - Hydronephrosis
- Nocturia
- Pain
- Haematuria

22. Coeliac sprue
- Non tropical sprue / Gluten sensitive enteropathy / Idiopathic steatorrhoea
- Significant loss of villi in the small intestine
- Surface area for absorption ↓
- 2 forms
  - Childhood form - Coeliac disease
  - Adult form - Idiopathic steatorrhoea
- Genetic abnormality in Gluten and Gliadin (Gluten derivative) sensitivity
- Antibodies
  - IgA-Antigliadin
  - IgA-Antiendomysial
- Elimination of Gluten from diet → Symptoms relieved.
- Role of heredity
  - Familial
  - HLA association

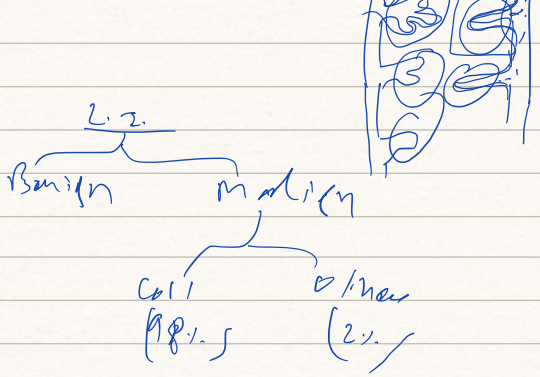
Pathogenesis
- Not clear
- Hypersensitivity reaction → Gluten stimulated antibodies
- Inherited enzyme deficiency in mucosal cells → Toxic effects of Gluten
- Long term coeliac sprue → ↑ incidence of intestinal carcinoma

L.I / Colon



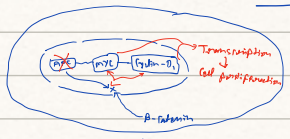
23. **Colorectal carcinoma**

- 98% of all malignant large intestinal tumours
- Average age → 60 yrs
- Common in males than females (2:1)



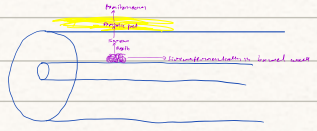
Etiology
- Geographic variations
- Dietary factors
- Adenoma-carcinoma sequence
- HNPCC (Hereditary Non-polyposis Colonic Carcinoma) / Lynch syndrome
  - hLMH$_1$ – Chromosome 3
  - hLMH$_2$ – Chromosome 2
  - → mutation → DNA instability
- Other factors
  - Pre-existing diseases
    - IBD
    - Diverticular disease

Genetic Basis
- APC (Adenomatous polyposis coli) mutations / β-catenin mechanism



- Point mutation in K-RAS gene – follows loss of APC gene
- Deletion of DCC gene (Deleted in Colorectal Carcinoma)
- Loss of p53
- Microsatellite instability mechanism
  - Loss of DNA repair gene → microsatellite becomes unstable during replication
    - TGF-β gene – Inhibit cell proliferation
    - BAX gene – Cause apoptosis

Spread
- Direct spread



- Lymphatic spread
- Haematogenous spread
  - Liver
  - Lung
  - Brain
  - Bone
  - Ovary

Clinical features
- Occult bleeding (Melaena)
- change in bowel habits
- Loss of weight (Cachexia)
- Loss of appetite (Anorexia)
- Weakness, anaemia, Malaise

Staging and prognosis
- Prognosis depends upon
  - Bowel involvement
  - Presence of metastasis
  - Grade of the tumor
  - Location of the tumor

- Staging system
  - Dukes–ABC staging
  - Astler-Coller staging
  - TNM staging.

24. Psoriasis

- Chronic inflammatory dermatosis
- 2 % population
- 15–30 yrs
- Brownish–Red papules and plaques
  - ↳ Covered with fine silvery white scales
    - ↳ Removal → Bleeding points (Auspitz sign)
- Common sites
  - Scalp
  - Upper back
  - Sacral region
  - Extensor surface of
    - Elbow
    - Knee
- Pitting of nails
- Psoriatic arthritis (RF is -ve)
- Acanthosis
- Absence of stratum granulosum
- Parakeratosis
- Munro microabscesses

25. Paraneoplastic Syndrome (PNS)

- Group of conditions developing in a patient with advanced cancer
- 10–15 % of the patients with advanced cancer
- Earliest manifestation of latent cancer
- Clinical syndromes included in PNS are
  - Endocrine syndrome
    - Hypercalcaemia – Parathormone like substance
    - Cushing's syndrome – ACTH or ACTH like substance
    - Polycythemia – Erythropoietin
    - Hypoglycemia – Insulin like substance
  - Neuromyopathic syndrome
    - Peripheral neuropathies
    - Cortical cerebellar degeneration
    - Myasthenia gravis
    - Polymyositis
  - Effects on osseus, joints and soft tissues
    - Hypertrophic osteoarthropathy
    - Clubbing of fingers
  - Haematologic and vascular syndrome
    - Venous thrombosis
    - Endocarditis
    - Disseminated intravascular coagulation
    - Leukemoid reaction
    - Normocytic-normochromic anaemia.
  - Gastrointestinal syndrome
    - Malabsorption
  - Renal syndrome

- Renal vein thrombosis
- Amyloidosis

- Cutaneous syndrome
- Amyloidosis

26. Alcoholic liver disease and Cirrhosis

- 3 Sequential stages
  - Alcoholic steatosis
  - Alcoholic Hepatitis
  - Alcoholic cirrhosis
- Ethanol metabolism
  - First step
    - Alcohol —ADH (-Cytosol, -Peroxysome, -SER)→ Acet aldehyde
  - Second step
    - Acet aldehyde —ALDH (-Mitochondria)→ Acetate
- Risk factors
  - Drinking patterns
    - Fatty liver → >90% of chronic alcoholics
    - Hepatitis → 10-20% cases
    - Cirrhosis → >10 yrs (60-80 gm ethanol/day)
  - Genders
    - females → more susceptible, 20-40 gm/day
  - Malnutrition
  - Infections
  - Genetic factors (ADH, ALDH, HLA)
  - Hepatitis-C infection
    - Development of disease with less alcohol intake (20-50 gm/day)

Pathogenesis

- Direct hepatotoxicity by ethanol
- Hepatotoxicity by ethanol metabolites
  - Production of protein-aldehyde adducts
  - Formation of malon-de-aldehyde acet-aldehyde (MAA)
- Oxidative stress
  - Generation of free radicals
- Immunological mechanism
  - CMI is impaired
- Inflammation
  - Intestinal cell injury — TNF-α, TNF-β, IL-1, IL-6
- Fibrogenesis
- Increased redox ratio
  - Lactic acidosis
- Retention of liver cell water and protein
  - Hepatomegaly
- Hypoxia
  - Hepatocellular necrosis
- Increased liver fat

Laboratory diagnosis
- Transaminases ↑
- Serum γ-GT ↑
- Serum alkaline phosphatase ↑
- Hyperbilirubinaemia
- PT time ↑
- Anaemia
- Leucocytosis

27. Hashimoto's thyroiditis
- Autoimmune thyroiditis / Chronic lymphocytic thyroiditis / Diffuse lymphocytic thyroiditis / Struma lymphomatosa / Goitrous autoimmune thyroiditis
- 3 principle features
  - Enlargement of thyroid
  - Lymphocytic infiltration of thyroid
  - Autoantibodies
- 30-50 yrs
- 10 times in female
- Rare in children
- Most common cause of goitrous hypothyroidism in regions where iodine supplies are adequate

Etiopathogenesis
- Other autoimmune disease association
  - Grave's disease
  - SLE
  - Sjogren's syndrome
  - Rheumatoid arthritis
  - Pernicious anaemia
  - DM type-1
- Immune destruction of thyroid cells
  - $CD_4^+ (T_H)$ cells → Induce infiltration of → $CD_8^+ (T_C)$ cells
  - $CD_4^+ (T_H)$ cells → Activates → Plasma B-cells → Autoantibody formation
- Detection of autoantibodies
  - Thyroid microsomal antibodies
  - Thyroglobulin autoantibodies
  - TSH receptor autoantibodies
  - Autoantibodies against T_3–T_4
- Inhibitory TSH receptor antibodies
  - → Hypothyroidism
- Genetic basis
  - HLA-DR_3
  - HLA-DR_5

Clinical features
- Painless, firm and goitrous enlargement
- Hypothyroidism (Usually)
- Hyperthyroidism – few cases (Hashitoxicosis)
- Increased frequency of malignant lymphoma
- No risk of thyroid carcinoma.

28. Oedema

- Abnormal and excessive accumulation of free fluid in the interstitial tissue space and serous cavities.
- Intracellular oedema (Hydropic degeneration)
- Free fluid in body cavities
  - Hydrothorax
  - Hydropericardium
  - Ascites
- Subcutaneous tissue
  - Pitting oedema
  - Non pitting oedema
- 2 main types
  - Localised
  - Generalised
- Depending upon fluid composition
  - Transudate – Without change in capillary permeability
  - Exudate – With change in capillary permeability

Pathogenesis

- Decreased plasma oncotic pressure
  - Hypoproteinaemia - <5 gm/dl [Albumin < 2.5 gm/dl)
  - Usually produces generalised oedema
  - Oedema of liver disease
  - Ascites
- Increased capillary hydrostatic pressure
  - Oedema of cardiac disease
  - Ascites of liver disease
  - Passive congestion - Mechanical obstruction of veins
  - Postural oedema
- Lymphatic obstruction
  - Causes Lymphoedema (Localised)
  - Radial mastectomy (Removal of axillary lymph nodes) – Oedema of effected arm
  - Pressure from outside on the main abdominal and thoracic duct
    - Chylo-thorax
    - Chylous-ascites
  - Lymphoedema in filariasis
  - Occlusion by malignant cells
  - Milroys disease / Hereditary lymphoedema – Abnormal development of lymph vessels
- Tissue factors
  - Normally insignificant to counteract the other forces.
  - Elevation of oncotic pressure of interstitial fluid
  - Lowered tissue tension
    - → Loose subcutaneous tissue – Eye lids, External genitalia
- Increased capillary permeability
  - Generalised oedema
    - Systemic infections
    - Anoxia
    - Poisoning
    - Anaphylactic reaction
  - Localised oedema
    - Inflammatory oedema
    - Angioneurotic oedema – Neurogenic or allergic in origin

- Sodium and water retention
  - Mechanisms
    - Intrinsic renal mechanism – Baroreceptors → SNS outflow → GFR ↓
    - Extrarenal mechanism – RAAS
    - ADH mechanism – Water retention
  - Oedema of cardiac disease
  - Ascites of liver
  - Oedema of renal disease

29. Fate of thrombus

Resolution
- Activation of fibrinolytic system
- Release of plasmin
- Dissolve the thrombus
- Lysis
  - Complete – Small thrombus
  - Incomplete – Large thrombus
- Thrombolytic substance
  - Streptokinase
  - Urokinase
  - Accenvate the fibrinolytic activity

Organisation
- If thrombus is not removed
- fibrin and cell debris are phagocytosed by
  - Neutrophils
  - Macrophages
- Endothelial cells, Leucocytes → Proteolytic enzymes – Digest the coagulum
- Fibroblast invades, Capillary grows → fibrovascular granulation tissue – Covered by endothelial cells
- Becomes part of vascular wall
- Recanalisation
- May undergo
  - Hyalinisation
  - Calcification

Propagation
- Enlarge in size by more deposition
- Obstruction of vessels

Thromboembolism
- Get dettached from the vessel wall
- Produce ill effects at the site of lodgement.

30. Liquefactive necrosis

- Focal bacterial infections, Fungal infections → Accumulation of inflammatory cells, Strong hydrolytic enzymes of leucocytes → Digest the tissue → Liquefactive necrosis
- Hypoxic/Ischaemic injury/death of CNS cells – Liquefactive necrosis
- Formation of cyst wall
- Cyst wall is formed by
  - Gliosis – In case of the brain
  - Inflammatory cells, Proliferating capillaries, Proliferating fibroblasts – In case of the abscess cavity
- Example
  - Infarct brain
  - Abscess cavity

3. Cellular adaptations

- Reversible cellular changes in the
  - Number
  - Size
  - Metabolism
  - Phenotype
  - Functions

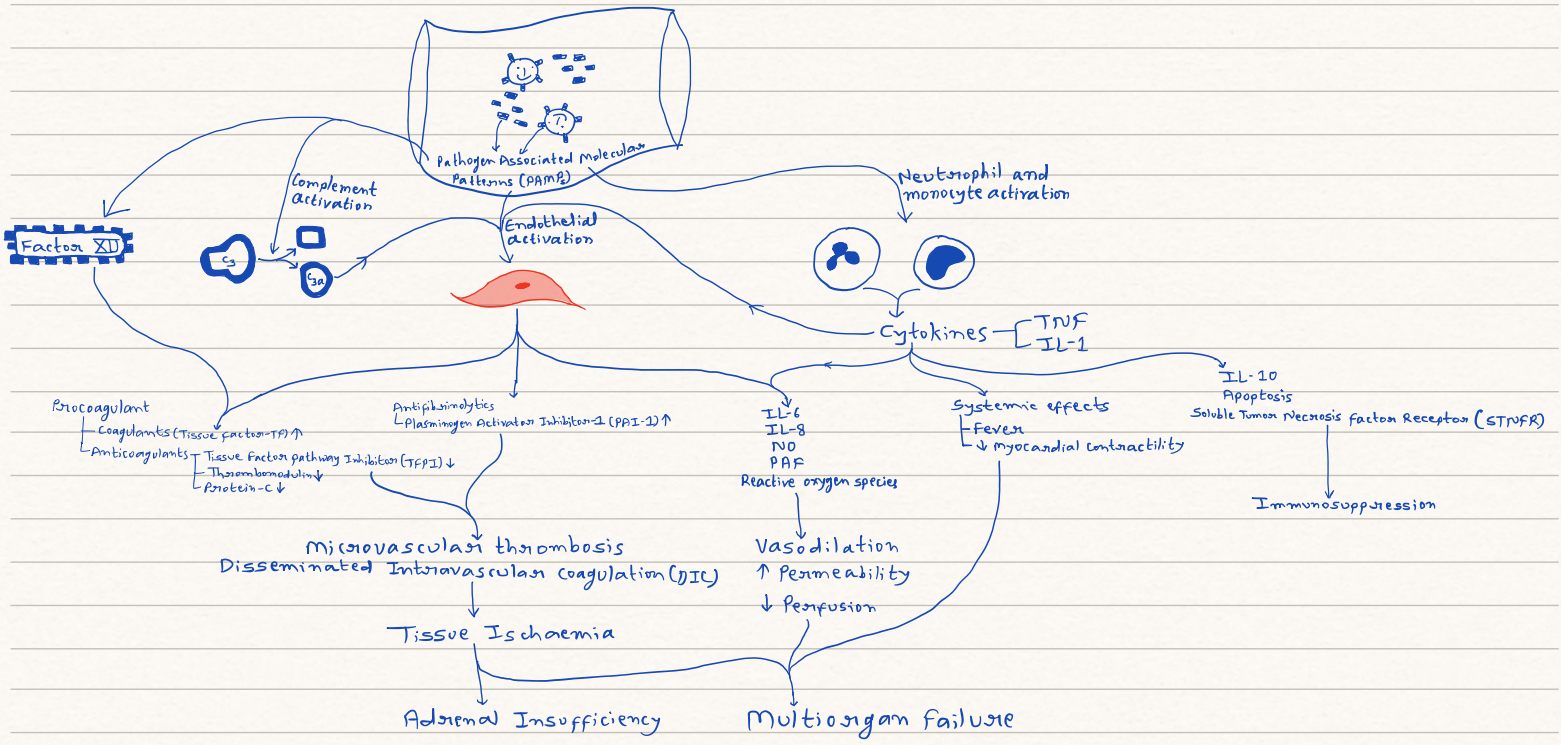
- Hypertrophy
  - Increased cell and organ size
  - Due to increased workload
  - Induced by growth factors
  - Occurs in tissues incapable of cell division
  - Physiologic adaptations
    - Physiologic enlargement of uterus during pregnancy
    - Hypertrophy of cardiac and skeletal muscles
  - Pathologic adaptations
    - Cardiac enlargement

- Hyperplasia
  - Increased cell number
  - Induced by hormones and growth factors
  - Occurs in tissues
    - Cells are able to divide
    - Contain abundant tissue stem cells
  - Physiologic adaptations
    - Hormonal hyperplasia – Breast (glandular epithelium)
    - Compensatory hyperplasia – Tissue regrows
  - Pathologic adaptations
    - Excessive hormonal and growth factor stimulation

- Atrophy
  - Decreased cell and organ size
  - Due to
    - Decreased nutrient supply
    - Disuse
  - Associated with
    - Decreased synthesis of cellular building blocks
    - Increased breakdown of cellular organelles
  - Ubiquitin proteasome pathway → Protein degradation
  - Autophagy

- Metaplasia
  - Change of phenotype in differeciated cells
  - In response to chronic irritation
  - Induced by alteration in tissue differentiation pathway of stem cells.
  - May result in
    - Reduced function
    - Increased tendency of malignant transformation
  - Tracheal/Bronchial ciliated columnar epithelial cells — Smoking → Strat. sq. epithelial cells
  - Lower oesophageal strat. sq. epithelium — Chronic gastric reflux → Gastric/Intestinal type columnar epithelium.

32. Pathogenesis of Septic shock



33. Rapidly Progressive Glomerulonephritis (RPGN)

- Acute reduction in renal function ⟶ Acute renal failure
- Formation of crescents
  - Outside glomerular capillaries
  - Formed by
    - Bowman capsule's parietal epithelial cells
    - Visceral epithelial cells
    - Mononuclear cells (Invading)
  - Stimulus – Presence of fibrin in the capsular space
- In adults (Male > female)

Etiopathogenesis

- Type-I RPGN / Anti-GBM disease
  - Serological marker – Serum C_3 level
  - Association
    - Goodpasture's syndrome
    - SLE
    - Vasculitis
    - Wegner's granulomatosis
    - Henoch-Scholein purpura
  - Goodpasture's syndrome
    - Acute renal failure
    - Pulmonary haemorrhage
    - Anti-GBM antibodies
      - Damage GBM
      - Cross-react with alveolar basement membrane
    - Characteristick deposits along GBM
      - Anti-GBM antibodies (IgG)
      - Complement proteins
    - Collagen type-IV ⟶ Goodpasture's antigen
- Type-II RPGN / Immune complex disease
  - Post-streptococcal GN in origin
  - Non-streptococcal in origin
  - Granular deposits along glomerular capillary wall
    - IgG
    - C_3

- Circulating immune complexes
- Complement level ↓

- Type-III RPGN/ Pauci immune GN
  - Association
    - Wegner's granulomatosis
    - Polyarteritis nodosa
  - Defect in humoral immunity
  - ANCA positive
  - Little or no glomerular immune deposits

Clinical features
- Acute renal failure
- Intrapulmonary haemorrhage
- Recurrent haemoptysis

34. Systemic lupus erythmatosus

- Systemic autoimmune / collagen disease
- 2 forms — Systemic / Disseminated form
  - Discoid form

Etiology
- Autoantibodies against nuclear and cytoplasmic components
- Autoantibodies
  - Anti-nuclear Antibodies (ANA)
  - Antibodies to double stranded DNA (Anti-dsDNA) — Specific to SLE
  - Anti-Smith Antibody (Anti-sm)
  - Others — Non-specific
    - Anti-ribonucleoproteins (Anti-RNP)
    - Anti-histone Antibody
    - Anti-phospholipid Antibody
    - Anti-ribosomal-P Antibody
- Source of Antibodies
  - Polyclonal activation of B-cells
    - Due to
      - Immunologic factors — Defects and abnormal functions of B and T cells
      - Genetic factors — HLA-II
      - Other factors
        - Drugs
        - Hormones
        - Infections

Pathogenesis
- Autoantibodies ⟶ Immunologic tissue injury
- Type-II Hypersensitivity
  - Autoantibodies against
    - RBC
    - Platlets
    - Leucocytes
  - Haematologic derangements
- Type-III Hypersensitivity
  - Ag-Ab complex formation
  - Deposits in
    - Renal glomeruli
    - Wall of small blood vessels

LE-cell phenomenon
- ANA can not penetrate the intact cells
- Damaged tissue cells ⟶ Exposure of nucleus to antibodies ⟶ Formation of homogenous mass of nuclear chromatin material (LE-body / Haematoxylin body) ⟶ Phagocytosed
  - Neutrophil (LE-cell)
  - Monocyte (Tart cell)
- LE-Cell is positive in 70% cases

Clinical features
- Female > male
- Manifestations
  - Nephritis
  - Skin lesions
  - Arthritis
  - Haematologic abnormalities
  - Neurologic abnormalities
- For SLE diagnosis, atleast four diagnostic criteria need to be fulfilled
  - Malar rash
  - Discoid rash
  - Photosensitivity of rash
  - Oral ulcers
  - Non erosive arthritis
  - Serositis
  - Proteinuria
  - Seizures and psychosis
  - Anaemia
  - Autoantibodies

35. NK-cell
- Cells of innate immunity / Natural immunity
- Two type of receptors
  - Inhibitory - Recognises MHC-I molecules
  - Activating - Recognises
    - Cells with DNA damage
    - Infected cells
    - Tumor cells
- 10-15% of circulating lymphocytes
- B-cell and T-cell markers are absent
- CD_3 negative
- CD_4 negative
- CD_8 negative
- CD_2 positive
- CD_{16} positive
- CD_{56} positive
- Recognises antibody coated target cells - Antibody Dependent Cell-mediated Cytotoxicity (ADCC)

36. Tumour Immunity

Tumour antigens
- Expression of surface antigens
- Old classification
  - Tumor specific antigens (TSA) - Located on tumor cells
  - Tumor associated antigens (TAA) - Located on tumor cells and normal cells
- Antigens
  - Oncoprotein from mutated oncogenes
    - RAS
    - BCL/ABL
    - CDK-4
  - Protein products of tumor suppressor genes
    - P_{53}
    - B-catenin
  - Overexpressed normal cellular proteins
    - Tyrosinase in melanoma
    - HER2/neu in Breast cancer
  - Abnormally expressed cellular proteins

- MAGE gene — Generally functional in male germ line
- GAGE gene — Expressed in melanoma
- BAGE gene
- RAGE gene

- Tumor antigens from viral oncoproteins
  - Oncoprotein of HPV in cervical cancer
  - EBNA proteins of EBV in Burkitts lymphoma
- Tumor antigens from randomly mutated genes
  - Due to random mutation by radiation and carcinogens
- Cell specific differentiation antigens
  - CD markers of various subtypes of Lymphoma
  - Prostate specific antigen (PSA) in prostate cancer
- Oncofoetal antigens
  - Alpha fetoprotein (AFP) in liver cancer
  - Carcino-embryonic antigen (CEA) in colon cancer
- Abnormal cell surface molecules
  - Glycoproteins
  - Glycolipids
  - Mucin

Anti-tumour immune responses

- Cell mediated mechanisms
  - Cytotoxic T-cell (CD_8 / CTL)
  - NK cells
    - Activation by IL-2
    - Destroy tumor cells — Directly / ADCC
  - Macrophage - Activation by γ-IFN
- Humoral mechanisms
  - In-vivo → No Antitumor humoral antibodies
  - In-vitro → May kill tumor cells
- Immune regulatory mechanisms
  - Immunosuppression
  - Self regulation of T-cell and NK cell
  - During cancer progression immunogenic cells may disappear

37. Vascular events in acute inflammation

- Alteration in the microvasculature
  - Haemodynamic change
  - Change in the vascular permeability
- Haemodynamic changes
  - Transient vasoconstriction
    - Normally - 35 seconds
    - Severe injury - ~5 minutes
  - Persistent progressive vasodilation
    - Involve mainly arterioles
    - Begin within half hour
    - Redness and warmth
  - Elevation in local hydrostatic pressure
    - Transudation
    - Swelling
  - Slowing/Stasis
    - [RBC] ↑

- Viscousity ↑
- Leucocytic margination
- Lewis experiment
  - Red line - Capillaries and venules
  - Flare - Adjacent arterioles
  - Wheel - Oedema

- Altered vascular permeability
  - Transudation → Exudation (Inflammatory oedema)
  - Starling forces
  - Mechanism
    - Contraction of endothelial cells
      - Venules
      - Temporary gaps
      - Contraction due to: Histamine, Bradykinin
    - Retraction of endothelial cells
      - Structural reorganisation of cytoskeleton causes reversible retraction
      - Venules
      - TNF-α and IL-1
    - Direct injury to endothelial cells
      - Appearance of physical gaps
      - Venules, capillaries and arterioles
    - Endothelial injury mediated by leucocytes
      - Adherence activates leucocytes → Proteolytic enzymes, Toxic oxygen species
      - Venules
    - Leakiness in neovascularisation
      - Vascular endothelial growth factor (VEGF)
      - Newly formed capillaries are excessively leaky.

38. Role of free radicals / Reactive oxygen species / Oxidative stress in cell injury

- Lipid peroxidation of membrane
  - Double bonds of membrane PUFA are vulnerable to attack by free radicals
  - Production of peroxides by reaction
    - Unstable
    - Reactive
    - Participate in autocatalytic chain
- Cross linking and other change in protein
  - Promote sulphydril mediated cross linking
    - Enzyme degradation
    - Loss of enzymatic activity
  - Polypeptide fragmentation
- DNA damage
  - Single strand breaks by reacting with thymine
  - Cell death
  - Aging
  - Malignant transformation
- Cytoskeletal damage
  - Interact with cytoskeletal elements
  - Interfere in mitochondrial aerobic phosphorylation → ATP depletion
- Conditions with free radical injury
  - Chemical toxicity
  - Chemical carcinogenesis

- Hyperoxia - Toxicity due to oxygen therapy
- Cellular aging
- Inflammatory damage
- Killing of microbial agents
- Atherosclerosis
- Destruction of tumor cells

3. Pulmonary embolism / Thromboembolism

- Most common form of venous thromboembolism
- Occlusion of pulmonary arterial tree

Etiology

- Common in hospitalised and bed-ridden patients
- Thrombi originating from leg veins of lower legs
  - Popliteal
  - Femoral
  - Iliac
  - → 95% of cases
- Superficial veins of legs

Pathogenesis

- Dettachment of thrombi → Thrombo-embolus → Right side of heart → Lungs
- If thrombus is large
  - Right ventricle and its outflow
  - Bifurcation of pulmonary artery - Saddle embolus
- If multiple emboli
  - Lower lobes of the lungs
- Paradoxical embolism
  - Right heart to left heart
  - Due to septal defect

Consequences

- Depends mainly on the size of occluded vessels
- Women are at higher risk
  - Reproductive age
  - Pregnancy
  - Contraceptive pills
- Sudden death
- Acute cor pulmonale
  - Right heart failure
  - Reflex vasoconstriction of pulmonary vessels
- Pulmonary infarction
  - Haemoptysis
  - Dyspnoea
- Pulmonary Haemorrhage
  - Haemoptysis
  - Dyspnoea
  - Chest pain
- Resolution
- Pulmonary hypertension, Chronic cor pulmonale and Pulmonary atherosclerosis

4. Factors effecting wound healing

- Local factors
  - Infections - Delays the process of healing

- Poor blood supply - Delays
- Foreign bodies - Delays
- Movements - Delays
- Ionising radiation - Delays
- Ultraviolet light - Facilitates
- Type
- Size
- Location

- Systemic factors
  - Age
  - Nutrition
    - Protein
    - Vitamine-C
    - Zinc
  - Systemic infections - Delay
  - Administration of glucocorticoids → Anti-inflammatory → Fastens
  - Uncontrolled diabetics - Delay
  - Haematologic abnormalities - Delay
    - Defects in neutrophil functions
    - Neutropenia
    - Bleeding disorders

41. **Types of infarction**

- Classified depending on different features
- According to their colour
  - Pale/Anaemic
    - Due to arterial occlusion
    - Compact organs
      - Heart
      - kidney
      - Spleen
  - Red/Haemorrhagic
    - Caused by
      - Pulmonary artery obstruction - Lungs
      - Arterial occlusion
      - Venous occlusion
      - (Arterial occlusion, Venous occlusion) - Intestine
    - Soft tissues
- According to their age
  - Recent/Fresh
  - Old/Healed
- According to presence or absence of infection
  - Bland - Free of bacterial contamination
  - Septic - Infected

42. **Chemical carcinogenesis**

- 3 sequential stages
- Initiation
  - Induced by initiator chemical carcinogens
  - Initiator carcinogens
    - Direct acting - Do not require metabolic activation
    - Indirect acting - Require metabolic activation

- Steps
  - metabolic activation
    - In liver by mono-oxidase of cytochrome P450 system
    - Carcinogen may be detoxified / deactivated
    - Determination of carcinogenic potential
      - Balance between activation and inactivation
      - Genes that code for cytochrome P450 dependent enzymes
      - Age, sex and nutritional status
  - Reactive electrophiles
    - Direct acting carcinogens - Already electrophilic (+ve)
    - Indirect acting carcinogens - Electrophilic after metabolic activation
    - Binds electron rich portion of
      - DNA
      - RNA
      - Other proteins
  - Target molecules
    - Primary target - DNA
    - Xeroderma pigmentosum
      - Hereditary defect in DNA repair mechanism
      - Prone to develop skin cancers
    - most effected gene
      - Growth promotor gene - RAS
      - Tumor suppressor gene - P53
  - Initiated cell
    - Unrepaired damage of DNA becomes permanent if there is atleast one cycle of proliferation
    - Vulnerable to the promoters of carcinogenesis

- Promotion of carcinogenesis
  - Promotors of carcinogenesis are different from initiators
    - Enhance the effect of direct acting carcinogens or procarcinogens
- Progression of carcinogenesis
  - Phenotypic features of malignancy
    - Morphology
    - Biochemical composition
    - Molecular features
  - New progeny cells inherit genetic and biochemical characteristics

Carcinogenic chemicals in humans

- Initiator carcinogens
  - Direct acting
    - Alkylating agents
      - Anticancer drugs
      - β-propiolactone
      - Epoxides
    - Acylating agents
      - Acetyl imidazole
      - Dimethyl carbamyl chloride
  - Indirect acting
    - Polycyclic aromatic hydrocarbons
    - Aromatic amines and azo-dyes
    - Natural occuring products
      - Aflatoxin - B_1
      - Actinomycin - D
      - Mitomycin - C
    - Miscellaneous
      - Nitrosamine and nitrosamide

- Vinyl chloride
- Asbestos
- Arsenic compounds

- Promotor carcinogens
  - Phorbol esters
  - Hormones
  - miscellaneous
    - Dietary fat

43. Atherosclerosis

- Specific form of arteriosclerosis
- Affects the intima of large and medium sized muscular arteries
  - Aorta
  - Coronary artery
  - Cerebral arteries
- Fibro-fatty plaque/Atheroma
- Commonest in the arterial diseases

Etiology

- Prevalent in industrialised countries
- Risk factors
  - major risk factors
    - Dyslipidaemias
      - Apoproteins
        - surrounds the lipid for carrying it
        - Types - A/B/C/D
      - Total cholesterole
        - Normal - 140-200 mg/dl
      - Triglycerides
        - Normal - <160 mg/dl
      - LDL
        - Normal - <130 mg/dl
      - VLDL
      - HDL
        - Normal - <60 mg/dl
      - Omega-3 fatty acids
        - Lower the plasma cholesterol level
      - Familial hypercholesterolaemia
        - Autosomal codominant disorder
    - Hypertension
      - Doubles the risk of all CVS diseases
    - Smoking
      - HDL↓
      - Deranged coagulation system
      - Accumulation of CO in blood
    - Diabetes mellitus
      - Diabetic dyslipidaemia
        - metabolic syndrome (Insulin resistance)
        - Abnormal lipid profile
      - Frequency to develop gangrene of foot increased 100 times
      - Causes
        - Endothelial dysfunction
        - Platlet aggregation

- Constitutional risk factors
  - Age
  - Sex
    - Men – Appear earlier – ≤ 45 yrs
    - Women – ≤ 55 yrs
  - Genetic factors
  - Familial and racial factors
- Emerging risk factors
  - Higher incidence in developed countries
  - Obesity
  - Use of exogenous hormones / Endogenous oestrogen deficiency
  - Physical inactivity
  - Stressful life style
    - Type-A – ☹
    - Type-B – ☺
  - Homocystinuria
  - moderate alcohol consumption is beneficial
  - Prothrombotic factors and elevated fibrinogen levels
  - Infections

Pathogenesis

- Reaction to injury hypothesis
  - Most widely accepted
  - Endothelial injury
    - Hypertension, Chronic dyslipidaemia → Haemodynamic stress
      - Exposure of subendothelial CT
      - Endothelial injury
  - Intimal smooth muscle cell proliferation
    - Endothelial injury
      - Adherence
      - Aggregation
      - Platlet release reaction
    - Monocyte, Macrophage, Activated platlets → IL-1, TNF-α
      - Proliferation of intimal S.M. cells
      - Production of extracellular matrix
      - Growth factor synthesis
        - PDGF
        - Fibroblast growth factor
    - Activated T-lymphocytes
      - TGF-β, IFN-γ → Collagen synthesis by S.M. cells
    - Endothelial cells
      - Endothelin, NO → S.M. proliferation
  - Role of blood monocytes
    - Do not posses receptors for normal LDL
    - LDL → Entry into the intima → Oxidation → Oxidised LDL
      - Monocytes → Foam cells → Apoptosis → Death → Lipid core formation
      - Cytotoxic to endothelial cells
  - Role of dyslipidaemia
    - May initiate endothelial injury
  - Thrombosis
    - Subendothelial tissue exposure
    - Platlet aggregation
    - Proliferated S.M. cells
    - Foam cells
    - Fibrin and blood cell attachment

    → Thrombus becomes a part of atheromatous plaque
- Monoclonal hypothesis
  - S.M. cell proliferation is similar to cellular proliferation in neoplasms

- One of the two forms of G6PD isoenzymes – Monoclonality in origin
- May be initiated by mutation

Clinical effects
- Ischaemia and atrophy
- Infarction necrosis
- Thromboembolism
- Aneurysmal dilatation and rupture
- Major effects
  - Brain – Infarct
  - Heart – MI / IHD
  - Aorta – Aneurysm
  - Small intestine – IBD
  - Lower extremities – Gangrene

44. Myeloproliferative syndrome
- Group of neoplastic proliferation of multipotent haematopoietic stem cells
- Common stem cell origin
- 7 types
  - Chronic Myeloid Leukaemia
  - Chronic Neutrophilic leukaemia
  - Chronic Eosinophilic Leukaemia
  - Chronic Idiopathic Myelofibrosis
  - Polycythaemia Vera
  - Essential Thrombocythaemia
  - Chronic Myeloproliferative Disease
- Chronic Myeloid Leukaemia
  - Reciprocal translocation between chromosome 9 and 22 forming Philadelphia chromosome
  - t(9;22), q(34;11), BCR/ABL (ABL)
  - BCR/ABL fusion product
    - Tyrosine kinase like activity – Inhibit apoptosis
    - DNA binding ability of ABL is altered
    - Binding to cytoskeletal actin microfilaments is increased
  - Mechanism
    - P53, Rb – Structural alterations
    - RAS, MYC – Structural alterations
    - Release of IL-1β
    - Inactivation of phosphatase-A2 (Tumor suppressor protein)
  - Clinical features
    - 20% of all leukaemias
    - Children – Juvenile CML
    - Manifestations
      - Anaemia
      - Hypermetabolism
      - Splenomegaly
      - Bleeding tendencies
      - Priapism
      - Gout
      - Juvenile CML – Lymph node enlargement
  - Treatment

- Imatinib oral therapy
  - Competitively inhibit ATP binding site of ABL kinase
  - Induces apoptosis in BCR/ABL positive cells
  - 97-% cases are treated
- Allogenic bone marrow (stem cell) transplantation
- Interferon-α
- Chemotherapy
- Others
  - Splenectomy
  - Leucopheresis
  - Splenic irradiation

- Polycythaemia Vera
  - All myeloid components ↑ - Pancytosis (Red cells, granulocytes, platlets)
  - Chromosomal abnormality
    - Trisomy of 8
    - 20q
    - 9p
  - Clinical features
    - Due to
      - Hyperviscousity
      - Hypervolaemia
      - Hypermetabolism
      - ↓ cerebral perfusion
    - Headache
    - Vertigo
    - Tinnitus
    - Syncope
    - Comma
    - Death
    - Risk of thrombosis ↑
    - Risk of haemorrhage
    - Splenomegaly - Abdominal fullness
    - Pruritis
    - Gout
    - Urate stones
  - Treatment
    - Phlebetomy (Venesection)
    - Anticoagulant therapy
    - Chemotherapy
    - Uricosuric drugs
    - Interferon-α - Reduces JAK-2 expression

- Essential Thrombocythaemia
  - Platlet count ↑
  - Absence of control by thrombopoietin - Regulates endomytosis in megakaryocytes
  - Clinical features
    - Haemorrhagic and thrombocytic events are common
    - Arterial/Venous thrombosis
    - Minor trauma → Bruises
    - Spontaneous bleeding
    - Transient ischaemic attack/Frank stroke
  - Treatment

- Not require therapy (Benign course)
- Given if platlet count > 1 million

- Chronic Idiopathic Myelofibrosis
  - Extramedullary haematopoiesis at multiple sites
    - Liver
    - Spleen
  - Overproduction of TGF-β → fibrosis in bone marrow
  - Osteonectin → Osteosclerosis
  - Vascular Endothelial Growth factor (VEGF) → Marrow angiogenesis
  - Clinical features
    - Anaemia
    - Massive splenomegaly
    - Hepatomegaly
    - Petechial problems
    - Lymphadenopathy
    - Ascites
    - Bone pain
    - Hyperuricaemia
  - Treatment
    - Does not require any special therapy
    - Splenectomy may be necessary

45. Diabetes mellitus

- Chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism
- ~ 1% population suffers from DM

Classification
- Older classification
  - Primary
  - Secondary
  - Juvenile onset
  - Maturity onset
  - IDDM
  - NIDDM

  (Primary, Secondary, Juvenile onset, Maturity onset, IDDM, NIDDM — Become obsolete)
- Based on etiology
  - Type-1 DM
    - 10% cases of DM
    - 2 subtypes
      - Subtype 1A - Autoimmune destruction of β-cells
      - Subtype 1B - Negative for autoimmune markers
    - Commonly < 35 yrs
  - Type-2 DM
    - 80% cases of DM
    - Commonly > 40 yrs
    - In obese adolescents
  - Gestational DM
    - About 4% of pregnant women
    - Revert back to normal glycaemia after delivery
  - Others - About 10% cases of DM

Pathogenesis

- Hyperglycaemia may result from
  - Reduced insulin secretion
  - Decreased glucose use by the body
  - Increased glucose production
- Normal insulin metabolism
  - Glucose is the major stimulus for both synthesis and release of insulin
  - Synthesis - Preproinsulin (86 A.A) → Proinsulin (A+C+B) Peptides → Insulin (A+B) Peptides (51 A.A)
  - Release Hyperglycaemia → GLUT-2 transporter → Glucose —Glucokinase→ G-6-P → Mitochondria → ATP↑
    ATP↑ → Alters the ion channel activity → Ca^{+2} influx → Insulin release
  - Action
    - 50% degraded by liver
    - Insulin → Insulin receptor (Intrinsic Tyrosine kinase activity) → Insulin receptor substrate 1 & 2 (IRS 1 & 2) → Phosphorylation and dephosphorylation activities → mitogenic and anabolic actions
      - Glucose transport
      - Glycogenesis
      - Protein synthesis
      - Lipogenesis
    - Low insulin level
      - Glucogenesis
      - Glycogenolysis
- Type-1 DM pathogenesis
  - Genetic susceptibility
    - Identical twins - If one has DM-1, other has 50% chance
    - HLA
      - DR3
      - DR4
      - DQ
  - Autoimmune factors
    - Islet cell antibodies against
      - Glutamic Acid Decarboxylase (GAD)
      - Insulin
    - Insulitis - Lymphocytic infiltration around the pancreatic islets
    - Selective destruction of β-cells
    - T-cell mediated autoimmunity
    - Association with other autoimmune diseases
  - Environmental factors
    - Certain viral and dietary proteins share antigenic properties with human cell surface proteins
    - Certain viral infections
    - Experimental induction with certain chemicals
    - Geographic and seasonal variations
    - Exposure to bovine milk proteins
- Type-2 DM pathogenesis
  - Basic metabolic defect
    - Impaired insulin secretion (Delayed secretion)
    - Insulin resistance
  - Complex etiology
  - No autoimmune and HLA association
  - Genetic factors
    - Stronger basis than DM-1
    - Identical twins - If one has DM-2, other has 80% chance
    - Both parents are DM-2 positive - 40% chance in offsprings
  - Constitutional factors

- Insulin resistance
  - Glucose uptake ↓
  - Hepatic synthesis of glucose ↑
  - Hyperglycaemia in obesity
  - Possible cause
    - Polymorphism in various post-receptor intracellular signal pathway molecules
    - Elevated free fatty acids
- Impaired insulin secretion
  - In early course - Hyperinsulinaemia due to compensatory increased secretion
  - Eventually failure of β-cells to secrete adequate insulin
  - Causes
    - Islet amyloid polypeptide (Amylin)
    - Chronic hyperglycaemia surrounding the islets (Glucose toxicity)
    - Free fatty acids (Lipotoxicity)
- Increased hepatic glucose synthesis

Clinical features

- Type-1 DM
  - Onset of symptoms often abrupt
  - Polyuria
  - Polydypsia
  - Polyphagia
  - Progressive loss of weight
  - Ketoacidosis
  - Hypoglycaemic episodes
- Type-2 DM
  - Onset of symptoms is slow and insidious
  - Asymptomatic or may present
    - Polyuria
    - Polydypsia
  - Obese / Weight loss
  - Unexplained weakness
  - Ketoacidosis is infrequent

Pathogenesis of complications

- microvasculature complications
  - Nephropathy
  - Neuropath
  - Retinopathy
- Non-enzymatic protein glycosylation
  - Free amino group of various proteins binds with glucose
    - Hb
    - Lens crystalline protein
    - Basement membrane
- Polyol pathway mechanism
  - Glucose —Acid reductase→ Sorbitol —Sorbitol dehydrogenase→ Fructose
    - Sorbitol → Entry of water in cell → Swells → Damage
    - Sorbitol → Myoinositol deficiency → Damage schwan cells
- Excessive Oxygen free radicals

Complications of diabetes

- Acute complication
  - Diabetic ketoacidosis
  - Hyperosmolar hyperglycaemic non-ketotic coma

- Hypoglycaemia
- Late systemic complication
  - Atherosclerosis
  - Diabetic microangiopathy
  - Diabetic nephropathy
  - Diabetic neuropathy Diabetic Neuropath
  - Diabetic retinopathy
  - Impections

Diagnosis of diabetes

- Urine testing
  - Glucosuria
    - Renal glucosuria
    - Alimentary glucosuria
  - Ketonuria
- Simple blood sugar estimation
  - Diabetes - >126 mg/dl fasting plasma glucose level
- Screening by fasting glucose test
- Oral Glucose Tolerance Test
  - High carbohydrate diet for 3 days
  - Overnight fast for atleast 8 hours
  - 75 gm glucose in 300 ml water
  - Blood and urine specimen / half hour for 2 hours
  - Normal fasting blood glucose level = 100 mg/dl
  - 100-125 mg/dl fasting value - Impaired fasting glucose tolerance
  - Fasting value > 126 mg/dl - Diabetes
  - 75 gm oral glucose after 2 hour > 200 mg/dl - Diabetes
  - Random blood glucose value > 200 mg/dl) - Diabetes
- Other tests
  - Glycosylated Hb
  - Glycated albumin
  - Extended GTT
  - Intravenous GTT
  - Cortisone primed GTT
  - Insulin assay
  - Proinsulin assay
  - C-peptide assay
  - Islet autoantibodies