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ANAEMIA—GENERAL CONSIDERATIONS

Anaemia is defined as a haemoglobin concentration in blood below the lower limit of the normal range for the age and sex of the individual. In adults, the lower extreme of the normal haemoglobin is taken as 13.0 g/dl for males and 11.5 g/dl for females. Newborn infants have higher haemoglobin level and, therefore, 15 g/dl is taken as the lower limit at birth, whereas at 3 months the normal lower level is 9.5 g/dl. Although haemoglobin value is employed as the major parameter for determining whether or not anaemia is present, the red cell counts, haematocrit (PCV) and absolute values (MCV, MCH and MCHC) provide alternate means of assessing anaemia.

Pathophysiology of Anaemia

Subnormal level of haemoglobin causes lowered oxygencarrying capacity of the blood. This, in turn, initiates compensatory physiologic adaptations such as follows:

Increased release of oxygen from haemoglobin;

Increased blood flow to the tissues; maintenance of the blood volume; and

Redistribution of blood flow to maintain the cerebral blood supply.

Clinical Features of Anaemia

The haemoglobin level at which symptoms and signs of anaemia develop depends upon 4 main factors:
1. The speed of onset of anaemia: Rapidly progressive anaemia causes more symptoms than anaemia of slow-onset as there is less time for physiologic adaptation.

2. The severity of anaemia: Mild anaemia produces no symptoms or signs but a rapidly developing severe anaemia (haemoglobin below 6.0 g/dl) may produce significant clinical features.

3. The age of the patient: The young patients due to good cardiovascular compensation tolerate anaemia quite well as compared to the elderly. The elderly patients develop cardiac and cerebral symptoms more prominently due to associated cardiovascular disease.

4. The haemoglobin dissociation curve: In anaemia, the affinity of haemoglobin for oxygen is depressed as 2,3-BPG in the red cells increases. As a result, oxyhaemoglobin is dissociated more readily to release free oxygen for cellular use, causing a shift of the oxyhaemoglobin dissociation curve to the right.

SYMPTOMS.

In symptomatic cases of anaemia, the presenting features are: tiredness, easy fatiguability, generalised muscular weakness, lethargy and headache. In older patients, there may be symptoms of cardiac failure, angina pectoris, intermittent claudication, confusion and visual disturbances.

Classification of Anaemias several types of classifications of anaemias have been proposed. Two of the widely accepted classifications are based on the pathophysiology and morphology (Table 12.3). PATHOPHYSIOLOGIC CLASSIFICATION.

Depending upon the pathophysiologic mechanism, anaemias are classified into 3 groups:

I. Anaemia due to blood loss. This is further of 2 types:

A. Acute post-haemorrhagic anaemia

B. Anaemia of chronic blood loss

II. Anaemiadue to impaired red cell formation. A disturbance due to impaired red cell production from various causes may produce anaemia. These are as under:

A. Cytoplasmic maturation defects 1. Deficient haem synthesis: iron deficiency anaemia 2. Deficient globin synthesis: thalassaemic syndromes

B. Nuclear maturation defects Vitamin B12 and/or folic acid deficiency: megaloblastic anaemia

C. Haematopoietic stem cell proliferation and differentiation abnormality e.g. 1. Aplastic anaemia 2. Pure red cell aplasia

D. Bone marrow failure due to systemic diseases (anaemia of chronic disorders) e.g. 1. Anaemia of inflammation/infections, disseminated malignancy 2. Anaemia in renal disease 3. Anaemia due to endocrine and nutritional deficiencies (hypometabolic states) 4. Anaemia in liver disease

E. Bone marrow infiltration e.g. 1. Leukaemias 2. Lymphomas 3. Myelosclerosis 4. Multiple myeloma

F. Congenital anaemia e.g. 1. Sideroblastic anaemia 2. Congenital dyserythropoietic anaemia.

MORPHOLOGIC CLASSIFICATION. Based on the red cell size, haemoglobin content and red cell indices, anaemias are classified into 3 types:

1. Microcytic, hypochromic: MCV, MCH, MCHC are all reduced e.g. in iron deficiency anaemia and in certain noniron deficient anaemias (sideroblastic anaemia, thalassaemia, anaemia of chronic disorders).

2. Normocytic, normochromic: MCV, MCH, MCHC are all normal e.g. after acute blood loss, haemolytic anaemias, bone marrow failure, anaemia of chronic disorders.

3. Macrocytic: MCV is raised e.g. in megaloblastic anaemia due to deficiency of vitamin B12 or folic acid.

IRON DEFICIENCY ANAEMIA

The commonest nutritional deficiency disorder present throughout the world is iron deficiency but its prevalence is higher in the developing countries. The factors responsible for iron deficiency in different populations are variable and are best understood in the context of normal iron metabolism.

Pathogenesis

Iron deficiency anaemia develops when the supply of iron is inadequate for the requirement of haemoglobin synthesis. Initially, negative iron balance is covered by mobilisation from the tissue stores so as to maintain haemoglobin synthesis. It is only after the tissue stores of iron are exhausted that the supply of iron to the marrow becomes insufficient for haemoglobin formation and thus a state of iron deficiency anaemia develops. The development of iron deficiency depends upon one or more of the following factors:

1. Increased blood loss

2. Increased requirements

3. Inadequate dietary intake

4. Decreased intestinal absorption.

Etiology

1. FEMALES IN REPRODUCTIVE PERIOD OF LIFE. The highest incidence of iron deficiency anaemia is in women during their reproductive years of life. It may be from one or more of the following causes:

i) Blood loss. This is the most important cause of anaemia in women during child-bearing age group. Commonly, it is due to persistent and heavy menstrual blood loss such as occurs in various pathological states and due to insertion of IUCDs. Young girls at the onset of menstruation may develop mild anaemia due to blood loss. Significant blood loss may occur as a result of repeated miscarriages.

ii) Inadequate intake. Inadequate intake of iron is prevalent in women of lower economic status. Besides diet deficient in iron, other factors such as anorexia, impaired absorption and diminished bioavailability may act as contributory factors. iii) Increased requirements. During pregnancy and adolescence, the demand of body for iron is increased. During a normal pregnancy, about 750 mg of iron may be siphoned off from the mother—about 400 mg to the foetus, 150 mg to the placenta, and 200 mg is lost at parturition and lactation. If several pregnancies occur at short intervals, iron deficiency anaemia certainly follows.

2. POST-MENOPAUSAL FEMALES. Though the physiological demand for iron decreases after cessation of menstruation, iron deficiency anaemia may develop in postmenopausal women due to chronic blood loss. Following are among the important causes during these years: i) Post-menopausal uterine bleeding due to carcinoma of the uterus. ii) Bleeding from the alimentary tract such as due to carcinoma of stomach and large bowel and hiatus hernia.

3. ADULT MALES. It is uncommon for adult males to develop iron deficiency anaemia in the presence of normal dietary iron content and iron absorption. The vast majority of cases of iron deficiency anaemia in adult males are due to chronic blood loss. The cause for chronic haemorrhage may lie at one of the following sites: i) Gastrointestinal tract is the usual source of bleeding which may be due to peptic ulcer, haemorrhoids, hookworm infestation, carcinoma of stomach and large bowel, oesophageal varices, hiatus hernia, chronic aspirin ingestion and ulcerative colitis. Other causes in the GIT are malabsorption and following gastrointestinal surgery. ii) Urinary tract e.g. due to haematuria and haemoglobinuria. iii) Nose e.g. in repeated epistaxis. iv) Lungs e.g. in haemoptysis from various causes.

4. INFANTS AND CHILDREN. Iron deficiency anaemia is fairly common during infancy and childhood with a peak incidence at 1-2 years of age. The principal cause for anaemia at this age is increased demand of iron which is not met by the inadequate intake of iron in the diet. Normal full-term infant has sufficient iron stores for the first 4-6 months of life, while premature infants have inadequate reserves because iron stores from the mother are mainly laid down during the last trimester of pregnancy. Therefore, unless the infant is given supplemental feeding of iron or ironcontaining foods, iron deficiency anaemia develops.

Clinical Features

1. ANAEMIA
2. EPITHELIAL TISSUE CHANGES

MEGALOBLASTIC ANAEMIA

The megaloblastic anaemias are disorders caused by impaired DNA synthesis and are characterised by a distinctive abnormality in the haematopoietic precursors in the bone marrow in which the maturation of the nucleus is delayed relative to that of the cytoplasm. Since cell division is slow but cytoplasmic development progresses normally, the nucleated red cell precursors tend to be larger which Ehrlich in 1880 termed megaloblasts. 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.

Etiology and Classification of Megaloblastic Anaemia

I. VITAMIN B12 DEFICIENCY

A. Inadequate dietary intake e.g. strict vegetarians, breast-fed infants.

B. Malabsorption

1. Gastric causes: pernicious anaemia, gastrectomy, congenital lack of intrinsic factor.

2. Intestinal causes: tropical sprue, ileal resection, Crohn's disease, intestinal blind loop syndrome, fish-tapeworm infestation.

II. FOLATE DEFICIENCY

A. Inadequate dietary intake e.g. in alcoholics, teenagers, infants, old age, poverty.

B. Malabsorption e.g. in tropical sprue, coeliac disease, partial gastrectomy, jejunal resection, Crohn's disease.

C. Excess demand

1. Physiological: pregnancy, lactation, infancy.

2. Pathological : malignancy, increased haematopoiesis, chronic exfoliative skin disorders, tuberculosis, rheumatoid arthritis.

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

III. OTHER CAUSES

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

B. Unknown etiology e.g. in Di Guglielmo's syndrome, congenital dyserythropoietic anaemia, refractory megaloblastic anaemia.

Clinical Features

Deficiency of vitamin B12 and folate may cause following clinical manifestations which may be present singly or in combination and in varying severity:

1. Anaemia. Macrocytic megaloblastic anaemia is the cardinal feature of deficiency of vitamin B12 and/or folate. The onset of anaemia is usually insidious and gradually progressive.

2. Glossitis. Typically, the patient has a smooth, beefy, red tongue.

3. Neurologic manifestations. Vitamin B12 deficiency, particularly in patients of pernicious anaemia, is associated with significant neurological manifestations in the form of subacute combined, degeneration of the spinal cord and peripheral neuropathy, while folate deficiency may occasionally develop neuropathy only. The underlying pathologic process consists of demyelination of the peripheral nerves, the spinal cord and the cerebrum. Signs and symptoms include numbness, paraesthesia, weakness, ataxia, poor finger coordination and diminished reflexes.

4. Others. In addition to the cardinal features mentioned above, patients may have various other symptoms. These include: mild jaundice, angular stomatitis, purpura, melanin pigmentation, symptoms of malabsorption, weight loss and anorexia.

Sickle Cell Anaemia

Sickle cell anaemia (SS) is a homozygous state of HbS in the red cells in which an abnormal gene is inherited from each parent. SS is a severe disorder associated with protean clinical manifestations and decreased life expectancy.

PATHOGENESIS.

1.Basic molecular lesion: In HbS, basic genetic defect is the single point mutation in one amino acid out of 146 in haemoglobin molecule— there is substitution of valine for glutamic acid at 6-residue position of the β-globin, producing Hb $\alpha_2\beta_2^s$.

2.Mechanism of sickling: During deoxygenation, the red cells containing HbS change from biconcave disc shape to an elongated crescent-shaped or sickle-shaped cell. This process termed sickling occurs both within the intact red cells and in vitro in free solution. The mechanism responsible for sickling upon deoxygenation of HbS-containing red cells is the polymerisation of deoxygenated HbS which aggregates to form elongated rod-like polymers. These elongated fibres align and distort the red cell into classic sickle shape.

3. Reversible-irreversible sickling: The oxygen-dependent sickling process is usually reversible. However, damage to red cell membrane leads to formation of irreversibly sickled red cells even after they are exposed to normal oxygen tension.

4.Factors determining rate of sickling: Following factors determine the rate at which the polymerisation of HbS and consequent sickling take place: i) Presence of non-HbS haemoglobins: The red cells in patients of SS have predominance of HbS and a small part consists of non-HbS haemoglobins, chiefly HbF (2-20% of the total haemoglobin). HbF-containing red cells are protected from sickling while HbA-containing red cells participate readily in co-polymerisation with HbS. ii) Intracellular concentration of HbS. iii) Total haemoglobin concentration. iv) Extent of deoxygenation. v) Acidosis and dehydration. vi) Increased concentration of 2, 3-BPG in the red cells.

CLINICAL FEATURES.

The clinical manifestations of homozygous sickle cell disease are widespread. The symptoms begin to appear after 6th month of life when most of the HbF is replaced by HbS. Infection and folic acid deficiency result in more severe clinical manifestations. These features are as under:

1. Anaemia. There is usually severe chronic haemolytic anaemia (primarily extravascular) with onset of aplastic crisis in between. The symptoms of anaemia are generally mild since HbS gives up oxygen more readily than HbA to the tissues.

2. Vaso-occlusive phenomena. Patients of SS develop recurrent vaso-occlusive episodes throughout their lives due to obstruction to capillary blood flow by sickled red cells upon deoxygenation or dehydration. Vaso-obstruction affecting different organs and tissues results in infarcts which may be of 2 types: i) Microinfarcts affecting particularly the abdomen, chest, back and joints and are the cause of recurrent painful crises in SS. ii) Macroinfarcts involving most commonly the spleen (splenic sequestration, autosplenectomy), bone marrow (pains), bones (aseptic necrosis, osteomyelitis), lungs (pulmonary infections), kidneys (renal cortical necrosis), CNS (stroke), retina (damage) and skin (ulcers), and result in anatomic and functional damage to these organs.

3. Constitutional symptoms. In addition to the features of anaemia and infarction, patients with SS have impaired growth and development and increased susceptibility to infection due to markedly impaired splenic function.

THALASSAEMIAS

The thalassaemias are a diverse group of hereditary disorders in which there is reduced synthesis of one or more of the globin polypeptide chains. Thus, thalassaemias, unlike haemoglobinopathies which are qualitative disorders of haemoglobin, are quantitative abnormalities of polypeptide globinchain synthesis. Thalassaemias were first described in people of Mediterranean countries (North Africa, Southern Europe) from where it derives its name 'Mediterranean anaemia.'

The Word 'thalassa' in Greek means 'the sea' since the condition was found commonly in regions surrounding the Mediterranean sea. The condition also occurs in the Middle East, Indian subcontinent, South-East Asia and, in general in blacks.

PATHOPHYSIOLOGY OF ANAEMIA IN THALASSAEMIA

A constant feature of all forms of thalassaemia is the presence of anaemia which occurs from following mechanisms:

α-Thalassaemia: In α-thalassaemia major, the obvious cause of anaemia is the inability to synthesise adult haemoglobin, while in α-thalassaemia trait there is reduced production of normal adult haemoglobin.

β-Thalassaemia: In β-thalassaemia major, the most important cause of anaemia is premature red cell destruction brought about by erythrocyte membrane damage caused by the precipitated α-globin chains. Other contributory factors are: shortened red cell lifespan, ineffective erythropoiesis, and haemodilution due to increased plasma volume.

CLINICAL FEATURES.

Hb Bart's hydrops foetalis is incompatible with life due to severe tissue hypoxia. The condition is either fatal in utero or the infant dies shortly after birth. If born alive, the features similar to severe Rh haemolytic disease are present.

Herediatory acquired aneamia

The abnormalities of red cell membrane are readily identified on blood film examination. There are 3 important types of inherited red cell membrane defects: hereditary spherocytosis, hereditary elliptocytosis (hereditary ovalocytosis) and hereditary stomatocytosis.

PATHOGENESIS.

The molecular abnormality in hereditary spherocytosis is a defect in proteins which anchor the lipid bilayer to the underlying cytoskeleton.

1. Spectrin deficiency. Almost all cases have deficiency in the structural protein of the red cell membrane, spectrin. Spectrin deficiency correlates with the severity of anaemia. Mutation in spectrin by recessive inheritance called α− spectrin causes more severe form of anaemia, while mutation by dominant inheritance forming β -spectrin results in mild form of the disease.

2. Ankyrin abnormality.About half the cases of hereditary spherocytosis have defect in ankyrin, protein that binds protein 3 and spectrin. Homozygous state with recessive inheritance pattern has severe anaemia while heterozygotes with more common dominant inheritance pattern have milder anaemia. Inherited mutation in spectrin or ankyrin causes defect in anchoring of lipid bilayer cell membrane. Red cells with such unstable membrane but with normal volume, when released in circulation, lose their membrane further, till they can accommodate the given volume. This results in formation of spheroidal contour and smaller size of red blood cells, termed microspherocytes. These deformed red cells are not flexible, unlike normal biconcave red cells. These rigid cells are unable to pass through the spleen, and in the process they lose their surface membrane further. This produces a subpopulation of hyperspheroidal red cells in the peripheral blood which are subsequently destroyed in the spleen.

CLINICAL FEATURES.

The disorder may be clinically apparent at any age from infancy to old age and has equal sex incidence. The family history may be present. The major clinical features are as under:

1. Anaemia is usually mild to moderate.

2. Splenomegaly is a constant feature.

3. Jaundice occurs due to increased concentration of unconjugated (indirect) bilirubin in the plasma (also termed congenital haemolytic jaundice).

4. Pigment gallstones are frequent due to increased bile pigment production. Splenectomy offers the only reliable mode of treatment.

haemophilia

Classic haemophilia or haemophilia A is the second most common hereditary coagulation disorder next to von Willebrand's disease occurring due to deficiency or reduced activity of factor VIII (anti-haemophilic factor). The disorder is inherited as a sex-(X-) linked recessive trait and, therefore, manifests clinically in males, while females are usually the carriers. However, occasional women carriers of haemophilia may produce factor VIII levels far below 50% and become symptomatic carriers, or rarely there may be true female haemophilics arising from consanguinity within the family (i.e. homozygous females). The chances

of a proven carrier mother passing on the abnormality to her children is 50:50 for each son and 50:50 for each daughter.

A haemophilic father will have normal sons as they inherit his Y chromosome only that does not carry the genetic abnormality. The disease has been known since ancient times but Schönlein in 1839 gave this bleeder's disease its present name haemophilia. In 1952, it was found that haemophilia was not always due to deficiency of factor VIII as was previously considered but instead blood of some patients was deficient in factor IX (Christmas factor or plasma thromboplastin component). Currently, haemophilia A (classic haemophilia) is the term used for the disorder due to factor VIII deficiency, and haemophilia B (Christmas disease) for the disorder when factor IX is deficient.

The frequency of haemophilia varies in different races, the highest incidence being in populations of Britain, Northern Europe and Australia. Western literature reports give an overall incidence of haemophilia in 1 in 10,000 male births. Another interesting facet of the haemophilia which has attracted investigators and researchers is the occurrence of this disorder in the blood of royal families in Great Britain and some European countries.

PATHOGENESIS.

Haemophilia A is caused by quantitative reduction of factor VIII in 90% of cases, while 10% cases have normal or increased level of factor VIII with reduced activity. Factor VIII is synthesised in hepatic parenchymal cells and regulates the activation of factor X in intrinsic coagulation pathway. Factor VIII circulates in blood complexed to another larger protein, von Willebrand's factor (vWF), which comprises 99% of the factor VIII-vWF complex.

The genetic coding, synthesis and functions of vWF are different from those of factor VIII and are considered separately below under von Willebrand's disease. Normal haemostasis requires 25% factor VIII activity. Though occasional patients with 25% factor VIII level may develop bleeding, most symptomatic haemophilic patients have factor VIII levels below 5%.

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 intracranial haemorrhage and oropharyngeal bleeding are rare, but when they occur they are the most feared complications.

DIABETES MELLITUS

Definition and Epidemiology As per the WHO, diabetes mellitus (DM) is defined as a hetrogeneous metabolic disorder characterised by common feature of chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism. DM is a leading cause of morbidity and mortality world over. It is estimated that approximately 1% of population suffers from DM. The incidence is rising in the developed countries of the world at the rate of about 10% per year, especially of type 2 DM, due to rising incidence of obesity and reduced activity levels. DM is expected to continue as a major health problem owing to its serious complications, especially end-stage renal disease, IHD, gangrene of the lower

extremities, and blindness in the adults. It is anticipated that the number of diabetics will exceed 250 million by the year 2010.

Classification and Etiology

The older classification systems dividing DM into primary (idiopathic) and secondary types, juvenile-onset and maturity onset types, and insulin-dependent (IDDM) and non-insulin dependent (NIDDM) types, have become obsolete and undergone major revision due to extensive understanding of etiology and pathogenesis of DM in recent times.

Pathogenesis

Depending upon etiology of DM, hyperglycaemia may result from the following:

1. Reduced insulin secretion

2. Decreased glucose use by the body

3. Increased glucose production.

PATHOGENESIS OF TYPE 1 DM. The basic phenomenon in type 1 DM is destruction of β -cell mass, usually leading to absolute insulin deficiency. While type 1B DM remains idiopathic, pathogenesis of type 1A DM is immune-mediated and has been extensively studied. Currently, pathogenesis of type 1A DM is explained on the basis of 3 mutually-interlinked mechanisms: genetic susceptibility, autoimmune factors, and certain environmental factors .

1. Genetic susceptibility. Type 1A DM involves inheritance of multiple genes to confer susceptibility to the disorder: i) It has been observed in identical twins that if one twin has type 1A DM, there is about 50% chance of the second twin developing it, but not all. This means that some additional modifying factors are involved in development of DM in these cases. ii) About half the cases with genetic predisposition to type 1A DM have the susceptibility gene located in the HLA region of chromosome 6 (MHC class II region), particularly HLA DR3, HLA DR4 and HLA DQ locus.

2. Autoimmune factors. Studies on humans and animal models on type 1A DM have shown several immunologic abnormalities.

3. Environmental factors. Epidemiologic studies in type 1A DM suggest the involvement of certain environmental factors in its pathogenesis, though role of none of them has been conclusively proved. In fact, the trigger may precede the occurrence of the disease by several years. It appears that certain viral and dietary proteins share antigenic properties with human cell surface proteins and trigger the immune attack on β-cells by a process of molecular mimicry. These factors include the following:

i) Certain viral infections preceding the onset of disease e.g. mumps, measles, coxsackie B virus, cytomegalovirus and infectious mononucleosis.

ii) Experimental induction of type 1A DM with certain chemicals has been possible e.g. alloxan, streptozotocin and pentamidine.

Complications of Diabetes

As a consequence of hyperglycaemia of diabetes, every tissue and organ of the body undergoes biochemical and structural alterations which account for the major complications in diabetics which may be acute metabolic or chronic systemic. Both types of diabetes mellitus may develop complications which are broadly divided into 2 major groups:

I. Acute metabolic complications: These include diabetic ketoacidosis, hyperosmolar nonketotic coma, and hypoglycaemia.
II. Late systemic complications: These are atherosclerosis, diabetic microangiopathy, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and infections.

Complication

- Diabetic ketoacidosis
- Hyperosmolar hyperglycaemic nonketotic coma
- Hypoglycaemia
- Atherosclerosis
- Diabetic microangiopathy
- Diabetic nephropathy.
- Diabetic neuropathy.
- Diabetic retinopathy.
- Infections. Diabetics have enhanced susceptibility to various infections such as tuberculosis, pneumonias, pyelonephritis, otitis, carbuncles and diabetic ulcers. This could be due to various factors such as impaired leucocyte functions, reduced cellular immunity, poor blood supply due to vascular involvement and hyperglycaemia per se.

HYPERTHYROIDISM (THYROTOXICOSIS)

Hyperthyroidism, also called thyrotoxicosis, is a hypermetabolic clinical and biochemical state caused by excess production of thyroid hormones. The condition is more frequent in females and is associated with rise in both T3 and T4 levels in blood, though the increase in T3 is generally greater than that of T4.

ETIOPATHOGENESIS. Hyperthyroidism may be caused by many diseases but three most common causes are: Graves' disease (diffuse toxic goitre), toxic multinodular goitre and a toxic adenoma. Less frequent causes are hypersecretion of pituitary TSH by a pituitary tumour, hypersecretion of TRH, thyroiditis, metastatic tumours of the thyroid, struma ovarii, congenital hyperthyroidism in the newborn of mother with Graves' disease, hCG-secreting tumours due to mild thyrotropic effects of hCG (e.g. hydatidiform mole, choriocarcinoma and testicular tumours), and lastly, by excessive doses of thyroid hormones or iodine called jodbasedow disease.

CLINICAL FEATURES. Patients with hyperthyroidism have a slow and insidious onset, varying in severity from case to case. 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. The skin of these patients is warm, moist and flushed. Weakness of skeletal muscles and osteoporosis are common. Typical eye changes in the form of exophthalmos are a common feature in Graves' disease. Serum levels of T3 and T4 are elevated but TSH secretion is usually inhibited.

HYPOTHYROIDISM

Hypothyroidism is a hypometabolic clinical state resulting from inadequate production of thyroid hormones for prolonged periods, or rarely, from resistance of the peripheral tissues to the effects of thyroid hormones. The clinical manifestations of hypothyroidism, depending upon the age at onset of disorder, are divided into 2 forms:

1. Cretinism or congenital hypothyroidism is the development of severe hypothyroidism during infancy and childhood.

2. Myxoedema is the adulthood hypothyroidism.

Cretinism

A cretin is a child with severe hypothyroidism present at birth or developing within first two years of postnatal life. This is the period when brain development is taking place; in the absence of treatment the child is both physically and mentally retarded. The word 'Cretin' is derived from the French, meaning Christ-like because these children are so mentally retarded that they are incapable of committing sins.

ETIOPATHOGENESIS. The causes of congenital hypothyroidism are as follows:

1. Developmental anomalies e.g. thyroid agenesis and ectopic thyroid.

2. Genetic defect in thyroid hormone synthesis e.g. defect in iodine trapping, oxidation, iodination, coupling and thyroglobulin synthesis.

3. Foetal exposure to iodides and antithyroid drugs.

4. Endemic cretinism in regions with endemic goitre due to dietary lack of iodine (sporadic cretinism, on the other hand, is due to developmental anomalies and genetic defects in thyroid hormone synthesis described above).

CLINICAL FEATURES.

The clinical manifestations usually become evident within a few weeks to months of birth. The presenting features of a cretin are: slow to thrive, poor feeding, constipation, dry scaly skin, hoarse cry and bradycardia. As the child ages, clinical picture of fullydeveloped cretinism emerges characterised by impaired skeletal growth and consequent dwarfism, round face, narrow forehead, widely-set eyes, flat and broad nose, big protuberant tongue and protuberant abdomen.

Neurological features such as deaf-mutism, spasticity and mental deficiency are more evident in sporadic cretinism due to developmental anomalies and dyshormonogenetic defects. Characteristic laboratory findings include a rise in TSH level and fall in T3 and T4 levels.

Myxoedema

The adult-onset severe hypothyroidism causes myxoedema. The term myxoedema connotes non-pitting oedema due to accumulation of hydrophilic mucopolysaccharides in the ground substance of dermis and other tissues.

ETIOPATHOGENESIS.

There are several causes of myxoedema listed below but the first two are the most common causes:

1. Ablation of the thyroid by surgery or radiation.

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

3. Endemic or sporadic goitre.

4. Hypothalamic-pituitary lesions.

5. Thyroid cancer.

6. Prolonged administration of antithyroid drugs.

7. Mild developmental anomalies and dyshormonogenesis.

CLINICAL FEATURES.

The onset of myxoedema is slow and a fully-developed clinical syndrome may appear after several years of hypothyroidism. The striking features are cold intolerance, mental and physical lethargy, constipation, slowing of speech and intellectual function, puffiness of face, loss of hair and altered texture of the skin. The laboratory diagnosis in myxoedema is made by low serum T3 and T4 levels and markedly elevated TSH levels as in the case of cretinism but cases with suprathyroid lesions (hypothalamic-pituitary disease) have low TSH levels.