Unit-III

HAEMATOLOGICAL DISEASES:

⇒ **Anaemia:** Anaemia is defined as reduced haemoglobin concentration in blood below the lower limit of the normal range for the age and sex of the individual. If haemoglobin concentration is < 9 gm/dl.

* **Iron deficiency anaemia:** The anaemia is regarded as severe when Hb level is below 9 gm/dl, it is caused by deficiency of iron in the bone marrow and may be due to iron deficiency, excessive high requirement or malabsorption. RBCs are microcytic (cells are smaller than normal) and hypochromic (less pigmented) bcoz of their low Hb content.

- **Aetiology:** The cause of iron deficiency anaemia are:

A.) **Increased blood loss:**
- Due to menorrhagia (abnormal heavy bleeding at the time of menstruation).
- Uterine e.g., excessive menstruation in reproductive years, repeated miscarriages, at onset of menarche, post-menopausal uterine bleeding.
- Gastrointestinal e.g., peptic ulcer, duodenal ulcer, haemorrhoids (piles) hookworm infestation, ulcerative colitis, chronic aspirin ingestion.
- Renal tract e.g., haematuria, haemoglobinuria.
- Nose e.g., Repeated epistaxis
- Lungs e.g., haemoptysis

B.) **Increased requirements:**
- Spurts in growth in infancy, childhood and adolescence
- Prematurity
- Pregnancy and lactation (In pregnancy, when iron requirement in women are 1gd (3mg), both for foetal growth and to support the additional requirement for mother).

C.) **Inadequate dietary intake:**
- Poor economic status
- Anorexia e.g., in pregnancy.

D.) **Decreased absorption:** (or malabsorption)
- Partial or total gastrectomy.
- Achlorhydria
- Intestinal malabsorption such as in coeliac disease.

Predisposing factors:
- Sex (menstruation)
- Genetics

Precipitating factors
- Inadequate iron intake
- Blood loss
- Pregnancy

Decreased intake of iron with foods, with blood loss
↓
Iron in the body is used up
↓
Decreased iron reserves needed for Hb production
↓
Decreased RBC production due to lack of Hb
↓
Iron deficiency anaemia
↓
Less oxygen and haemoglobin

Hypochromic RBC due to less Hb.

Headache due to less O_2 supply to brain

Weakness due to less overall oxygen supply
↓
If prolonged: Chest pain, Shortness of breath even with rest, paresthesias, Low RBC and Hematocrit levels.

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* **Megaloblastic anaemia:** Maturation of erythrocytes is impaired when deficiency of vitamin B_{12} or folic acid occurs and abnormally large RBCs (**megaloblast**) are found in the blood. When deficiency of Vit. B_{12} or folic acid occurs the rate of DNA or RNA synthesis is reduced, that's why delaying cell division. The cells can grow larger than normal b/w divisions. Circulating cells are immature, larger than normal and some are nucleated. Mean cell volume > 94 femtoliter ($1 fL = 10^{-15} L$).

– A hypersegmented neutrophil with 6 lobed nucleus is noted in the pernicious anaemia

– Megaloblasts are both morphologically and functionally abnormal with the result that the mature red cells formed from them and released into the peripheral blood are also abnormal in shape and size, the most prominent abnormality being macrocytosis.

• **Etiologic classification of megaloblastic anaemia:** on the basis of etiology megaloblastic anaemia is classified into 2 types:

A.) Vitamin B_{12} deficiency anaemia (or pernicious anaemia)

B) Folic acid (Folate) deficiency anaemia

A) **Vitamin B_{12} deficiency anaemia:** Absorption of vitamin B_{12} is in females rather than males b/w 45 to 65 years of age. It is a auto-immune disease in which antibodies destroy intrinsic factor and parietal cells in the stomach.

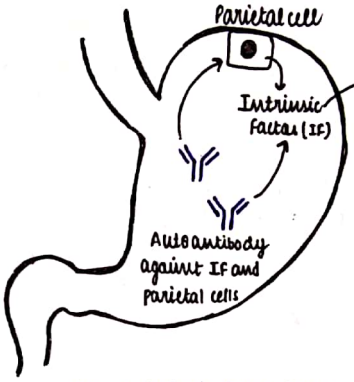
– **Etiology:**

a.) Inadequate dietary intake e.g., strict vegetarians, breastfed infant.

b) Malabsorption:

I.) **Gastric causes:** Pernicious anaemia, gastrectomy (IF is not available), chronic gastritis (inflammation in stomach).

II.) **Intestinal causes:** Ileal resection, Ileitis (inflammation in ileum), Crohn's disease, Tapeworm infection.



Intrinsic factor (IF) required for vitamin B_{12} absorption

↓

- Chronic atrophic gastritis
- Vitamin B_{12} deficiency.
- Ted risk of gastric cancer
- Ted risk of carcinoid tumour
- Anaemia (pernicious).

Fig; Intrinsic factor / vitamin B_{12} complex (normally absorbed in terminal ileum).

– **Complications:**

a) Subacute combined degeneration of spinal cord. Demyelination of lateral and posterior columns of white and grey mater.

b) Ulceration of tongue and glossitis (inflammation in parenchymal cells of tongue).

B) **Folic acid deficiency anaemia:** Folate deficiency anaemia is the lack of folic acid in the blood. Folic acid is a B-vitamin that helps you in RBC production and deficiency of it leads to the folic acid deficiency anaemia.

- **Etiology:**

a.) Dietary deficiency e.g., in alcoholics, infants (if their is delay in establishing a mixed diet), anorexia (loss of appetite), old age and poverty.

b.) Malabsorption e.g., in tropical sprue (A disease of tropical regions is characterized by fatty diarrhoea and malabsorption of nutrients), Coeliac disease, partial gastrectomy, jejunal resection, crohn's disease.

c.) Excessive demand:

I.) Physiological: pregnancy, lactation, infancy.

II.) Pathological: Malignancy, increased hematopoiesis, tuberculosis and rheumatoid arthritis.

d.) Excess urinary folate loss e.g., in active liver disease, congestive heart failure

e.) Impaired metabolism e.g., inhibitors of dihydrofolate (DHF) reductase such as methotrexate and pyrimethamine; alcohol, congenital enzyme deficiencies.

f.) Haemodialysis

- **Complications:**

a.) **Anaemia:** Macrocytic megaloblastic anaemia is the cardinal feature of deficiency of vitamin B_{12} and/or Folate.

b.) **Glossitis:** Typically the patient has a smooth, beefy, red tongue.

c.) **Neurological manifestations:** Vit B_{12} defi Folate deficiency may occasionally develops neuropathy.

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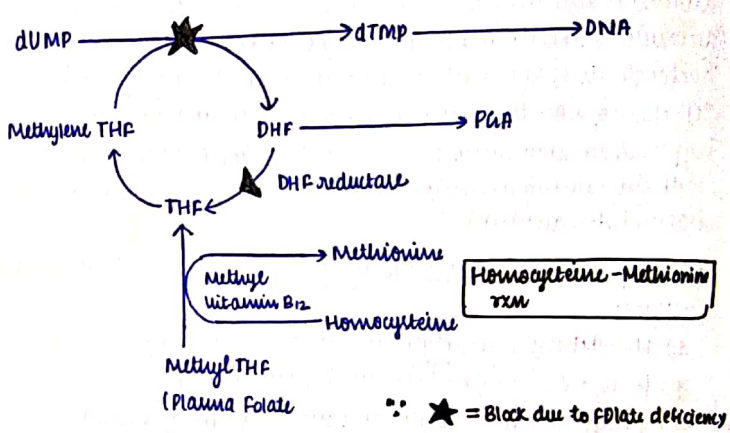
Thymidylate Synthetase reaction



Fig; Biochemical basis of megaloblastic anaemia (Folate deficiency).

∵ THF = Tetrahydrofolate
DHF = Dihydrofolate
PGA = Pteroyl glutamic acid
dUMP = deoxy uridylate monophosphate
dTMP = deoxy thymidylate monophosphate.

⇒ **Haemolytic anaemias:** Haemolytic anaemias are defined as anaemias resulting from an increase in the rate of red cell destruction. Normal life span of RBCs is 120 ± 30 days and after that haemoglobin of RBC is liberated in spleen. In haemolytic anaemia life span of RBCs is shortened. In fact, compensatory bone marrow hyperplasia may cause 6 to 8 folds ↑ in the Red cell production without causing anaemia to the patient so, called Compensated haemolytic anaemia.

* **Classification of haemolytic anaemia:** It is classified into 2 main categories:

1.) Hereditary haemolytic anaemias are usually the result of intrinsic red cells defect (i.e., intracorpuscular)

2.) Acquired haemolytic anaemias caused by a variety of extrinsic environmental factors (e.g., extracorpuscular).

1.) **Hereditary haemolytic anaemia / con-genital haemolytic anaemia:** In this anaemia, genetic abnormality leads to the synthesis of abnormal haemoglobin, reducing cell O_2 carrying capacity and life span of RBCs. The most common type of con-genital haemolytic anemias are:

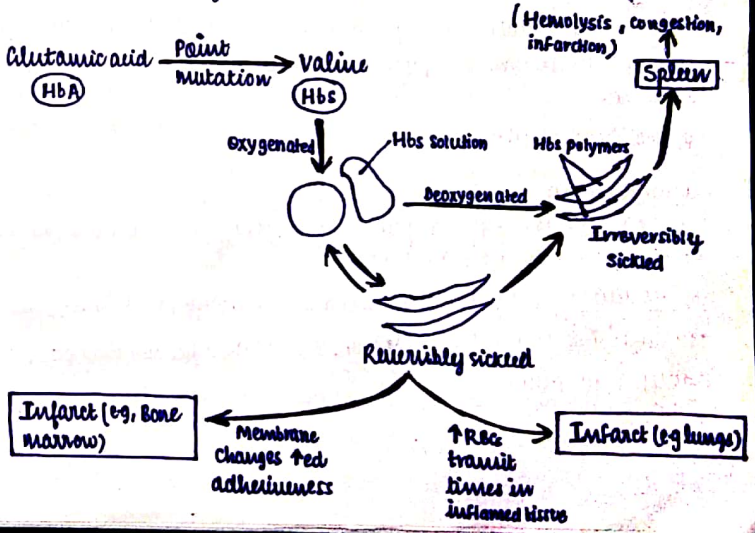
A.) Sickle cell anaemia

B.) Thalasemia

A) **Sickle cell anaemia:** The abnormal Hb molecules becomes deoxygenated making the erythrocytes mis-shapen (long-curved shape / sickle shape). The lifespan of RBCs is reduced by early haemolysis. These cells do not move smoothly via smooth blood vessels, this ↑ses the viscosity of blood and reduces the rate of blood flow and leading to intravascular clotting, ischaemia and infarction. It results from 2 successive genes that forms abnormal β-chains.

Normal β-Globulin				Mutant / abnormal β-globulin			
DNA: TGA	GGA	CTC	CTC	DNA: TGA	GGA	CAC	CTC
mRNA: ACU	CCU	GAG	GAG	mRNA: ACU	CCU	GUG	CTC
Amino acid: Thr	Pro	Glu	Glu	Amino acid: Thr	Pro	Val	Glu

• **Pathophysiology of sickle cell anaemia:** There is point mutation in the β-globulin chain of haemoglobin, causing the hydrophillic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position, which leads the mis-shapen (sickle shape) of RBCs and that's why **Sickle cell anaemia.**



• Aetiology:

• Blacks are more affected than other race. Some affected individuals have a degree of immunity to malaria because the life span of the sickled cells is less than the time needed for the malaria parasite to mature inside the cells.

• Complications:

- Due to intravascular clotting and ischaemia, causing severe pain in long bones, chest or the abdomen.
- Excessive haemolysis results in high levels of circulating bilirubin. This in turn frequently leads to gall stones (cholelithiasis) and the inflammation of the gall bladder (cholecystitis).

B) Thalassemia: (or cooley's anaemia or MediterRranean anaemia): This inherited condition is most common in Mediterranean countries.

• There is reduced globulin synthesis with resultant reduced Hb production and fed fragility of the cell membrane, leading to early haemolysis. ultimately severe cases may cause mortality in infants or young children.

• Classification of Thalassemia: It is of 2 types:

I.) α-Thalassemia

II.) β-Thalassemia

I.) α-Thalassemia: α-Thalassemia is the result of changes in the genes for the α-globin component in Hb. It is autosomal recessive disease.

- Aetiology: i.) Mutation in the DNA of cells that produce Hb.
  ii.) It is a form of thalassemia involving the genes HBα and HBβ.
  iii.) It is most commonly inherited in a mendelian recessive fashion.

II.) β-Thalassemia: Specifically, it is characterized by a genetic deficiency in the synthesis of β-globulin chains.

- Aetiology: i) autosomal recessive disorder.

• Pathophysiology of thalassemia:

Imbalance in the production of peptide chains
↓
Excessive unpaired peptide chain in Hb
↓
Precipitation on cell membrane
↓ → More no of RBCs are destroyed in bone marrow
Increased haemolysis → spleen enlarges (in spleen)
↓
Only few RBCs are in circulation ← Thalassemia.

• Complications: Heart diseases (heart failure and arrhythmias), chronic liver hepatitis, cirrhosis, hypogonadism, hypothyroidism, diabetes, osteoporosis, thrombophillia and pseudoxanthoma elasticum

2.) Acquired haemolytic anaemias: 'acquired' means haemolytic anaemia in which no familial or racial factors has been identified.

• Aetiology:

a.) Chemical agents: eg, lead, arsenic compounds and sulphonamide drugs causes acquired haemolytic anaemia

b.) Microbial toxins: toxins produced by microbes e.g., Streptococcus pyogenes, Clostridium perfringens.

c.) Autoimmunity: In this disease, individuals make antibodies to their own red cell antigens, causing haemolysis. e.g., carcinoma, viral infection and other autoimmune diseases.

d.) Blood transfusion reaction: Haemolysis occurs within the cardiovascular system when adverse rxn b/w blood of incompatible recipient and donor due to antibodies production.

e.) Parasitic diseases: eg., Malaria

f.) Ionising radiations: e.g., x-rays, Radioactive isotopes.

g.) Physical damage to cells: during artificial heart valves, kidney dialysis machines.

•Signs: Fever, chills, lumbar pain and shock.

* Haemophilia: It is a group of inherited clotting disorders, carried by genes present on the X-chromosome (i.e, inheritance is sex linked). The faulty genes codes for abnormal clotting factors (Factor VIII and Factor IX), and if inherited by a male child always leads to expression of the disease. Women inheriting one copy are carriers, but, provided their 2nd x-chromosome bears a normal copy of gene, their blood clotting is normal. It is possible, but unusual for a women to inherit two copies of the abnormal gene and have haemophilia.

•Symptoms: Repeatitive episodes of severe and prolonged bleeding at any site, even in absence of trauma. Recurrent bleeding into joints is common, consequently leads to severe pain and in the long-term cartilage is damaged.

•Classification of Haemophilia: It is of 2 types:

1.) Haemophilia A
2.) Haemophilia B

1.) Haemophilia A: It is characterized specifically by a mutation on the clotting Factor VIII (Blood clotting protein / anti-haemophilic factor) gene of the X-chromosome.

- Pathogenesis: Hae A is noted mutation at the chromosomal locus X_{q28} and can cause an absence of protein made by Factor VIII. Mutation found in individuals with Hae A includes gene inversion (45%), mis-sense mutation (20%).

- Clinical Features: Patients of haemophilia suffer from bleeding for hours or days after the injury. The clinical severity of the disease correlates well with plasma level of factor VIII activity. Haemophilic

bleeding can involve any organ but occurs most commonly as recurrent painful haemarthroses and muscle haematomas, and sometimes as haematuria. Spontaneous intercranial haemorrhage and oropharyngeal bleeding are rare, but when they occur they are the most feared complications.

2.) Haemophilia B (or Christmas disease): It is caused by mutation on the clotting factor IX (Christmas factor or plasma thromboplastin component).

- In it point mutation occurs at $X_{q27.1}$ to $X_{q27.2}$. The mutation often results in a lack of functional protein or the production of a disfunctional protein product.

- Haemophilia B is rare than haemophillia A and factor IX is deficient is resulting in deficiency of clotting factor III (thromboplastin).
- Both haemophillia A and haemophilia B are completely penetrant (a group of gene) and occurs in 100% of ♂ and only 10% of ♀ carriers.
- Aetiology of haemophillia: Point mutation, heredity

Hemophilic male (x^hy)

Normal female (XX)		
	XX^h (carrier female)	Xy (Normal male)
	XX^h (carrier female)	Xy (Normal male)

Normal male (xy)

Carrier female (x^hy)		
	XX^h (carrier female)	X^hy (haemophilic male)
	XX (Normal female)	Xy (Normal male)

Fig: Inheritance patterns of haemophilia

- Pathophysiology of haemophilia:

Due to etiological factors: Heredity, spontaneous mutation
↓
Abnormal X-chromosomes
↓
Mutation of genes in X-chromosomes
↓
Deficiency of factor VIII and IX
↓
Limited formation of prothrombin activators
↓
Limited thrombin production
↓
Fibrinogen is not converted into fibrin
↓
Limited clots formed
↓
Uncontrolled bleeding
↓
Signs of haemophillia

ENDOCRINE SYSTEM:

⇒ Diabetes:

1.) **Diabetes mellitus**: It is defined as the heterogeneous metabolic disorder of pancreatic islets cells of langerhans characterized by **hyperglycemia** (excessive sugar in the blood), **glycosuria** (excretion of glucose in the urine), **hyperlipemia** (excess lipid in blood), negative nitrogen balance and sometimes ketonemia.

* It is caused by an inability to produce and use insulin.

* **Aetiology of diabetes mellitus**: The diabetes mellitus can be occur due to:

A) Autoimmune β-cell destruction leading to insulin deficiency.

B) Idiopathic

C) Progressive loss of β-cell insulin secretion with insulin resistance.

D) Genetic defect of β-cell function due to mutation in enzymes.

E) Disease of exocrine pancreas e.g., cystic fibrosis, Chronic pancreatitis, pancreatic tumours.

F) Endocrinopathies (eg, acromegaly, cushing's syndrome).

G) Genetic syndromes (eg, Down's syndrome, Klinefelter's syndrome, Turner's syndrome).

* **Pathogenesis of diabetes mellitus**: Depending upon the etiology of diabetes mellitus, hyperglycemia may result from the following:

- Reduced insulin secretion,
- Decreased glucose use by the body,
- Increased glucose production.

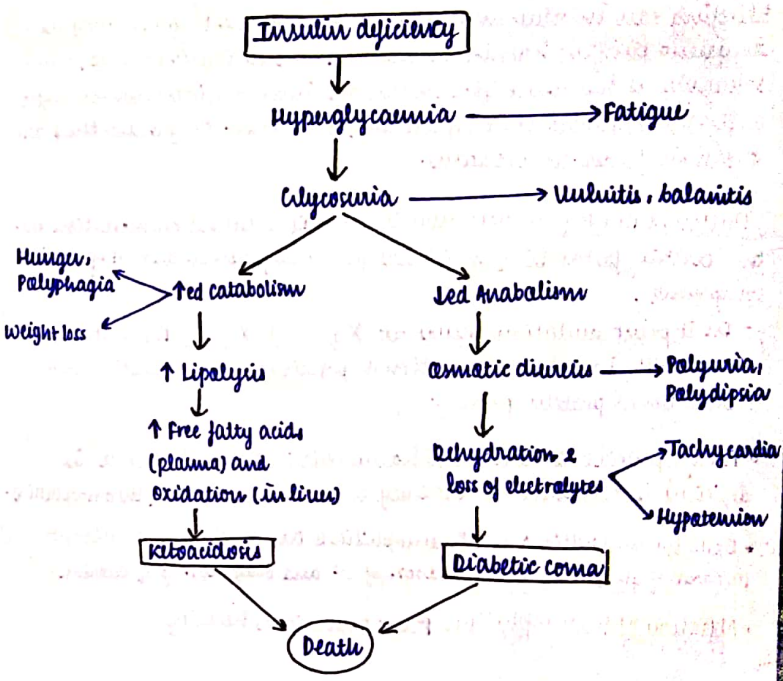


Fig: Pathophysiological basis of common signs and symptoms due to uncontrolled hyperglycaemia in diabetes mellitus

* **Complications of diabetes mellitus**: It includes:

- **Hyperglycaemia**: excessive sugar / glucose in blood.
- **Glycosuria**: Excretion of glucose through urine which leads to vulvitis (inflammation in vulva or sex organs in ♀) and balanitis (inflammation in sex organs in ♂).

- **Polyuria:** production of abnormally large volumes of dilute urine.
- **Polydipsia:** Constant and excessive thirst with dryness of mouth.
- **Polyphagia:** excessive eating or appetite.
- **Tachycardia:** ↑ heat beat.
- **Hypotension:** ↓ Blood pressure
- **Ketoacidosis:** Accumulation of acid in the blood when blood sugar and glucagon are too high for long period.

* **Classification of diabetes mellitus:** Diabetes mellitus is classified into the 2 categories:

A) Type 1 Diabetes mellitus

B) Type 2 Diabetes mellitus

A) **Type 1 Diabetes mellitus:** [or Juvenile-onset diabetes] insulin dependent diabetes mellitus (IDDM)]. It is divided into 2 subtypes:

a) **Subtype 1A (immune-mediated) DM** characterized by autoimmune destruction of β-cells which usually leads to insulin deficiency.

b) **Subtype 1B (idiopathic) DM** characterized by insulin deficiency with tendency to develop ketosis but these patients are negative for autoimmune markers.

- **Pathogenesis of type 1 Diabetes mellitus:** Basic phenomenon in type 1 diabetes mellitus is destruction of β-cell mass, usually leading to absolute insulin deficiency.

– Subtype 1B DM remains idiopathic and pathogenesis of Subtype 1A DM is immune mediated.

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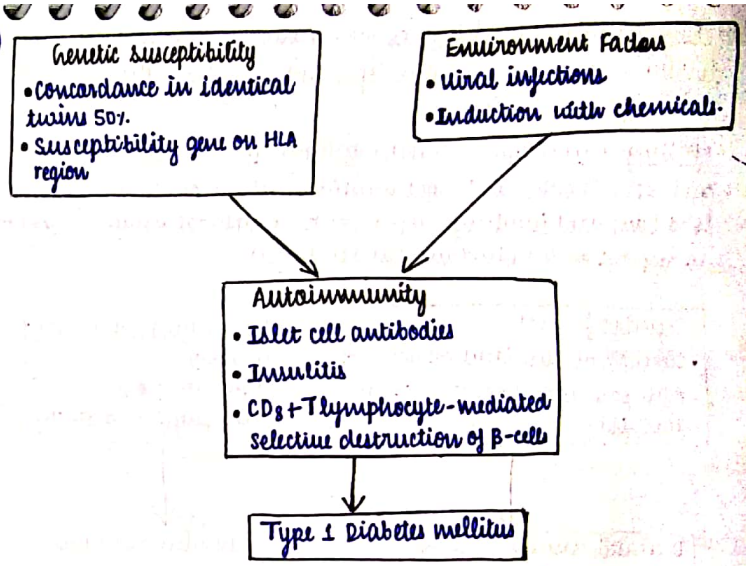

Fig: Pathogenesis of type 1 diabetes mellitus.

- **Clinical features of type 1 diabetes mellitus:**

a) Patients of type 1 DM usually manifest at early age, generally below the age of 35.

b) The onset of symptoms is often abrupt.

c) At presentation, these patient have **polyuria**, **polydipsia** and **polyphagia**.

d) The patients are not obese but have generally progressive loss of weight.

e) These patients are prone to develop metabolic complications such as **ketoacidosis** and **hypoglycemic episodes**.

B) **Type 2 diabetes mellitus:** It was previously c/a maturity onset diabetes (MOD), as non-insulin dependent diabetes mellitus (NIDDM) of obese and non-obese type.

- **Pathogenesis of type 2 diabetes mellitus:** The basic metabolic defect in type 2 DM is either a delayed insulin secretion relative to glucose load (impaired insulin secretion), or the peripheral tissues are unable to respond to insulin (insulin resistance).

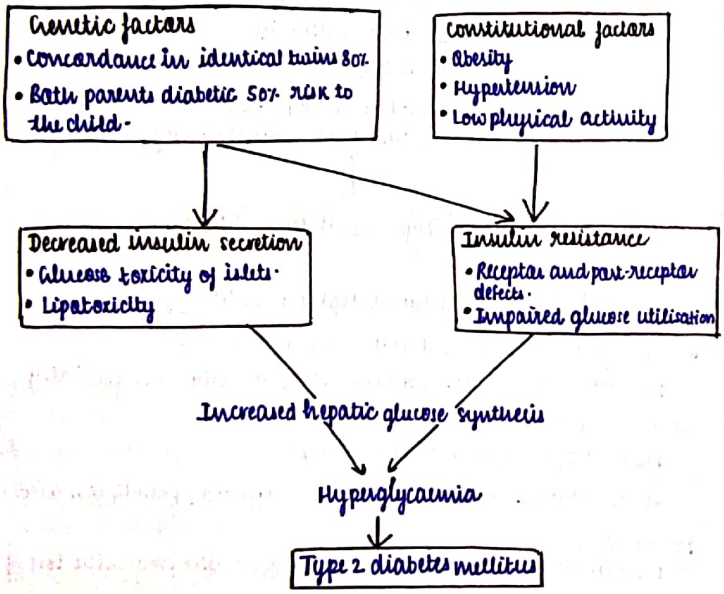

Fig: Pathogenesis of type 2 diabetes mellitus

- **Clinical features of type 2 Diabetes mellitus:**

a) This form of diabetes generally manifests in middle life or beyond, usually above the age of 40.

b) The onset of symptoms in type 2 DM is slow and insidious.

c) Generally, the patient is asymptomatic when the diagnosis is made on the basis of glucosuria or hyperglycaemia during physical examination, or may present with polyuria and polydipsia

d) The patients are frequently obese and have unexplained weakness and loss of weight.

e) Metabolic complications such as Ketoacidosis are infrequent

* **Difference between type 1 and type 2 diabetes mellitus:**

Features	Type 1 DM (IDDM)	Type 2 DM (NIDDM)
	Juvenile onset diabetes (JOD) or insulin dependent diabetes mellitus (IDDM)	Maturity onset diabetes (MOD) or non-insulin dependent diabetes mellitus (NIDDM)
Pathogenesis	Lack of insulin due to autoimmune destruction of β-cells.	Insulin resistance, impaired insulin secretion
Insulitis (disease of pancreas caused by the infilteration of lymphocytes	More common	Less common
Age at onset	Early (below 35 years)	Later (≥ 40 years)
Amyloidosis (accumulation of amyloid protein are islet cells)	Infrequent	Common in chronic cases
Blood insulin level	Decreased insulin	Normal or increased insulin
Islet cell antibodies	Yes	No

weight	Normal	obese / non-obese
Clinical mag management	Insulin and diet	Diet, exercise, oral drugs, insulin
Acute complications	Ketoacidosis (accumulation of acid in blood due to accumulation of ketone bodies).	Hyperosmolar coma / diabetic coma

* Pathological changes of diabetes mellitus: A wide spread pathological changes in thickening of capillary basement membrane, ↑ed in vessel wall matrix and cellular proliferation (↑ no. of same cells) resulting in vascular complications like narrowing of lumen, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, Nephropathy and peripheral vascular insufficiency.

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2) Diabetes insipidus: It is a disorder of posterior pituitary gland. The deficient secretion of ADH causes diabetes mellitus. The causes of ADH (anti-diuretic hormone / vasopressin) deficiency are:

- Inflammatory and neoplastic lesions of the hypothalamo-hypophyseal axis.
- Destruction of neurohypophysis (→ or posterior pituitary gland) due to surgery, radiation, head injury.
- Idiopathic cause.

* Complications: The main features of diabetes insipidus are excretion of a very large volume of dilute urine of low specific gravity (below 1.010), polyuria and polydipsia, dehydration and it leads to mortality.

- In childrens, Enuresis (bed wetting or involuntary urination especially by childrens at night).
- 'water and electrolyte balance is disturbed' unless fluid intake is greatly ↑ed to compensate for excess loss of water.

↓ or absent ADH
↓
↓ reabsorption of H_2O
↓
Polyuria → ↓ Renal insufficiency

Severe thirst (polydipsia) → ↓ cardiac output → ↓ Hypotension → ↓ Hypovalemic shock

Fig: Pathogenesis of diabetes insipidus

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⇒ **Thyroid diseases:** A medical condition in which thyroid gland is affected and leads to impaired production of thyroid hormones i.e., T_3 (triiodothyronine), T_4 (thyroxine) and thyroglobulin.

✱ Diseases of the thyroid gland includes:

1) Hyperthyroidism (thyrotoxicosis)
2) Hypothyroidism
3) Thyroiditis
4) Thyroid carcinoma.

1) **Hyperthyroidism (thyrotoxicosis):** It is a hypermetabolic clinical and biochemical state caused by excess production of thyroid hormones.

• **Etiopathogenesis:** Hyperthyroidism may be caused by following disease:

A) Graves's disease (diffuse toxic goitre)
B) Toxic multinodular goitre
C) Toxic adenoma
D) Thyroid storm.

Other causes of hyperthyroidism involves: hypersecretion of pituitary TSH by a pituitary ~~TSH~~ tumour, hypersecretion of TRH, thyroiditis, metastatic tumours of the thyroid etc.

• **Clinical features:** The usual symptoms are emotional instability, nervousness, palpitation, fatigue, weight loss in spite of good appetite, heat intolerance, perspiration, menstrual disturbances and fine tremors of the outstretched hands.

- Cardiac manifestations in the form of tachycardia, palpitations and cardiomegaly are invariably present in hyperthyroidism.

• **Graves's disease:** (or Diffuse toxic goitre or Basedow's disease), primary hyperplasia, exophthalmic goitre is characterised by:

- Hyperthyroidism (thyrotoxicosis)
- Diffuse thyroid enlargement
- ophthalmopathy.

The disease is more frequent b/w the age 30 to 40 years and has five times increased prevalence among females.

Graves disease is an autoimmune disease.

B-cells
↓
Plasma cells
↓
Antibodies immobilize antigen
↓
Immune system produces auto-antibodies c/a thyroid stimulating immunoglobulin (TSI)
Attach to thyroid cells
↓
TSIs mimics the action of the TSH
↓
TSI binds to TSH receptors
↓
Thyroid gland is stimulated to produce excess amount of thyroid hormones

Fig: Pathophysiology of graves's disease

• **Nodular goitre (multinodular goitre, Adenomatous goitre):** Nodular goitre is regarded as the end-stage of long-standing simple goitre. It is

characterised by most extreme degree of tumour-like enlargement of the thyroid gland and characteristic nodularity.

- **Aetiology:** Etiologic factors implicated in endemic and non-endemic or sporadic variety of simple goitre are involved in the etiology of nodular goitre too.

- **Pathogenesis of nodular goitre:**

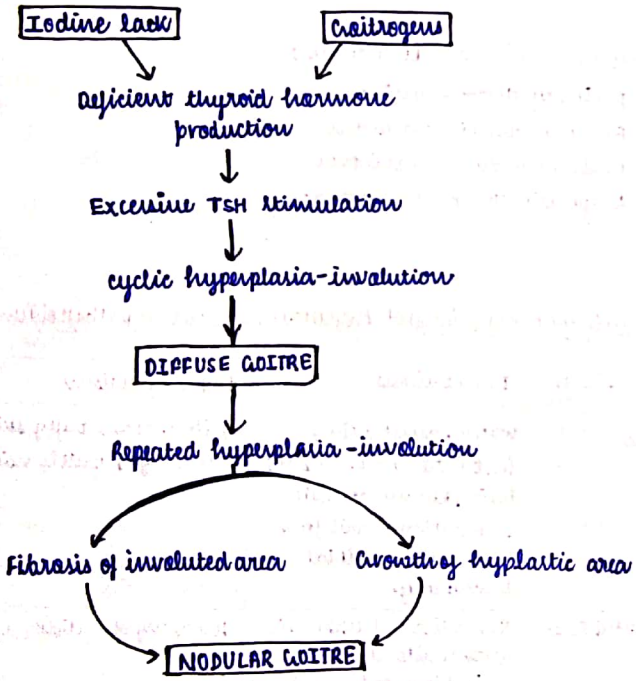

Fig: Pathogenesis of simple and nodular goitre

2) **Hypothyroidism:** Hypothyroidism is a hypometabolic clinical state resulting from inadequate production of thyroid hormone. The clinical manifestations of hypothyroidism, depending upon the age of onset of disorder, are divided into 2 forms:

A) Cretinism or congenital hypothyroidism.

B) Myxoedema.

A) **Cretinism:** It is the development of severe hypothyroidism during infancy and childhood. Cretinism leads to mentally retarded children.

- **Etiopathogenesis:** The causes of congenital hypothyroidism are:
  - a) Developmental anomalies i.e., thyroid agenesis and ectopic thyroid.
  - b) Genetic defect in thyroid hormone synthesis e.g., defect in iodine trapping, oxidation, iodination, coupling & thyroglobulin synthesis.
  - c) Foetal exposure to iodides & antithyroid drugs.
  - d) Endemic cretinism in regions [illegible] with endemic goitre due to dietary lack of iodine.

- **Clinical features:** Slow to thrive, poor feeding, constipation, dry scaly skin, hoarse cry and bradycardia.
  Cretinism leads to impaired skeletal growth and consequent dwarfism, round face, narrow forehead, broad nose.
  Neurological features such as deaf-mutism, spasticity & mental deficiency.

B) **Myxoedema:** The adult-onset severe hypothyroidism causes myxoedema. The term myxoedema indicates non-pitting oedema due to accumulation of hydrophilic mucopolysaccharides in the ground substance of dermis & other tissues.

• **Etiopathogenesis:** The causes of myxoedema are:

a.) Ablation of the thyroid by surgery or radiation.

b.) Autoimmune (lymphocytic) thyroiditis (termed primary idiopathic myxoedema).

c.) Endemic or sporadic goitre.

d.) Hypothalamic-pituitary lesions.

e.) Thyroid cancer

f.) Prolonged administration of antithyroid drugs.

• **Clinical features:** Cold intolerance, mental and physical lethargy, constipation, slowing of speech and intellectual function, puffiness of face, loss of hair & altered texture of the skin.

3.) **Thyroiditis:** It is the inflammation of the thyroid due to non-infectious causes and classified as:

A.) **Acute thyroiditis:**

a.) Bacterial infection e.g., Staphylococcus, Streptococcus.

b.) Fungal infection e.g., Aspergillus, pneumocystis.

c.) Radiation injury.

B.) **Subacute thyroiditis:**

a.) Granulomatous thyroiditis

b.) Lymphocytic thyroiditis

c.) Tuberculous thyroiditis

C.) **Chronic thyroiditis:**

a.) Autoimmune thyroiditis (Hashimato's or chronic lymphocytic thyroiditis)

b.) Invasive fibrous thyroiditis or Riedel's thyroiditis.

• **Hashimato's (Autoimmune, chronic lymphocytic thyroiditis):** It is also called diffuse lymphocytic thyroiditis or goitrous autoimmune thyroiditis is characterised by 3 features:

I.) Diffuse firm, goitrous enlargement of the thyroid.

II.) Lymphocytic infilteration of the thyroid gland.

III.) Presence of thyroid autoantibodies.

4.) **Thyroid carcinoma:** It includes:

A.) papillary thyroid carcinoma

B.) Follicular thyroid carcinoma

C.) Medullary thyroid carcinoma

D.) Anaplastic thyroid carcinoma

⇒ **Manifestations (signs) of thyrotoxicosis and hypothyroidism:**

System / organ	Thyrotoxicosis	Hypothyroidism
Skin	warm, moist skin, heat intolerence, fine thin hair, Plummer's nail (separation of nail from nails bed), peritibial dermopathy.	Yellow, coal, puffy skin (scaelling), brittle nail.
Eyes and Face	Retraction of upper lid with white stair, Periorbital oedema, loss of temporal aspects of eyebrow, puffy non-pitting faces and large tongue.	Drooping of eyelids

Cardiovascular System	Decreased peripheral vascular resistance, Tachycardia, ↑ Stroke volume, ↑ cardiac output, heart failure, ↑ inotropic (i.e.) ↑ force of contraction of cardiac muscle) and ↑ chronotropic (muscular movement ↑) effects, Arrhythmia & angina.	↑ed peripheral vascular resistance, ↓ heart rate, ↓ stroke vaume, ↓ cardiac output, ↓ BP, low output heart failure. Prolonged PR interval, Flat T-wave Pericardial effusion (accumulation of fluid in pericardium).
Respiratory system	Dyspnoea (Forceful breathing), ↓ vital capacity.	Pleural effusion, hypoventilation and CO_2 retention.
GIT	↑ed appetite, ↑ frequency of bowel movement & hypoproteinemia.	↓ed appetite, ↓ frequency of bowel movement, Ascites (more abdominal fluid).
CNS	Nervousness, hyperkinesis, emotional liability.	Lethargy, general slowing of mental process & neuropathy.
Musculoskeletal system	weakness & muscle fatigue, ↑ed deep tendon reflax, hypercalcemia, osteoporosis (↓ tendency of bones).	Stiffness and muscle fatigue, ↓ deep tendon reflax, ↑ alkaline phosphatase, LDH (Lactate dehydrogenase) and AST (Aspartate transaminase).
Renal System	Mild polyuria, ↑ renal blood flow, ↑ GFR (glomerular filteration rate).	Impaired water excretion.
Haemopoetic system	Anaemia, ↑ed erythropoiesis.	↓ RBC formation, Anaemia (Normochromic due to reduced RBC turn over.
Reproductive system	Menstrual irregularity, ↓ fertility, ↑ gonadal steroid metabolism.	Hypermenorrhoea, ↓ed libido, impotency.
Metabolic system	↑ed BMR, negative nitrogen balance, hyperglycemia, ↑ free fatty acids (lipolysis), ↓ cholesteral & triglycerides, ↑ hormone degradation. ↑ Requirement of fat and water soluble vitamins, ↑ed drug metabolism.	↑ed BMR, Positive nitrogen balance, delayed degradation of insulin with ↑ed cholesteral and triglycerides, ↓ hormone degradation, ↓ requirement for fat & water soluble vitamin, ↓ drug metabolism.

* Disorders of sex hormones:

⇒ **In females:** Androgen excess refers to over production of σ^{3} hormones which consequently results in equilibrium imbalance in hormone. It leads to: Hirsutism and alopecia. Disorders of other hormone like oestrogen & progesterone is discussed below:

1.) **Hirsutism:** Hirsutism is the growth of excessive hair in a male pattern. This would include face, chest, abdomen and back.

- Polycystic ovarian syndrome, congenital adrenal hyperplasia, ovarian tumours or adrenal tumours are the disorders which leads to hirsutism
- Hirsutism occurs due to over production of androgens.

2.) **Alopecia:** Loss of hair on the head / scalp.

3.) **Polycystic ovarian syndrome (PCOS):** This disorder is characterised by oligomenorrhea (irregular menstrual cycle) or Amenorrhoea (absence of menstrual cycle). It results in obesity, infertility, diabetes, heart disease and uterine cancer in young ♀.

- **Aetiology:** Insulin resistance is poor response of body tissue to insulin.
- **Complication:** Hyperandrogenism, acne

4.) **Menstrual cycle irregularities:** Perimenopause or menopausal transition begins 2 to 8 years before menopause due to decline in level of oestrogen and progesterone.

- **Symptoms:** Hot flashes (sudden sweating), Insomnia (a persistant problem falling and staying asleep), Fatigue, loss of libido, vaginal dryness and depression. Long term oestrogen deficiency can result in osteoporosis (thinning of the bones).

5.) **Cushing syndrome:** It occurs due to over-production of cortisol released by cortex of adrenal gland.

- **Symptoms:** Breakdown of muscle protein and redistribution body fats results in spindly arms and legs alongwith round moon face, buffalo hump on the back side & hanging abdomen.
- **Characteristics:** Facial skin is flushed (Redness on face), Hyperglycemia (↑ level of cortisol), osteoporosis, Hypertension, ↓ed resistance to stress and mood swing (due to fluctuation of catecholamines).

6.) **Infertility:** Person do not have ability to produce child.

⇒ **In males:** Male harmone sex disorders:

1.) **Hypogonadism:** It refers to the decreased production of testosterone. This can result from the pituitary gland (master gland in the brain for harmone production) not stimulating testicles to make testosterone or the failure of the testicles to produce testosterone in adequate amount.

- **Symptoms:** ↓ libido, Erectile dysfunction (It is the inability to acquire or maintain an erection of male sexual organ that is satisfactory for sexual intercourse), ↓ed energy, ↓ed muscle mass & thinning of bones. Testicles size may also ↓ and sperm count may also ↓.
- **Causes:** This can be results from the pituitary gland which is unable to stimulate testis for production of testosterone.
  - Any medical condition which can ↓ the blood flows to male sex organ.

- Ischaemia due to formation of atheroma (65)
- Smoking, diabetes, hypertension, alcohol abuse & depression.

2.) Gynecomastia: The increase in the size of breast tissue in men is referred to gynecomastia due to abnormal hormonal balance.

• Causes: Hypogonadism, thyroid disease, malnutrition, testicular cancer, adrenal gland cancer, liver and kidney disease.

#Nervous system:

* Parkinson's disease | Parkinsonism: It is an "extrapyramidal motor disorder" and chronic neurological old age disease in basal ganglia. (Dopamine ↓, Ach ↑)

e. It is a chronic degenerative disorder that primarily affects the neurons of the basal ganglia.

• Sign and Symptoms:
- Abnormality in the posture and movement.
- Pill rolling movement with very high amplitude and low frequency.
- Involuntary tremors (Shaking)
- Muscular rigidity (Cogwheel rigidity)
- Hypokinesia (a weak and imperfect response of a muscle to stimuli) with 2° manifestations (symptoms) [i.e., Bradykinesia (slowness of movement), weakness tremor and rigidity contribute to it].
- Self contradictory loss or impairment of the power of voluntary movement.
- Diplomatic face (expressionless face).
- Defective posture
- Sialorrhea (excessive secretion of saliva) due to ↑ed acetyl choline level.
- Fronto-temporal dementia (without mind) (loss of memory for short period)

• Epidemiology: Parkinson disease affect 1% of the population over the age of 65 years.

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• **Aetiology:**

1) Heredity

2) Encephalitis infection in response to brain trauma, tumors, hydrocephalous or ischaemia.

3) Arteriosclerosis

4) Neurotoxins such as cyanide, manganese and carbon monoxide

5) **Drug induced parkinsonism:** Antipsychatic drugs (or neuroleptic drugs), drugs like reserpine, Metoclopromide, chlorpromazine, phenothiazine and Haloperidol blocks dopaminergic pathway in basal ganglia and leads to drug induced temporary parkinson disease.

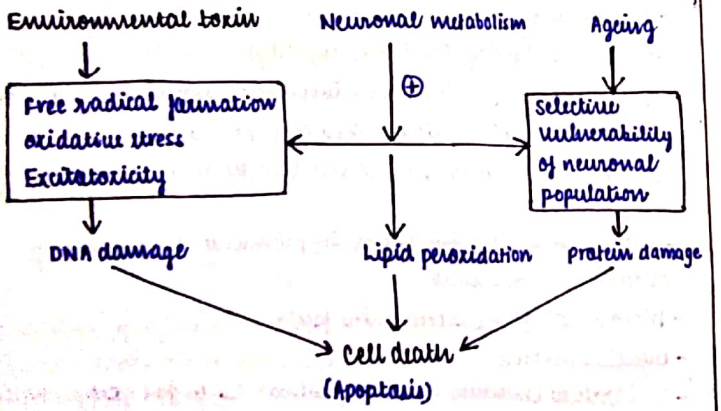

Fig: Mechanism of selective neuronal vulnerability in parkinsonism

• **Pathophysiology of parkinsonism:** Parkinsonism occurs due to the defect in dopaminergic pathway which results in deficiency of dopamine in nigrostriatal pathway [this pathway starts from substantia nigra pars compacta to neostriatum i.e. nucleus caudatess-putamen].

– Dopamine in stratum controls muscle tone and coordinate movement and imbalance b/w dopaminergic (inhibitory) and cholinergic (excitatory) neurotransmitter leads to motor defect.

Antipsychatic drugs, encephalitis & other causes
↓
Affects the substantia nigra
↓
Destruction of dopamine producing neurons within the basal ganglia
↓
Reduces the amount of available straital dopamine (inhibitory effects)
↓
Increase in acetylcholine level (excitatory effects).
↓
Excitatory activity of Ach is inadequately balanced.
↓
Difficulty in controlling & initiating valuntary movements.

Fig; Pathophysiology of parkinson's disease

• **Morphological change:** Atrophy in brain cells.

– Microscopically, depigmentation of substantia nigra and locus

cerulens due to the loss of neuromelanin pigment from neurons and accumulation of neuromelanin pigment in the glial cells.
- Some of the residual neurons in these areas contain intracytoplasmic, eosinophillic, elongated inclusions c/a Lewy bodies. The inclusions are composed of α-Synuclein.

(67)

* **Alzheimer's disease:** It is a "neurological disorder".
- It is characterized by 'deposition of senile plaques' mainly composed of (Fibrilogenic amyloid $\beta_{1\text{to}40/1\text{to}42}$) fragment in neocortex and formation of neurofibrillary tangles (NFTs) in hippocampus as a result of defect in cholinergic pathway (↓ level of Ach). Ach neurotransmitter is responsible for learning and memory.
- Loss of neurons & synapses in cerebral cortex. Degeneration of temporal, parietal, frontal lobe.

• **Symptoms:**
- Senile dementia (loss of memory of short period due to aging).
- Poor judgement
- Inability to concentrate.
- Loss of coordination.
- Personality change
- Confusion, fearfulness, Agitation.
- Emotional liability
- Deterioration of personal hygiene
- Impaired communication; Language problem (can't find right word or name for familiar person, object, place)
- Loss of sense of time and place

• **Aetiology:**
- Deficiency in acetyl choline or Nor-epinephrine.
- Exposure of Al and Mg.
- Repeated head trauma.
- Abnormality in chromosome 14 & 21.
- Deposition of β-amyloid protein.

• **Pathogenesis of Alzheimer's disease:** Two microscopic features are characteristics of Alzheimer's disease.
1) **Extracellular amyloid plaques:** consisting of amorphous extracellular deposits of amyloid-β protein.

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2.) **Neurofibrillary tangles:** Comprises of filaments of phosphorylated tau proteins.

- **Pathophysiology of alzheimer's disease:**

Cleared by β-Secretase / α-Secretase → Mutation of amyloid precursor protein (APP) on chromosome No 21.

↓

α secretase has two genes 1 & 2, when these undergoes mutation they lead to increased cleaving of α-secretase. Then fed cleaving of APP results in increased production of β-amyloid protein → Increased production of amyloid precursor protein (APP)

↓

Produces amyloid protein

↓

Accumulation of β-Amyloid protein (due to increased production of APP)

↓

Directly neurotoxin

↓

Accumulation of NFTs → Alzheimer's disease ← Loss of cholinergic nerve cells

↓

Loss of memory, Function & Cognition

Fig; Pathophysiology of alzheimer's disease

- **Morphological changes:** Bilateral atrophy in brain and reduced in weight of brain.

- Microscopic features are:

a.) Senile neuritic plaque is the most conspicuous lesion & consists of focal rounded eosinophilic areas which has a central core containing Aβ protein.

b) Amyloid angiopathy is deposition of same amyloid material in the vessel wall of the brain.

c.) Neurofibrillary tangles (NFTs) within cytoplasm of neurons.

d.) Granulovacuolar degeneration is presence of multiple small intraneuronal cytoplasmic vacuoles.

* **Schizophrenia:** It is the splitting of perception and interpretation from reality. It is a chronic, psychiatric brain disorder and a leading social economic burden, worldwide with lifetime prevalence that affect approximately 1% of the world population.

• **Symptoms of schizophrenia:** Symptoms of Schizophrenia is classified into 3 categories: positive, negative and cognitive symptoms. These are:

1) **Positive symptoms:** Positive symptoms occurs due to defect in occipetal lobe and a false perception or image forms). i.e.,
- **Hallucinations** (A perception of having seen, heard, touch, taste, smell, something that was not actual),
- **Delusions** (A false belief held despite of strong evidence against it),
- **Agitation** (nervous excitement i.e., shaking),
- **Stereotypy behaviour** (i.e.) aimless activity e.g., locomotor activity, and purposeless movement).

2) **Negative symptoms:** Negative symptoms occurs due to defect in limbic system e.g.,
- Social and emotional behaviour
- Lack of pleasure
- Lack of motivation

3) **Cognitive symptoms:** Impairment in attention and working memory (procedural memory means skill and habit i.e., driving, swimming etc).

• **Aetiology:** It includes:
a) Genetic factors
b) Nutritional deficiencies
c) Maternal stress and injections.
d) Growth retardation.

• **Pathophysiology of schizophrenia:** There is imbalance b/w dopamine (inhibitory neurotransmitters) and glutamate (excitatory nts):

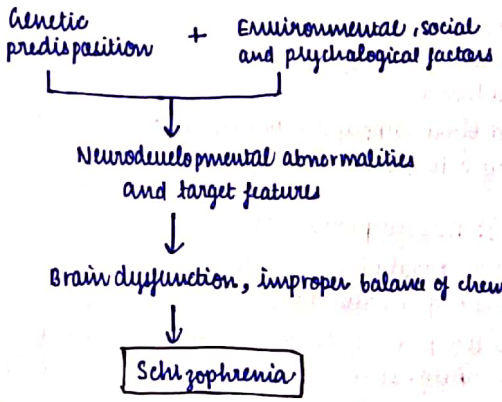


Fig: Nature of schizophrenia

- Pathophysiology of schizophrenia includes:
a) Reduction in grey matter and irregularities of white matter across brain areas.
b) Dopaminergic neurotransmitter dysfunction in beginning of hallucinations.

* **Stroke:** Stroke means "Cerebral ischaemia". Stroke is a "Focal neurological deficit" (damage to the brain from interruption of its blood supply).

- It is a sudden onset of weakness, numbness, paralysis, problem with vision and sudden interruption of blood flow to a particular area of the brain.

- **Aetiology:** This includes:
  - Primary cause is heart or blood vessel disease.
  - Hypertension
  - Atherosclerosis
  - Hyperlipidemia
  - Decreased blood supply due to thrombosis
  - Coronary artery disease (CAD).

- **Symptoms:** The symptoms of stroke involves:
  - **Hemiplegia** (paralysis of one side of the body alongwith disturbances of speech and vision).
  - **Coma** (It is a period of prolonged/ unconsciousness brought by illness or injury. It is a medical condition in which blood flow i.e, oxygen & nutrients to the brain result in cell mortality and disability in elder person. It last for longer than 24 hours).
  - Double vision
  - One side of face droopes or feel numbness.
  - Speech difficulty
  - Headache and vomiting.
  - Altered consciousness.
  - Muscle weakness on one side of the body
  - Difficulty in walking, speaking and understanding.
  - Loss of balance or coordination.
  - confusion, trouble in speaking.
  - Trouble in seeing with one or both eyes

- **Classification of stroke:** Stroke is classified into 2 categories:

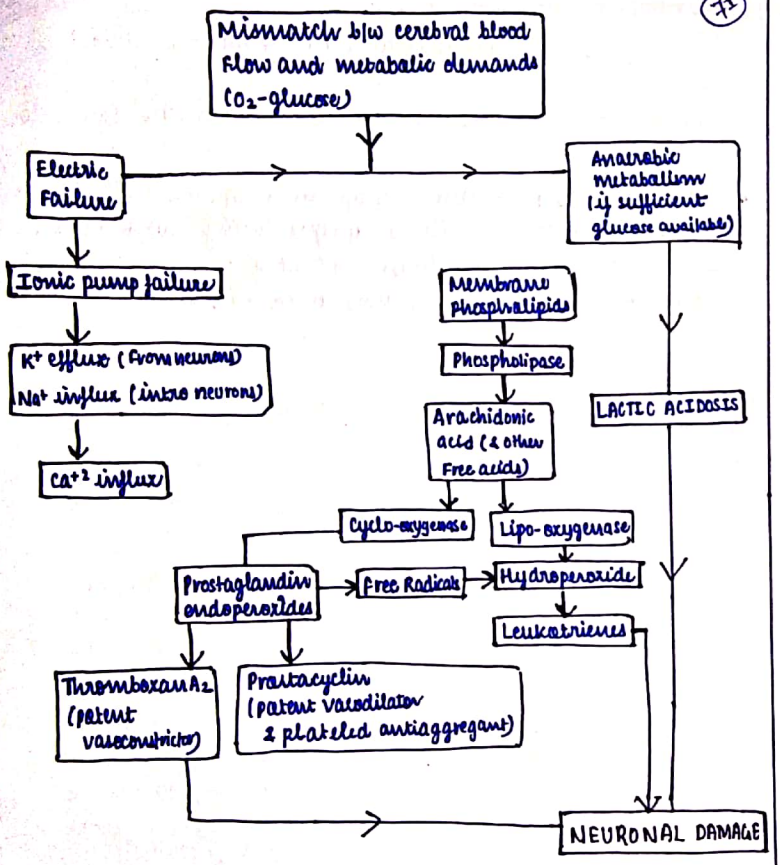
A) **Ischaemic stroke**, caused when a blood vessel supplying the brain is occluded by a clot. It is responsible for 75% of all strokes.

B) **Haemorrhagic stroke:** It is caused when a cerebral artery ruptures. It is of 2 types:

I) **Intracerebral hemorrhage:** Bleeding within brain itself due to intraventricular hemorrhage.

II) **Subarachnoid hemorrhage:** Bleeding outside the brain but within skull between arachnoid and pia mater

- **Pathophysiology of stroke:**
  - **For ischaemic stroke:** Ischaemic stroke occurs because of loss of blood supply to the part of brain. Brain tissues cease to function if deprived of O_2. Ischaemia also includes production of oxygen free radicals which reacts with and damage a no. of cellular and extracellular elements. It can also result in loss of structural integrity of brain tissues.
  - **For haemorrhagic stroke:** The causes of hemorrhagic stroke may be hypertension, drug induced bleeding. Tissue injury causes compression of tissues.



Fig; Pathophysiology of stroke

* **Epilepsy:** Epilepsy is a group of CNS disorder of cerebral cortex characterized by "paroxysmal cerebral dysrhythmia" brief episodes of loss of consciousness with or without characteristic body movements (convulsions).

- Epilepsy has a focal origin in brain manifestations depends upon the site of focus region in which discharge spread, depression, magnification and amplification of generated nerve impulses.
- Epilepsy is defined as a disorder of brain characterized by an enduring predisposition to generate epileptic seizure and by psychologic, cognitive and social consequence of this condition. The definition of epilepsy requires occurrence of at least one seizure.

- **Convulsions/Seizure:** It is transient alteration of behaviour due to disordered, synchronous and rhythmic firing of population of neurons in cerebral cortex.
- **Drug induced seizure:** Pentylene tetrazole (PTZ) is a chemical used for inducing seizure in experimental animal for screening of anti-epileptic drug.
- **Epidemiology of epilepsy:** Higher incidence is noticed in early childhood and in elder person. Low incidence of epilepsy occurs in early adult life.
- **Symptoms of epilepsy:** It includes Nausea, vomiting, sweating, flushing, dizziness, Illusions, Hallucinations, memory distortion, unproved fear & pleasure, depression & anger.
- **Aetiology:** It includes:
  - Head injury
  - Stroke
  - Tumour

- Meningitis
- Underdeveloped brain
- Genetics.

• **Mechanism of Epilepsy:** There are 3 mechanisms:

I:) **Prolongation of sodium channel inactivation:** Repetitive occasional sudden excessive firing of depolarised ~~nerve~~ neurons (discharge of grey matter) is noted due to sodium channel depolarisation.

II:) **Imbalance between GABA (γ-amino butyric acid) & Glutamate neurotransmitters:** There imbalance between ↓ GABA (inhibitory) and ↑ Glutamate (excitatory).

III:) **Voltage sensitive T-type calcium current:**

Thalamus (Low frequency T-type Ca^{+2} current generation) $\rightleftharpoons$ Neocortex (Glutamate (high frequency))

• **Classification of epilepsy:**

1:) **Specialized / Generalized seizures:** convulsive or not.

a:) **Absence seizure:** Loss of consciousness.

b:) **Myoclonic seizure:** Multiple spikes in EEG

c:) **Clonic seizures:** Clonic contraction of muscles.

d:) **Tonic seizure:** Autonomic manifestation

e:) **Tonic-clonic seizure:** Major convulsions.

f:) **Atonic seizure:** Loss of postural tone.

2:) **Partial seizures:** (Focal or Local)

a:) **Simple partial seizure:** It includes convulsions without consciousness.

b:) **Complex partial seizure:** Confused behaviour with consciousness.

• **Pathophysiology:** First visible symptom is repeated seizure due to malfunction of ion channels on synapse during neurotransmission.

- Chemical imbalance includes low level of Na, Ca, O_2, sugar and brain injury includes infection, stroke, tumors etc.

* **Depression:** Depression is the "mood disorder" characterized by persistently low mood and a feeling of sadness and loss of interest. It is persistent problem lasting on an average 6 to 8 months.

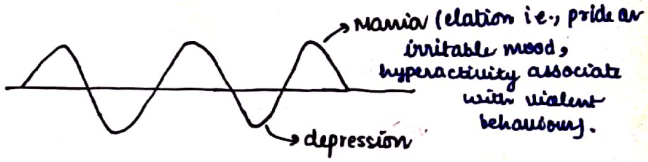
- **Types of depression:** 2 types:
  A) Major depressive disorder
  B) Bipolar disorder (Manic-depressive disorder).

A) **Major depressive disorder:** It is a common and serious medical illness, that negatively affects how one feels, the way one think and how one acts.

- It causes feeling of sadness or loss of interest in activities once enjoyed. It can lead to a variety of emotional and physical problems & can decrease a persons ability to function at work and at a home.
- Major depression is characterized by sad mood.
- **Symptoms:** sad mood, low energy, guilty, agitation, change in appetite (weight loss, gain weight unrelated to diet), Melancholia (It is a form of insanity (उन्माद)), suicidal thought (means ↑ed risk of self harm).

B) **Bipolar depression:** cycle of mood swing from 'mania' to depression occur over time commonly include disordered autonomic function e.g., change in rhythmic activity sleep and appetite and behaviour as well as persistent abnormality of mood & ↑ed risk of suicide.

- **Symptoms:** personality disorder includes characteristic personality style as a avoidant, paranoid state (it is a type of mental illness in which patient assumes itself), pattern of behaviour includes abuse of alcohol or narcotic substance, Hypochondriasis (↓ in interest in activity).



- **Causes of depression:**
  - Early childhood trauma
  - Drug and alcohol abuse
  - Chronic illness, insomnia.
  - Less activity of frontal lobe of brain.
  - Stressful events.

- **Neurochemical changes during depression:**
  1) **Serotonin (5HT):** It is located in the group of neurons (serotonergic neurons) in Raphe region of pons and upper brain stem, which has widespread projections to the forebrain and is implicated in the regulation of sleep & wakefulness.
  2) Decreased level of Biogenic amines (nor-epinephrin, epinephrin)
  3) Brain derived neurotrophic factor (BDNF) ⇒ ↓ level in hippocampus
  4) Cortisol hormone is responsible for regulation of stress ⇒ ↑ed level