МИНИСТЕРСТВО ОБРАЗОВАНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ

УО «ВИТЕБСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»

Кафедра патологической анатомии с курсом судебной медицины

И.В.Самсонова, В.А.Клопова

ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ
Курс лекций
Часть II. Частная патология

I.V.Samsonova, V.A.Klopova

PATHOLOGICAL ANATOMY
Lecture course
Part II. Systemic pathology

учебно-методическое пособие

Рекомендовано учебно-методическим объединением по высшему медицинскому, фармацевтическому образованию в качестве учебно-методического пособия для студентов учреждений высшего образования, обучающихся по специальности 1-79 01 01 «Лечебное дело»

Витебск
2020

УДК 616-091.8(07)
ББК 52.517я73
S 19

Рецензенты: к.м.н., доцент, заместитель начальника УЗ «ВОКПАБ» С.В.Малашенко;
кафедра патологической анатомии с курсом судебной медицины УО «Гомельский государственный медицинский университет»

Самсонова, И.В.

S 19 ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ. Курс лекций. Часть II. Частная патология. = Pathological anatomy. Lecture course. Part II. Systemic pathology. I.V.Samsonova, V.A.Klopova. – Vitebsk, VSMU, 2020. – 493 p.

ISBN 978-985-466-911-3

The contents of the textbook “Pathological Anatomy. Lecture Course. Part II. Systemic Pathology” corresponds with the basic educational plan and program proved by Ministry of the Health Care of Republic of Belarus in 2015.

Most essential topics covering the complete course of pathological anatomy are represented in the textbook.

The lecture course is prepared for students of medical faculties of high medical educational establishments.

УДК 616-091.8(07)
ББК 52.517-я73

ISBN 978-985-466-911-3

DISEASES OF BLOOD

ANAEMIAS

Anaemia is defined as a haemoglobin and/ or erythrocytes 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.

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

I. Anaemias due to blood loss.

1. Acute post-haemorrhagic anaemia.

2. Chronic post-haemorrhagic anaemia.

II. Anaemia due to impaired red cell production. 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 B_{12} 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 infections
2. Anaemia in renal disease
3. Anaemia in liver disease
4. Disseminated malignancy
5. Endocrinopathies

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

III. Anaemia due to increased red cell destruction (haemolytic anaemias). This is further divided into 2 groups:

1. Haemolytic anaemias due to intravascular haemolysis.
   a) toxic,
   b) infectious,
   c) posttransfusion,
   d) immune.
2. Haemolytic anaemias due to exravascular haemolysis mainly (Hereditary, intracorpusculae).
   a) abnormalities of red cell membrane,
   b) red cell enzyme defects,
   c) disorders of haemoglobin.

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 non-iron 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 B_{12} or folic acid.

ANAEMIA OF BLOOD LOSS

Depending upon the rate of blood loss due to haemorrhage, the effects of post-haemorrhagic anaemia appear.

ACUTE BLOOD LOSS. When the loss of blood occurs suddenly, the following events take place:

i) Immediate threat to life due to hypovolaemia which may result in shock and death.

ii) If the patient survives, shifting of interstitial fluid to intravascular compartment with consequent haemodilution with low haematocrit.

iii) Hypoxia stimulates production of erythropoietin resulting in increased marrow erythropoiesis.

CHRONIC BLOOD LOSS develops in slow but continuous blood loss (in bleeding from hemorrhoidal vein, uterine bleeding, and hemophilia). Skin becomes pale, bone marrow hyperplasia and extra medullary haemopoiesis are also seen. Metaplasia of yellow bone marrow into red bone marrow occurs in tube bones. Due to hypoxia fat dystrophy develops in parenchymatous organs (heart, liver).

When the loss of blood is slow and insidious, the effects of anaemia will become apparent only when the rate of loss is more than rate of produc-

tion and the iron stores are depleted. This results in iron deficiency anaemia as seen in other clinical conditions discussed below.

HYPOCHROMIC ANAEMIA

Hypochromic anaemiasare classified into 2 groups:

I. Hypochromic anaemia due to iron deficiency.

II. Hypochromic anaemias other than iron deficiency. The latter category includes 3 groups of disorders sideroblastic anaemia, thalassaemia and anaemia of chronic disorders.

IRON DEFICIENCY ANAEMIA

The commonest nutritional deficiency disorder present throughout the world is iron deficiency but its prevalence is higher in the developing countries.

Iron Metabolism

The amount of iron obtained from the diet should replace the losses from the skin, bowel and genitourinary tract. These losses together are about 1 mg daily in an adult male or in a non-menstruating female, while in a menstruating woman there is an additional iron loss of 0.5-1 mg daily. The iron required for haemoglobin synthesis is derived from 2 primary sources - ingestion of foods containing iron (e.g. leafy vegetables, beans, meats, liver etc) and recycling of iron from senescent red cells.

Absorption. Iron is absorbed mainly in the duodenum and proximal jejunum. Iron from diet containing haem is better absorbed than non-haem iron. Absorption of non-haem iron is enhanced by factors such as ascorbic acid (vitamin C), citric acid, amino acids, sugars, gastric secretions and hydrochloric acid. Iron absorption is impaired by factors like medicinal antacids, milk, pancreatic secretions, phytates, phosphates, ethylene diamine tetra-acetic acid (EDTA) and tannates contained in tea.

Non-haem iron is released as ferrous or ferric form but is absorbed almost exclusively as ferrous form. Iron balance in the body is maintained largely by regulating the absorptive intake by intestinal mucosal cells, so called mucosal block. The factors which determine this mucosal intelligence are unknown. When the demand for iron is increased (e.g. during pregnancy, menstruation, periods of growth and various diseases), there is increased iron absorption, while excessive body stores of iron cause reduced intestinal iron absorption.

Distribution. In an adult, iron is distributed in the body as under:

1. Haemoglobin – present in the red cells, contains most of the body iron (65%).

2. Myoglobin – comprises a small amount of iron in the muscles (3.5%).

3. Haem and non-haem enzymes – e.g. cytochrome, catalase, peroxidases, succinic dehydrogenase and flavoproteins constitute a fraction of total body iron (0.5%).

4. Transferrin-bound iron – circulates in the plasma and constitutes another fraction of total body iron (0.5%).

All these forms of iron are in functional form.

5. Ferritin and haemosiderin – are the storage forms of excess iron (30%). They are stored in the mononuclear-phagocyte cells of the spleen, liver and bone marrow and in the parenchymal cells of the liver.

Transport. Iron is transported in plasma bound to a (3-globulin, transferrin, synthesised in the liver. Transferrin-bound iron is made available to the marrow where the immature red cell precursors utilise iron for haemoglobin synthesis. Transferrin is reutilised after iron is released from it. A small amount of transferrin iron is delivered to other sites such as parenchymal cells of the liver. Normally, transferrin is about one-third saturated. But in conditions where transferrin-iron saturation is increased, parenchymal iron uptake is increased. Virtually, no iron is deposited in the mononuclear-phagocyte cells (RE cells) from the plasma transferrin-iron but instead these cells derive most of their iron from phagocytosis of senescent

red cells. Storage form of iron (ferritin and haemosiderin) in RE cells is normally not functional but can be readily mobilised in response to increased demands for erythropoiesis. However, conditions such as malignancy, infection and inflammation interfere with the release of iron from iron stores causing ineffective erythropoiesis.

Excretion. The body is unable to regulate its iron content by excretion alone. The amount of iron lost per day is 0.5-1 mg which is independent of iron intake. This loss is nearly twice more (i.e. 1-2 mg/day) in menstruating women. Iron is lost from the body as a result of desquamation of epithelial cells from the gastrointestinal tract, from excretion in the urine and sweat, and loss via hair and nails. Iron excreted in the faeces mainly consists of unabsorbed iron and desquamated mucosal cells.

Pathogenesis. Iron deficiency anaemia develops when the supply of iron is inadequate for the requirement of haemoglobin synthesis. Initially, the negative iron balance is made good 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 so that 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.

The relative significance of these factors varies with the age and sex of the patient. Accordingly, certain groups of individuals at increased risk of developing iron deficiency can be identified (see below). In general, in developed countries the mechanism of iron deficiency is usually due to chronic occult blood loss, while in the underdeveloped countries poor intake of iron or defective absorption are responsible for iron deficiency anaemia.

Etiology. Iron deficiency anaemia is always secondary to an underlying disorder. Based on the above mentioned pathogenetic mechanisms, the following etiologic factors are involved in development of iron deficiency anaemia at different age and sex:

1. Females in reproductive period of life. The highest incidence of iron deficiency anaemia is in women during their reproductive period 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 ILJCDs. 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 post-menopausal women due to chronic blood loss. Among the important causes are:

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. The 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 iron-containing foods, iron deficiency anaemia develops.

SIDEROBLASTIC ANAEMIA

The sideroblastic anaemias comprise a group of disorders of diverse etiology in which the nucleated erythroid precursors in the bone marrow, show characteristic 'ringed sideroblasts.'

TYPES OF SIDEROBLASTIC ANAEMIAS

Based on etiology, sideroblastic anaemias are classified into hereditary and acquired types. The acquired type is further divided into primary and secondary forms.

I. Hereditary sideroblastic anaemia. This is a rare X-linked disorder associated with defective enzyme activity of aminolevulinic acid (ALA) synthetase required for haem synthesis. The affected males have moderate to marked anaemia while the females are carriers of the disorder and do not develop anaemia. The condition manifests in childhood or in early adult life.

II. Acquired sideroblastic anaemia. The acquired sideroblastic anaemias are classified into primary and secondary types.

A. Primary acquired sideroblastic anaemia. Primary, idiopathic, or refractory acquired sideroblastic anaemia occurs spontaneously in middle-aged and older individuals of both sexes. The disorder has its pathogenesis in disturbed growth and maturation of erythroid precursors at the level of haematopoietic stem cell, possibly due to reduced activity of the enzyme, ALA synthetase. The anaemia is of moderate to severe degree and appears insidiously. The bone marrow cells commonly show chromosomal abnormalities, neutropenia and thrombocytopenia with associated bleeding diathesis. The spleen and liver may be either normal or mildly enlarged, while the lymph nodes are not enlarged. Unlike other types of sideroblastic anaemia, this type is regarded as a myelodysplastic disorder in the FAB (French-American-British) classification and thus, can be a preleukaemic disorder. About 10% of individuals with refractory acquired sideroblastic anaemia develop acute myelogenous leukaemia.

B. Secondary acquired sideroblastic anaemia. Acquired sideroblastic anaemia may develop secondary to a variety of drugs, chemicals, toxins, haematological and various other diseases.

1. Drugs, chemicals and toxins: Isoniazid, an antituberculous drug and a pyfidoxine antagonist, is most commonly associated with development of sideroblastic anaemia by producing abnormalities in pyridoxine metabolism. Other drugs occasionally causing acquired sideroblastic anaemia are: cycloserine, chloramphenicol and alkylating agents (e.g. cyclophosphamide). Alcohol and lead also cause sideroblastic anaemia. All these agents cause reversible sideroblastic anaemia which usually resolves following removal of the offending agent.

2. Haematological disorders: These include myelofibrosis, polycythaemia vera, acute leukaemia, myeloma, lymphoma and haemolytic anaemia.

3. Miscellaneous: Occasionally, secondary sideroblastic anaemia may occur in association with a variety of inflammatory, neoplastic and autoimmune diseases such as carcinoma, myxoedema, rheumatoid arthritis and SLE.

ANAEMIA OF CHRONIC DISORDERS

One of the commonly encountered anaemia is in patients of a variety of chronic systemic diseases in which anaemia develops secondary to disease process but there is no actual invasion of the bone marrow. In general, the anaemia in chronic disorders is usually normocytic normochromic but can have mild degree of microcytosis and hypochromia unrelated to iron deficiency. The severity of anaemia is usually directly related to the primary disease process. The anaemia is corrected only if the primary disease is alleviated.

Pathogenesis. A number of factors may contribute to the development of anaemia in chronic systemic disorders, and in many conditions, the anaemia is complicated by other causes such as iron, B_{12} and folate deficiency, hypersplenism, renal failure with consequent reduced erythropoietic activity, endocrine abnormalities etc. However, in general, 2 factors appear to play significant role in the pathogenesis of anaemia in chronic disorders. These are: defective red cell production and reduced red cell life-span.

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 precusors 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.

The underlying defect for the asynchronous maturation of the nucleus is defective DNA synthesis due to deficiency of vitamin B_{12} (cobalamin) and/or folic acid (folate). Less common causes are interference with DNA synthesis by congenital or acquired abnormalities of vitamin B_{12} or folic acid metabolism. Before considering the megaloblastic anaemia, a brief account of vitamin B_{12} and folic acid metabolism is considered in order.

VITAMIN B_{12} METABOLISM

Biochemistry. Vitamin B_{12} or cobalamin is a complex organometallic compound having a cobalt atom situated within a corrin ring, similar to the structure of porphyrin from which haem is formed. In humans, there are 2 metabolically active forms of cobala-

min — methyl-cobalamin and adenosyl-cobalamin, which act as coenzymes. The therapeutic vitamin B_{12} preparation is called cyanocobalamin.

Sources. The only dietary sources of vitamin B_{12} are foods of animal protein origin such as kidney, liver, heart, muscle meats, fish, eggs, cheese and milk. In contrast to folate, vegetables contain practically no vitamin B_{12}. Cooking has little effect on its activity. Vitamin B_{12} is synthesized in the human large bowel by microorganisms but is not absorbed from this site and, thus, the humans are entirely dependent upon dietary sources. The 'average daily requirement for vitamin B_{12} is 2-4 μg.

Absorption. After ingestion, vitamin B_{12} in food is released and forms a stable complex with gastric R-binder. R-binder is a form of glycoprotein found in various secretions (e.g. saliva, milk, gastric juice, bile), phagocytes and plasma. On entering the duodenum, the vitamin B_{12}-R-binder complex is digested releasing vitamin B_{12} which then binds to intrinsic factor (IF). The IF is a glycoprotein of molecular weight 50,000 produced by the parietal cells of the stomach and its secretion roughly parallels that of hydrochloric acid. The vitamin B_{12}-IF complex, on reaching the distal ileum, binds to the specific receptors on the mucosal brush border, thereby enabling the vitamin to be absorbed. The IF, therefore, acts as cell-directed carrier protein similar to transferrin. The receptor-bound vitamin B_{12}-IF complex is taken into the ileal mucosal cells where after several hours the IF is destroyed, vitamin B_{12} released and is transferred to another transport protein, transcobalamin (TC) II. The vitamin B_{12}-TC II complex is finally secreted into the portal circulation from where it is taken by the liver, bone marrow and other cells. There are 2 major vitamin B_{12} binding proteins — TC I and TC II, and a minor protein TC III. TC I is not essential for vitamin B_{12} transport but functions primarily as a storage protein while TC III is similar to TC II and binds a small amount of vitamin B_{12}.

Tissue stores. Normally, the liver is the principal storage site of vitamin B_{12} and stores about 2 mg of the vitamin, while other tissues like kidney, heart and brain together store about 2 mg. The body stores of vitamin B_{12} are adequate for 2-4 years. Major source of loss is via bile and shedding of intestinal epithelial cells. A major part of the excreted vitamin B_{12} is reabsorbed in the ileum by the IF resulting in enterohepatic circulation.

Functions. Vitamin B_{12} plays an important role in general cell metabolism, particulary essential for normal haematopoiesis and for maintenance of integrity of the nervous system. Vitamin B_{12} acts as a co-enzyme for 2 main biochemical reactions in the body:

• Firstly, as methyl cobalamin (methyl B_{12}) in the methylation of homocysteine to methionine by methyl tetrahydrofolate (THF). The homocysteine-methionine reaction is closely linked to folate metabolism: when this reaction is impaired, folate metabolism is deranged and results in defective DNA synthesis responsible for megaloblastic maturation.

• Secondly, as adenosyl cobalamin (adenosyl B_{12}) in propionate metabolism for the conversion of methyl malonyl co-enzyme A to succinyl co-enzyme A: lack of adenosyl B_{12} leads to large increase in the level of methyl malonyl CoA and its precursor, propionyl CoA. This results in synthesis of certain fatty acids which are incorporated into the neuronal lipids. This biochemical abnormality may contribute to the neurologic complications of vitamin B_{12} deficiency.

FOLATE METABOLISM

Biochemistry. Folate or folic acid, a yellow compound, is a member of water-soluble B complex vitamins with the chemical name of pteroyi glutamic acid (PGA). Folic acid does not exist as such in nature but exists as folates in polyglutamate form (conjugated folates). For its metabolic action as co-enzyme, poly-glutamates must be reduced to dihydro- and tetrahydrofolate forms.

Sources. Folate exists in different plants, bacteria and animal tissues. Its main dietary sources are fresh green leafy vegetables, fruits, liver, kidney, and to a lesser extent, muscle meats, cereals and milk. Folate is labile and is largely destroyed by cooking and canning. Some amount of folate synthesised by bacteria in the human large bowel is not available to the

body since its absorption takes place in the small intestine. Thus, humans are mainly dependent upon diet for its supply. The average daily requirement is 100-200 μg.

Absorption and transport. Folate is normally absorbed from the duodenum and upper jejunum and to a lesser extent, from the lower jejunum and ileum. However, absorption depends upon the form of folate in the diet. Polyglutamate form in the foodstuffs is first cleaved by the enzyme, folate conjugase, in the mucosal cells to mono- and diglutamates which are readily assimilated. Synthetic folic acid preparations in poly-glutamate form are also absorbed as rapidly as mono-and diglutamate form because of the absence of natural inhibitors. Mono- and diglutamates undergo further reduction in the mucosal cells to form tetrahydrofolate (THF), a monoglutamate. THF circulates in the plasma as methylated compound, methyl THF, bound to a protein. Once methyl THF is transported into the cell by a carrier protein, it is reconverted to polyglutamate.

Tissue stores. The liver and red cells are the main storage sites of folate, largely as methyl THF polyglutamate form. The total body stores of folate are about 10-12 mg enough for about 4 months. Normally, folate is lost from the sweat, saliva, urine and faeces.

Functions. Folate plays an essential role in cellular metabolism. It acts as a coenzyme for 2 important biochemical reactions involving transfer of 1-carbon units (viz. methyl and formyl groups) to various other compounds. These reactions are as under:

• Thymidylate synthetase reaction. Formation of deoxy thymidylate monophosphate (dTMP) from its precursor form, deoxy uridylate monophosphate (dUMP).

• Methylation of homocysteine to methionine. This reaction is linked to vitamin B_{12} metabolism.

These biochemical reactions are considered in detail below together with biochemical basis of the megaloblastic anaemia.

Biochemical Basis of Megaloblastic Anaemia. The basic biochemical abnormality common to both vitamin B_{12} and folate deficiency is a block in the DNA synthesis pathway and that there is an inter-relationship between vitamin B_{12} and folate metabolism in the methylation reaction of homocysteine to methionine.

Deficiency of folate from any cause results in reduced supply of the coenzyme, methylene-THF, and thus interferes with the synthesis of DNA. Deficiency of vitamin B_{12} traps folate as its transport form, methyl-THF, thereby resulting in reduced formation of the active form, methylene-THF, needed for DNA synthesis. This is referred to as methyl-folate trap hypothesis. An alternative hypothesis of inter-relationship of B_{12} and folate is the formate-saturation hypothesis. According to this hypothesis, the active substrate is formyl-THF. Vitamin B_{12} deficiency results in reduced supply of formate to THF causing reduced generation of the active compound, formyl THF.

Etiology and Classification of Megaloblastic Anaemia. The etiology of megaloblastic anaemia varies in different parts of the world.

1. Vitamin B_{12} deficiency. In Western countries, the deficiency of vitamin B_{12} is usually due to pernicious (Addisonian) anaemia. True vegetarians like in India and breast-fed infants have dietary lack of vitamin B_{12}. Gastrectomy by lack of intrinsic factor, and small intestinal lesions involving distal ileum where absorption of vitamin B_{12} occurs, may cause deficiency of the

vitamin. Deficiency of vitamin B_{12} takes at least 2 years to develop when the body stores are totally depleted.

2. Folate deficiency. Folate deficiency is more often due to poor dietary intake. Other causes include malabsorption, excess folate utilisation such as in pregnancy and in various disease states, alcoholism, and excess urinary folate loss. Folate deficiency arises more rapidly than vitamin B_{12} deficiency since the body's stores of folate are relatively low which can last for up to 4 months only.

Patients with tropical sprue are often deficient in both vitamin B_{12} and folate. Combined deficiency of vitamin B_{12} and folate may occur from severe deficiency of vitamin B_{12} because of the biochemical interrelationship with folate metabolism.

3. Other causes. In addition to deficiency of vitamin B_{12} and folate, megaloblastic anaemias may occasionally be induced by other factors unrelated to vitamin deficiency. These include many drugs which interfere with DNA synthesis, acquired defects of haematopoietic stem cells, and rarely, congenital enzyme deficiencies.

Clinical Features. Deficiency of vitamin $B_{]2}$ and folate may cause the 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 B_{12} 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 B_{12} 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.

Significant findings of marrow examination are as under:

i) *Marrow cellularity*. The marrow is hypercefluiar with a decreased myeloid-erythroid ratio.

ii) *Erythropoiesis.* The erythroid hyperplasia is due to characteristic megaloblastic erythropoiesis. Megaloblasts are abnormal, large, nucleated

erythroid precursors, having nuclear-cytoplasmic asynchrony i.e. the nuclei are less mature than the development of cytoplasm. The nuclei are large, having fine, reticular and open chromatin that stains lightly, while the haemoglobinisation of the cytoplasm proceeds normally or at a faster rate i.e. nuclear maturation lags behind that of cytoplasm. Megaloblasts with abnormal mitoses may be seen.

Features of ineffective erythropoiesis such as presence of degenerated erythroid precursors may be present.

iii) *Other cells.* Granulocyte precursors are also affected to some extent. Giant forms of metamyelocytes and band cells may be present in the marrow. Megakaryocytes are usually present in normal number but may occasionally be decreased and show abnormal morphology such as hypersegmented nuclei and agranular cytoplasm.

iv) Marrow iron. Prussian blue staining for iron in the marrow shows an increase in the number and size of iron granules in the erythroid precursors. Ring sideroblasts are, however, rare. Iron in the reticulum cells is increased.

PERNICIOUS ANAEMIA

(PA) was first described by Addison in 1855 as a chronic disorder of middle-aged and elderly individual of either sex in which intrinsic factor secretion ceases owing to atrophy of the gastric mucosa. The condition is, therefore, also termed Addisonian megaloblastic anaemia. The average age at presentation is 60 years but rarely it can be seen in children under 10 years of age (juvenile pernicious anaemia).

Pathogenesis. There is evidence to suggest that the atrophy of gastric mucosa in PA is caused by an against gastric parietal cells. The immunological abnormalities in pernicious anaemia are as under:

1. The incidence of PA is high in patients with other autoimmune diseases such as Graves' disease, myxoedema, thyroiditis, vitiligo, diabetes and idiopathic adrenocortical insufficiency.

2. Patients with PA have abnormal circulating auto-antibodies such as anti-parietal cell antibody (90% cases) and anti-intrinsic factor antibody (50% cases).

3. Relatives of patients with PA have an increased incidence of the disease or increased presence of auto-antibodies.

4. Corticosteroids have been reported to be beneficial in curing the disease both pathologically and clinically.

5. PA is more common in patients with agarrtrnaglo-bulinaemia supporting the role of cellular immune system in destruction of parietal cells.

Pathologic changes. The most characteristic pathologic finding in PA is gastric atrophy affecting the acid- and pepsin-secreting portion of the stom-

ach and sparing the antrum. Gastric epithelium may show cellular atypia. About 2-3% cases of PA develop carcinoma of the stomach. Other pathologic changes are secondary to vitamin B_{12} deficiency and include megaloblastoid alterations in the gastric and intestinal epithelium and neurologic abnormalities such as peripheral neuropathy and spinal cord damage.

Clinical Features. The disease has insidious onset and progresses slowly. The clinical manifestations are mainly due to vitamin B_{12} deficiency. These include anaemia, glossitis, neurological abnormalities (neuropathy, subacute combined degeneration of the spinal cord, retrobulbar neuritis), gastrointestinal manifestations (diarrhoea, anorexia, weight loss, dyspepsia), hepatosplenomegaly, congestive heart failure and haemorrhagic manifestations.

HAEMOLYTIC ANAEMIAS GENERAL ASPECTS

Definition and Classification. Haemolytic anaemias are defined as anaemias resulting from an increase in the rate of red cell destruction.

The premature destruction of red cells in haemolytic anaemia may occur by 2 mechanisms:

• **First**, the red cells undergo lysis in the circulation and release their contents into plasma (intravascular haemolysis). In these cases the plasma haemoglobin rises substantially and part of it may be excreted in the urine (haemoglobinuria).

• **Second**, the red cells are taken up by cells of the RE system where they are destroyed and digested (extra-vascular haemolysis). In extravascular haemolysis, plasma haemoglobin level is, therefore, barely raised.

Extravascular haemolysis is more common than the former. One or more factors may be involved in the pathogenesis of various haemolytic anaemias.

Haemolytic anaemias are broadly classified into 2 main categories:

I. Acquired haemolytic anaemias caused by a variety of extrinsic environmental factors (extra-corpuscular).

II. Hereditary haemolytic anaemias are usually the result of intrinsic red cell defects (intra-corpuscular).

Features of Haemolysis. A number of clinical and laboratory features are shared by various types of haemolytic anaemias.

General clinical features. Some of the general clinical features common to most congenital and acquired haemolytic anaemias are as under:

1. Presence of pallor of mucous membranes.

2. Positive family history with life-long anaemia in patients with congenital haemolytic anaemia.

3. Mild fluctuating jaundice due to unconjugated hyperbilirubinaemia.

4. Urine turns dark on standing due to excess of urobilinogen in urine.

5. Splenomegaly is found in most chronic haemolytic anaemias, both congenital and acquired.

6. Pigment gallstones are found in some cases.

ACQUIRED (EXTRACORPUSCULAR) HAEMOLYTIC ANAEMIAS

These anaemias are caused by a variety of extrinsic factors, namely: antibody (immunohaemolytic anaemia), mechanical factors (microangiopathic haemolytic anaemia), direct toxic effect (in malaria, clostridial infection etc), splenomegaly, and certain acquired membrane abnormalities (paroxysmal nocturnal haemoglobinuria). These are discussed below:

A. IMMUNOHAEMOLYTIC ANAEMIAS

Immunohaemolytic anaemias are a group of anaemias occurring due to antibody production by the body against its own red cells. Immune haemolysis in these cases may be induced by one of the following three types of antibodies:

1. Autoimmune haemolytic anaemia (AIHA) characterised by formation of autoantibodies against patient's own red cells. Depending upon the reactivity of autoantibody, AIHA is further divided into 2 types:

i) 'Warm' antibody AIHA in which the autoantibodies are reactive at body temperature (37°C).

ii) 'Cold' antibody AIHA in which the autoantibodies react better with patient's own red cells at 4°C.

2. Drug-induced immunohaemolytic anaemia.

3. Isoimmune haemolytic anaemia in which the antibodies are acquired by blood transfusions, pregnancies and haemolytic disease of the newborn.

An important diagnostic tool in all cases of immunohaemolytic anaemias is Coombs' antiglobulin test for detection of incomplete Rh-antibodies in saline directly (direct Coombs') or after addition of albumin (indirect Coombs').

B. MICROANGIOPATHIC HAEMOLYTIC ANAEMIA

Microangiopathic haemolytic anaemia is caused by mechanical trauma to the red cells in circulation. This type of haemolysis is characterised by red cell fragmentation (schistocytosis). There are 3 different ways by which microangiopathic haemolytic anaemia results:

1. External impact. Direct external trauma to red blood cells when they pass through microcirculation, especially over the bony prominences, may cause haemolysis during various activities e.g. in prolonged marchers, joggers, karate players etc. These patients develop haemoglobinaemia, haemoglobinuria (march haemoglobinuria), and sometimes myoglobinuria as a result of damage to muscles.

2. Cardiac haemolysis. A small proportion of patients who received prosthetic cardiac valves or artificial grafts develop haemolysis. This has been attributed to direct mechanical trauma to the red cells or shear stress from turbulent blood flow.

3. Fibrin deposit in microvasculature. Deposition of fibrin in the microvasculature exposes the red cells to physical obstruction and eventual fragmentation of red cells and trapping of the platelets. Fibrin deposits in the small vessels may occur in the following conditions:

i) Abnormalities of the vessel wall e.g. in hypertension, eclampsia, disseminated cancers, transplant rejection, haemangioma etc.

ii) Thrombotic thrombocytopenic purpura.

iii) Haemolytic-uraemic syndrome,

iv) Disseminated intravascular coagulation (DIC).

v) Vasculitis in collagen diseases.

C. HAEMOLYTIC ANAEMIA FROM DIRECT TOXIC EFFECTS

Haemolysis may result from direct toxic effects of certain agents. These include the following examples:

1. Malaria by direct parasitisation of red cells (black-water fever).
2. Bartonellosis by direct infection of red cells by the microorganisms.
3. Septicaemia with Clostridium welchii by damaging the red cells.
4. Other microorganisms such as pneumococci, staphylococci and Escherichia coli.
5. Copper by direct haemolytic effect on red cells in Wilson's disease and patients on haemodialysis.
6. Lead poisoning shows basophilic stippling of red blood cells.
7. Snake and spider bites cause haemolysis by their venoms.
8. Extensive burns.

D. HAEMOLYTIC ANAEMIA IN SPLENOMEGALY

Haemolytic anaemia is common in splenic enlargement from any cause. Normally, the spleen acts as a filter and traps the damaged red blood cells, destroys them and the splenic macrophages phagocytose the damaged red cells. A normal spleen poses no risk to normal red blood cells. But splenomegaly exaggerates the damaging effect to which the red cells are exposed. Besides haemolytic anaemia, splenomegaly is usually associated with pancytopenia. Splenectomy or reduction in size of spleen by appropriate therapy relieves the anaemia as well as improves the leucocyte and platelet counts.

E. PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA (PNH)

PNH is a rare acquired disorder of red cell membrane in which there is chronic intravascular haemolysis due to undue sensitivity of red blood cells to complement due to defective synthesis of a red cell membrane protein. The

defect affects all the cells of myeloid progenitor lineage (RBCs, WBCs, platelets) suggesting a defect at the level of stem cell. The disorder generally presents in adult life.

Clinical and laboratory findings. Clinical and laboratory findings are as under:

i) Haemolytic anaemia.

ii) Pancytopenia (mild granulocytopenia and thrombocytopenia frequent).

iii) Intermittent clinical haemoglobinuria; acute haemolytic episodes occur at night identified by passage of brown urine in the morning.

iv) Haemosiderinuria very common.

v) Venous thrombosis common complication.

The presence of inordinate sensitivity of red blood cells, leucocytes and platelets to complement in PNH can be demonstrated in vitro by Ham's test using red cell lysis at acidic pH or by sucrose haemolysis test.

About 20% cases of PNH may develop myeloproliferative or myelodysplastic disorder and some even develop acute myeloid leukaemia.

II. HEREDITARY (INTRACORPUSCULAR) HAEMOLYTIC ANAEMIA

Hereditary haemolytic anaemias are usually the result of intracorpuscular defects. Accordingly, they are broadly classified into 2 groups:

- Those due to hereditary abnormalities of red cell membrane; and
- Second are those with hereditay disorders of the interior of the red cells.

A. HEREDITARY ABNORMALITIES OF RED CELL MEMBRANE

There are 2 important types of inherited red cell membrane defects: hereditary spherocytosis and hereditary elliptocytosis (hereditary ovalocytosis).

Hereditary Spherocytosis is a common type of hereditary haemolytic anaemia of autosomal dominant inheritance in which the red cell membrane is abnormal.

Pathogenesis. The molecular abnormality in hereditary spherocytosis is a deficiency in the structural protein of the red cell membrane, spectrin. Deficiency of spectrin correlates with the severity of anaemia. This abnormality results in spheroidal contour and smaller size of red blood cells. These microspherocytes are not flexible, unlike normal biconcave red cells. These rigid red cells are unable to pass through the spleen and in the process 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.

Hereditary Elliptocytosis (Hereditary Ovalocytosis)

Hereditary elliptocytosis or hereditary ovalocytosis is another autosomal dominant disorder involving red cell membrane protein spectrin. The disorder is similar in all respects to hereditary spherocytosis except that the blood film shows oval or elliptical red cells and is clinically a milder disorder than hereditary spherocytosis.

Acquired cases of elliptocytosis include iron deficiency and myeloproliferative disorders.

B. HEREDITARY DISORDERS OF RED CELL INTERIOR

Inherited disorders involving the interior of the red blood cells are classified into 2 groups:

1. Red cell enzyme defects: These cause defective red cell metabolism involving 2 pathways:

i) Defects in the hexose monophosphate shunt: Common example is glucose-6-phosphate dehydrogenase. (G6PD) deficiency.

ii) Defects in the Embden-Meyerhof (glycolytic) pathway: Example is pyruvate kinase (PK) deficiency.

2. Disorders of haemoglobin: These are divided into 2 subgroups:

i) Abnormal haemoglobins (haemoglobinopathies): Examples are sickle syndromes and other haemoglobinopathies.

ii) Reduced globin chain synthesis: Common examples are various types of thalassaemias.

These disorders are discussed below.

RED CELL ENZYME DEFECTS G6PD DEFICIENCY

Among the defects in hexose monophosphate shunt, the most common is G6PD deficiency. It affects millions of people throughout the world. The G6PD gene is located on the X chromosome and its deficiency is, therefore, a sex (X)-linked trait affecting males, while the females are carriers and are asymptomatic. Several variants of G6PD have been described. The normal G6PD variant is des-

ignated as type B but blacks have normally A+ (positive) type G6PD variant. The most common and significant clinical variant is A-(negative) type found in black males. Like the HbS gene, the A-type G6PD variant confers protection against malaria. Individuals with A-G6PD variant have shortened red cell life-span but without anaemia. However, these individuals develop haemolytic episodes on exposure to oxidant stress such as viral and bacterial infections, certain drugs (antimalarials, sulfonamides, nitrofurantoin, aspirin, vitamin K), metabolic acidosis and on ingestion of fava beans (favism).

Pathogenesis. Normally, the red blood cells are well protected against oxidant stress because of adequate generation of reduced glutathione via the hexose monophosphate shunt. Individuals with inherited deficiency of G6PD, an enzyme required for hexose monophosphate shunt for glucose metabolism, fail to develop adequate levels of reduced glutathione in their red cells. This results in oxidation and precipitation of haemoglobin within the red cells forming Heinz bodies. Besides G6PD deficiency, deficiency of various other enzymes involved in the hexose monophosphate shunt may also infrequently cause clinical problems.

Clinical features. The clinical manifestations are those of an acute haemolytic anaemia within hours of exposure to oxidant stress. The haemolysis is, however, self-limiting even if the exposure to the oxidant is continued since it affects the older red cells only. Haemoglobin level may return to normal when the older population of red cells has been destroyed and only younger cells remain. Some patients may have only darkening of the urine from haemoglobinuria but more severely affected ones develop constitutional symptoms including jaundice. Treatment is directed towards the prevention of haemolytic episodes such as stoppage of offending drug. Blood transfusions are rarely indicated.

The diagnosis of G6PD enzyme deficiency is made by one of the screening tests (e.g. methaemoglobin reduction test, fluorescent screening test, ascorbate cyanide screening test) or by direct enzyme assay on red cells.

PYRUVATE KINASE DEFICIENCY

Pyruvate kinase (PK) deficiency is the only significant enzymopathy of the Embden-Meyerhof glycolytic pathway. The disorder is inherited as an autosomal recessive pattern. Heterozygote state is entirely asymptomatic, while the homozygous individual presents during early childhood with anaemia, jaundice and splenomegaly.

DISORDERS OF HAEMOGLOBIN

These geographic disorders are described below under 2 main headings: abnormal haemoglobins (haemoglobinopathies) and thalassaemias.

Abnormal haemoglobins (haemoglobinopathies)

Sickle syndromes

The most important and widely prevalent type of haemoglobinopathy is due to the presence of sickle haemoglobin (HbS) in the red blood cells. The red cells with HbS develop 'sickling' when they are exposed to low oxygen tension. Sickle syndromes have the highest frequency in black race and in Central Africa where falciparum malaria is endemic. Patients with HbS are relatively protected against falciparum malaria. Sickle syndromes occur in 3 different forms:

1. As heterozygous state for HbS: sickle cell trait (AS).
2. As homozygous state for HbS: sickle cell anaemia (SS).
3. As double heterozygous states e.g. sickle β-thalassaemia, sickle-C disease (SC), sickle-D disease (SD).

Heterozygous State: Sickle Cell Trait

Sickle cell trait is a benign heterozygous state of HbS in which only one abnormal gene is inherited. Patients with AS develop no significant clinical problems except when they become severely hypoxic and may develop sickle cell crises.

Homozygous State: 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 severely malignant disorder associated with protean clinical manifestations and decreased life expectancy.

Pathogenesis. The basic molecular lesion in HbS is the substitution of valine for glutamic acid at the *6* residue position of the (5-globin, producing Hb $a_2\beta^s{}_2$.

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). 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.

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 FIbS. Infection and folic acid deficiency result in more severe clinical manifestations. These features are as under:

1. *Anaemia*. There is usually severe 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, bones, lungs, kidneys, liver and skin, 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.

Double Heterozygous States

Double heterozygous conditions involving combination of HbS with other haemoglobinopathies may occur. Most common among these are sickle-β-thalassaemia, sickle C disease (SC), and sickle D disease (SD). All these disorders behave like mild form of sickle cell disease. Their diagnosis is made by haemoglobin electrophoresis and separating the different haemoglobins.

OTHER HAEMOGLOBINOPATHIES

Besides sickle haemoglobin, about 400 structurally different abnormal human haemoglobins have been discovered in different parts of the world. Some of them are associated with clinical manifestations, while others are of no consequence.

HbC Haemoglobinopathy is prevalent in West Africa and in American blacks. The molecular lesion in HbC is substitution of lysine for glutamic acid at β-6 globin chain position. The disorder of HbC may occur as benign homozygous HbC disease, or as asymptomatic heterozygous HbC trait, or as double heterozygous combinations such as sickle-HbC disease and HbC-β thalassaemia.

HbD Haemoglobinopathy occurs in North-West India, Pakistan and Iran. About 3% of Sikhs living in Punjab are affected with HbD haemoglobinopathy (called HbD Punjab, also known as Hb-Los Angeles). HbD Punjab arises from the substitution of glutamine for glutamic acid at β-121 globin chain position.

HbE Haemoglobinopathy is predominantly found in South-East Asia, India, Burma and Sri Lanka. HbE arises from the substitution of lysine for glutamic acid at β-26 globin chain position. Like other abnormal haemoglobins, HbE haemoglobinopathy may also occur as asymptomatic heterozygous HbE trait, compensated haemolytic homozygous HbE disease, or as double heterozygous states in combination with other haemoglobinopathies such as HbE-β thalassaemia and HbE-cx thalassaemia.

Haemoglobin O-Arab Disease was first identified in an Arab family but has now been detected in American blacks too. The homozygous form of the disease appears as mild haemolytic anaemia with splenomegaly.

Unstable-Hb Haemoglobinopathy. The unstable haemoglobins are those haemoglobin variants which undergo denaturation and precipitation within the red cells as Heinz bodies. These give rise to what is known as congenital non-spherocytic haemolytic anaemia or congenital Heinz body haemolytic anaemia. These disorders have either autosomal dominant inheritance or develop from spontaneous mutations. The unstable haemoglobins arise from either a single amino acid substitution in the globin chain or due to deletion of one or more amino acids within the β-globin chain so that the firm bonding of the haem group within the molecule is disturbed leading to formation of methaemoglobin and precipitation of globin chains as Heinz bodies.

Over 100 unstable haemoglobins have been described. They are named according to the place where they are encountered. For instance: Hb-Koln, Hb-Hammersmith, Hb-Zurich, Hb-Sydney, and so on. The diagnosis of unstable Hb disease is made by test for Heinz bodies and by haemoglobin electrophoresis.

THALASSAEMIA

The thalassaemias are a diverse group of hereditary disorders in which there is reduced rate of synthesis of one or more of the globin polypeptide chains. Thus, thalassaemias, unlike haemoglobinopathies which are quantitative disorders of haemoglobin, are quantitative abnormalities of polypeptide globin chain 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 around the Mediterranean basin. It also occurs in the Middle East, India, South-East Asia and, in general in blacks.

Thalassaemias are genetically transmitted disorders. Normally, an individual inherits two β-globin genes located one each on two chromosomes 11, and two a-globin genes one each on two chromosomes 16, from each parent i.e. normal adult haemoglobin (HbA) is $\alpha_2\ \beta_2$. Depending upon whether

the genetic defect or deletion lies in transmission of α- or β-globin chain genes, thalassaemias are classified into α- and β- thalassaemias. Thus, patients with α-thalassaemia have structurally normal α-globin chains but their production is impaired. Similarly, in β-thalassaemia, β-globin chains are structurally normal but their production is decreased. Each of the two main types of thalassaemias may occur as heterozygous (called α- and β-thalassaemia minor or trait), or as homogygous state (termed α- and β-thalassaemia major). The former is generally asymptomatic, while the latter is a severe congenital haemolytic anaemia.

Pathophysiology of anaemia in thalassaemia

A constant feature of all forms of thalassaemia is the presence of anaemia.

α-Thalassaemia: In a-thalassaemia major, the obvious cause of anaemia is the inability to synthesise adult haemoglobin, while in a-thalassaemia trait there is reduced production of normal adult haemoglobin. Accordingly, a-thalassaemias are classified into 4 types:

1. Four α-gene deletion: Hb Bart's hydrops foetalis.
2. Three α-gene deletion: HbH disease.
3. Two α-gene deletion: α-thalassaemia trait.
4. One α-gene deletion: α-thalassaemia trait (carrier).

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 life-span, ineffective erythropoiesis, and haemodilution due to increased plasma volume. A deficiency of β-globin chains in P-thalassaemia leads to large excess of α-chains within the developing red cells. Part of these excessive α-chains are removed by pairing with γ-globin chains as HbF, while the remainder unaccompanied α-chains precipitate rapidly within the red cell as Heinz bodies. The precipitated α-chains cause cell membrane damage. During their passage through the splenic sinusoids, these red cells are further damaged and develop pitting due to removal of the precipitated aggregates. Thus, such red cells are irreparably damaged and are phagocytosed by the RE cells of the spleen and liver causing anaemia, hepatosplenomegaly, and excess of tissue iron stores. Patients with β-thalassaemia minor, on the other hand, have very mild ineffective erythropoiesis, haemolysis and shortening of red cell life-span.

Depending upon the extent of reduction in β-chain synthesis, there are 3 types of β-thalassaemia:

1. Homozygous form: β-Thalassaemia major. It is the most severe form of congenital haemolytic anaemia. It is further of 2 types:

i) β° thalassaemia major characterised by complete absence of β-chain synthesis.

ii) β^+ thalassaemia major having incomplete suppression of β-chain synthesis.

2. β-Thalassaemia intermedia: It is β-thalassaemia of intermediate degree of severity that does not require regular blood transfusions. These cases are genetically heterozygous (β°/β or β^+/β).

3. Heterozygous form: β-Thalassaemia minor (trait).

APLASTIC ANAEMIA AND OTHER PRIMARY BONE MARROW DISORDERS

'Bone marrow failure' is the term used for primary disorders of the bone marrow which result in impaired formation of the erythropoietic precursors and consequent anaemia. It includes the following disorders:

1. Aplastic anaemia, most importantly.

2. Other primary bone marrow disroders such as: myelophthisic anaemia, pure red cell aplasia, and myelodysplastic syndromes.

APLASTIC ANAEMIA

Aplastic anaemia is defined as pancytopenia (i.e. simultaneous presence of anaemia, leucopenia and thrombocytopenia) resulting from aplasia of the bone marrow. The underlying defect in all cases appears to be sufficient reduction in the number of haematopoietic pluripotent stem cells which makes them unable to divide and differentiate.

Etiology and classification. Based on the etiology, aplastic anaemia is classified into 2 main types: primary and secondary.

A. Primary aplastic anaemia. Primary type of aplastic anaemia includes 2 entities: a congenital form called Fanconi's anaemia and an immunologically-mediated acquired form.

1. Fanconi's anaemia. This has an autosomal recessive inheritance and is often associated with other congenital anomalies such as skeletal and renal abnormalities, and sometimes mental retardation.

2. *Immune causes.* In many cases, suppression of haematopoietic stem cells by immunologic mechanisms may cause aplastic anaemia. The observations in support of autoimmune mechanisms are the clinical response to immunosupppressive therapy and *in vitro* marrow culture experiments.

B. Secondary aplastic anaemia. Aplastic anaemia may occur secondary to a variety of industrial, physical, chemical, iatrogenic and infectious causes.

1. Drugs. A number of drugs are cytotoxic to the marrow and cause aplastic anaemia. The association of a drug with aplastic anaemia may be either predictably dose-related or an idiosyncratic reaction.

• *Dose-related aplasia* of the bone marrow occurs with antimetabolites (e.g. methotrexate), mitotic inhibitors (e.g. daunorubicin), alkylating agents (e.g. busulfan), nitrosourea and anthracyclines. In such cases, withdrawal of the drug usually allows recovery of the marrow elements.

• *Idiosyncratic aplasia* is depression of the bone marrow due to qualitatively abnormal reaction of an individual to a drug when first administered. The most serious and most common example of idiosyncratic aplasia is associated with chloramphenicol. Other such common drugs are: sulfa drugs, oxyphenbutazone, phenylbutazone, chlorpromazine, gold salts etc.

2. *Toxic chemicals.* These include examples of industrial, domestic and accidental use of substances such as benzene derivatives, insecticides, arsenicals etc.

3. *Infections.* Aplastic anaemia may occur following viral hepatitis, Epstein-Barr virus infection, AIDS and other viral illnesses.

4. Miscellaneous. Lastly, aplastic anaemia has been reported in association with certain other illnesses such as SLE, and with therapeutic X-rays.

Clinical features. The onset of aplastic anaemia may occur at any age and is usually insidious. The clinical manifestations include the following:

1. Anaemia and its symptoms like mild progressive weakness and fatigue.

2. Haemorrhage from various sites due to thrombocytopenia such as from the skin, nose, gums, vagina, bowel, and occasionally in the CNS and retina.

3. Infections of the mouth and throat are commonly present.

4. The lymph nodes, liver and spleen are generally not enlarged.

MYELOPHTHISIC ANAEMIA

Development of severe anaemia may result from infiltration of the marrow termed as myelophthisic anaemia. The causes for marrow infiltrations include:

• Haematologic malignancies (e.g. leukaemia, lymphoma, myeloma),

• Metastatic deposits from non-haematologic malignancies (e.g. cancer breast, stomach, prostate, lung, thyroid),

• Advanced tuberculosis,

• Primary lipid storage diseases (Gaucher's and Niemann-Pick's disease).

• Osteopetrosis and myelofibrosis may rarely cause myelophthisis.

The type of anaemia in myelophthisis is generally normocytic normochromic with some fragmented red cells, basophilic stippling and normoblasts in the peripheral blood. Thrombocytopenia is usually present but the leucocyte count is increased with slight shift-to-left of myeloid cells i.e. a picture of *leucoerythroblastic reaction* consisting of immature myeloid cells

and normoblasts is seen in the peripheral blood. Treatment consists of reversing the underlying pathologic process.

PURE RED CELL APLASIA

This is a rare syndrome involving a selective failure in the production of erythroid elements in the bone marrow but with normal granulopoiesis and megakaryocytopoiesis. Patients have normocytic normochromic anaemia with normal granulocyte and platelet count. Reticulocytes are markedly decreased or are absent.

Pure red cell aplasia exists in two forms: congenital and acquired.

• *Congenital red cell aplasia (Blackfan-Diamond syndrome)* is a rare chronic disorder of unknown etiology. The disorder is corrected by glucocorticoids and marrow transplantation.

• *Acquired red cell aplasia* is seen in middle-aged adults in association with some other diseases, most commonly thymoma; others are SLE, lymphoma, T-cell chronic lymphocytic leukaemia or even without any precipitating factor. The condition probably results from selective cytotoxicity of marrow erythroblasts by complement-fixing IgG.

PATHOLOGY OF THE CARDIOVASCULAR SYSTEM

ATHEROSCLEROSIS

Atherosclerosis is a specific form of arteriosclerosis affecting primarily the intima of large and medium-sized muscular arteries and is characterised by fibrofatty plaques or atheromas. The term atherosclerosis is derived from athero–(meaning porridge) referring to the soft lipid-rich material in the centre of atheroma, and sclerosis (scarring) referring to connective tissue in the plaques. Atherosclerosis is the commonest and the most important of the arterial diseases. Though any large and medium-sized artery may be involved in atherosclerosis, the most commonly affected are the aorta, the coronary and the cerebral arterial systems. Therefore, the major clinical syndromes resulting from ischaemia due to atherosclerosis are the myocardial infarcts (heart attacks) and the cerebral infarcts (strokes); other less common sequelae are peripheral vascular disease, aneurysmal dilatation due to weakened arterial wall, chronic ischaemic heart disease, ischaemic encephalopathy and mesenteric occlusion.

Etiology. Atherosclerosis is widely prevalent in industrialised countries. However, majority of the incidences quoted in the literature are based on the major clinical syndromes produced by it, the most important interpretation being that death from myocardial infarction is related to underlying atherosclerosis. Cardiovascular disease, mostly related to atherosclerotic coronary heart disease or ischaemic heart disease (IHD) is the most common cause of death in the developed countries of the world.

These risk factors are divided into three groups:

I. Major constitutional risk factors: age, sex, genetic factors.

II. Major acquired risk factors: hyperlipidaemia, hypertension, diabetes mellitus, smoking.

III. Minor risk factors.

I. Major constitutional risk factors

Age, sex and genetic influences do affect the appearance of lesions of atherosclerosis.

1. Age. Atherosclerosis is an age-related disease. Though early lesions of atherosclerosis may be present in childhood, clinically significant lesions are found with increasing age. Fully-developed atheromatous plaques usually appear in the 4th decade and beyond. Evidence in support comes from the high death rate from IHD in this age group.

2. Sex. The incidence and severity of atherosclerosis are more in men than in women. The prevalence of atherosclerotic IHD is about three times higher in men in 4th decade than in women and the difference slowly de-

clines with age but remains higher at all ages in men. The lower incidence of IHD in women, especially in premenopausal age, is probably due to high levels of oestrogen and high-density lipoproteins, both of which have anti-atherogenic influence.

3. Genetic factors. Genetic factors play a significant role in atherogenesis. Hereditary genetic derangements of lipoprotein metabolism predispose the individual to high blood lipid level and familial hypercholesterolaemia.

4. Familial and racial factors: The familial predisposition to atherosclerosis may be related to other risk factors like diabetes, hypertension and hyper-lipoproteinaemia. Racial differences too exist; Blacks have generally less severe atherosclerosis than Whites.

II. Major acquired risk factors

There are four major acquired risk factors in atherogenesis – hyperlipidaemia, hypertension, cigarette smoking and diabetes mellitus.

1. Hyperlipidaemia. Virchow in 19th century first identified cholesterol crystals in the atherosclerotic lesions. Since then, extensive information on lipoproteins and their role in atherosclerotic lesions has been gathered. It is now well established that hypercholesterolaemia has directly proportionate relationship with atherosclerosis and IHD.

The main lipids in blood are cholesterol (normal 140-240 mg/dl) and triglycerides (below 160 mg/dl). An elevation of serum cholesterol levels above 260 mg/ dl in men and women between 30 and 50 years of age has three times higher risk of developing IHD as compared with people with serum cholesterol levels within normal limits. The concentration of cholesterol in the serum reflects the concentrations of different lipoproteins in the serum. The lipoproteins are divided into classes according to the density of solvent in which they remain suspended on centrifugation at high speed. The major classes of lipoprotein particles are chylomicrons, very-low density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Each of these lipid particles contain lipid core and associated proteins, apolipoproteins, which are designated by a letter and/or a number. The major fractions of lipoproteins and their varying effects on atherosclerosis and IHD are as under:

• Low-density lipoprotein (LDL) is richest in cholesterol and has the maximum association with atherosclerosis.

• Very-low-density lipoprotein (VLDL) carries much of the triglycerides and has less marked effect than LDL.

• High-density lipoprotein (HDL) is protective against atherosclerosis.

Many studies have demonstrated the harmful effect of diet containing larger quantities of saturated fats (e.g. in eggs, meat, milk etc) which raise the plasma cholesterol level.

2. Hypertension. Hypertension is the other major risk factor in the development of atherosclerotic IHD and cerebrovascular disease. It acts probably by mechanical injury to the arterial wall due to increased blood pressure. A systolic pressure of over 160 mmHg or a diastolic pressure of over 95 mmHg is associated with five times higher risk of developing IHD than in people with blood pressure within normal range (140/90 mmHg or less).

3. Smoking. The extent and severity of atherosclerosis are much greater in smokers than in non-smokers. Cigarette smoking is associated with higher risk of atherosclerotic IHD and sudden cardiac death. Men who smoke a pack of cigarettes a day are 3-5 times more likely to die of IHD than non-smokers. The increased risk and severity of atherosclerosis in smokers is due to reduced level of HDL and accumulation of carbon monoxide in the blood that produces carboxy-haemoglobin and eventually hypoxia in the arterial wall favouring atherosclerosis.

4. Diabetes mellitus. Clinical manifestations of atherosclerosis are far more common and develop at an early age in people with both insulin-dependent and non-insulin dependent diabetes mellitus. The risk of developing IHD is doubled, tendency to develop cerebrovascular disease is high, and frequency to develop gangrene of foot is about 100 times increased. The causes of increased severity of atherosclerosis are complex and numerous which include increased aggregation of platelets, increased LDL and decreased HDL.

III. Minor risk factors

There are a number of less important and minor risk factors having some role in the etiology of atherosclerosis. These are as under:

i) Higher incidence of atherosclerosis in developed countries and low prevalence in underdeveloped countries, suggesting the role of environmental influences,

ii) Obesity, if the person is overweight by 20% or more, is associated with increased risk,

iii) Use of oral contraceptives by women has been shown to have increased risk of developing myocardial infarction or stroke.

iv) Lack of exercise is associated with the risk of developing atherosclerosis and its complications,

v) Type A behaviour pattern or stress characterised by aggressiveness, competitive drive, ambitiousness and a sense of urgency, is associated with enhanced risk of IHD compared with type B behaviour of relaxed and happy-go-lucky type.

vi) Moderate consumption of alcohol appears to have slightly beneficial effect by raising the level of HDL cholesterol.

vii) Role of viruses in atherogenesis has been implicated recently. In chickens, avian herpesvirus (Marek disease virus), besides producing lymphoid tumour, also produces intimal cell proliferation of muscular arteries and alters the metabolism of lipid and cholesterol in these cells. Although a conclusive role of viral infection in pathogenesis of human atherosclerosis is as yet unproven, viral infection would explain intimal cell proliferation and monoclonal cell proliferation in atheromatous lesion.

Pathogenesis. As stated above, atherosclerosis is not caused by a single etiologic factor but is a multifactorial disease whose exact pathogenesis is still not known. A number of theories have been proposed since the times of Virchow.

• **Insudation hypothesis**. The concept hypothesised by Virchow in 1856 that atherosclerosis is a form of cellular proliferation of the intimal cells resulting from increased imbibing of lipids from the blood came to be called the 'lipid theory', currently known as 'response to injury hypothesis' and is nowadays the most widely accepted theory.

• **Encrustation hypothesis**. The proposal put forth by Rokitansky in 1852 that atheroma represented a form of encrustation on the arterial wall from the components in the blood forming thrombi composed of platelets, fibrin and leucocytes, was named as 'encrustation theory' or 'thrombogenic theory'. Since currently it is believed that encrustation or thrombosis is not the sole factor in atherogenesis but the components of thrombus (platelets, fibrin and leucocytes) have a role in atheromatous lesions, this theory has now been incorporated into the foregoing recent theory of response to injury.

Thus, there is no consensus regarding the origin and progression of lesion of atherosclerosis. The role of four key factors – arterial smooth muscle cells, endothelial cells, blood monocytes and hyperlipidaemia, is accepted by all. However, the areas of disagreement exist in the mechanism and sequence of events involving these factors in initiation, progression and complications of disease. Currently, pathogenesis of atherosclerosis is explained on the basis of the following two theories:

• Response-to-injury hypothesis, first described in 1973, and modified in 1986 and 1993 by Ross.

• Monoclonal theory, postulated by Benditt and Benditt in 1973.

1. Response-to-injury hypothesis. This theory is most widely accepted and incorporates aspects of two older historical theories of atherosclerosis – the lipid theory of Virchow and thrombogenic (encrustation) theory of Rokitansky.

• The original response to injury theory was first described in 1973 according to which the initial event in atherogenesis was considered to be endothe-

lial injury followed by smooth muscle cell proliferation so that the early lesions, according to this theory, consist of smooth muscle cells mainly.

• The modified response-to-injury hypothesis described subsequently in 1993 implicates lipoprotein entry into the intima as the initial event followed by lipid accumulation in the macrophages (foam cells now) which according to modified theory, are believed to be the dominant cells in early lesions.

i) *Endothelial injury*. It has been known for many years that endothelial injury is the initial triggering event in the development of lesions of atherosclerosis. Actual endothelial denudation is not an essential requirement, but endothelial dysfunction may initiate the sequence of events. Endothelial injury can be induced in experimental animals by mechanical trauma, haemodynamic forces, immunological and chemical mechanisms, chronic hyperlipidaemia, bacterial endotoxins, viruses, hypoxia and by carbon monoxide and tobacco products. In man, risk factors such as hypertension, cigarette smoking and chronic hyperlipidaemia can cause endothelial damage or alter endothelial function. The role of haemodynamic forces in causing endothelial injury is further supported by the distribution of atheromatous plaques at points of bifurcation or branching of blood vessels which are under greatest shear stress.

ii) *Intimal smooth muscle cell proliferation*. Endothelial injury causes adherence, aggregation and platelet release reaction at the site of exposed subendothelial connective tissue. Proliferation of intimal smooth muscle cells is stimulated by various mitogens, the most important of which is platelet-derived growth factor (PDGF); others are fibroblast growth factor, epidermal growth factor, and transforming growth factor-alpha (TGF-α). Proliferation can also be facilitated by loss of growth inhibitors such as TGF-β and heparin-like substances. Intimal proliferation of smooth muscle cells is accompanied by synthesis of matrix proteins — collagen, elastic fibre proteins and proteoglycans.

iii) *Role of blood monocytes*. Though blood monocytes do not possess receptors for normal LDL, LDL does appear in the monocyte cytoplasm to form foam cell by mechanism. Plasma LDL on entry into the intima undergoes oxidation. The 'oxidised LDL' so formed in the intima performs the following all-important functions on monocytes and endothelium:

• For monocytes, oxidised LDL acts to attract, proliferate, immobilise and activate them as well as is readily taken up by scavenger receptor on the monocyte to transform it to a lipid-laden foam cell.

• For endothelium, oxidised LDL is cytotoxic.

Death of foam cell by apoptosis releases lipid to form lipid core of plaque.

iv) *Role of hyperlipidaemia.* As stated already, chronic hyperlipidaemia in itself may initiate endothelial injury and dysfunction by causing increased permeability.

Secondly, increased serum concentration of LDL and VLDL promotes formation of foam cells, while high serum concentration of HDL has anti-atherogenic effect.

v) *Thrombosis.* As apparent from the foregoing, endothelial injury exposes subendothelial connective tissue resulting in formation of small platelet aggregates at the site and causing proliferation of smooth muscle cells. This causes mild inflammatory reaction which together with foam cells is incorporated into the atheromatous plaque. The lesions enlarge by attaching fibrin and cells from the blood so that thrombus becomes a part of atheromatous plaque.

2. Monoclonal hypothesis. This hypothesis is based on the postulate that proliferation of smooth muscle cells is the primary event and that this proliferation is monoclonal in origin similar to cellular proliferation in neoplasms (e.g. in uterine leiomyoma). The evidence cited in support of monoclonal hypothesis is the observation on proliferated smooth muscle cells in atheromatous plaques which have only one of the two forms of glucose-6-phosphate dehydro-genase (G6PD) isoenzymes, suggesting monoclonality in origin. The monoclonal proliferation of smooth muscle cells in atherosclerosis may be initiated by mutation caused by exogenous chemicals (e.g. cigarette smoke), endogenous metabolites (e.g. lipoproteins) and some viruses (e.g. Marek's disease virus in chickens, herpesvirus).

CLASSIFICAION OF ATHEROSCLEROSIS

Localization of the process: 1. Atherosclerosis of aorta. 2. Atherosclerosis of coronary arteries. 3. Atherosclerosis of cerebral arteries. 4. Atherosclerosis of renal arteries. 5. Atherosclerosis of mesenteric arteries. 6. Atherosclerosis of lower limbs arteries.

Clinical aspects:

I period (preclinical): a) vasomotor disturbances; b) complex of laboratory disturbances;

II period (clinical): a) ischemic; b) thrombonecrotic; c) sclerotic.

Fazes of course: 1. Progression of atherosclerosis. 2. Stabilization of process. 3. Regression of atherosclerosis.

Pathologic changes:

Microscopic stages of atherosclerosis:

1. Prelipid stage – is characterized by general metabolism impairment and increase of endothelium permeability.
2. Lipidosis – it means infiltration of tunica intima with lipoproteins and formation of lipid plaques.

3. Lyposclerosis is characterized by growth of connective tissue around lipoproteins (corresponds to stage of fibrous plaques).

4. Atheromatosis is characterized by degradation of lipoprotein plaques.

5. Ulcerative stage is characterized by formation of atheromatous ulcer on vascular surface usually with thrombus formation.

6. Atherocalcinosis – deposition of Ca2+ salts (dystrophic calcification).

Macroscopic stages of atherosclerosis:

1. Fatty streaks and dots,
2. Gelatinous lesions,
3. Atheromatous plaques,
4. Complicated plaques (plaques with ulceration, haemorrhages and thrombosis).
5. Calcification, or atherocalcification.

The clinical disease states due to luminal narrowing in atherosclerosis are caused by fully developed atheromatous plaques and complicated plaques. However, early lesions in the form of diffuse intimal thickening, fatty streaks and gelatinous lesions are often the forerunners in the evolution of atherosclerotic lesions.

1. Fatty streaks and dots. Fatty streaks and dots on the intima by themselves are harmless but may be the precursor lesions of atheromatous plaques. They are seen in all races of the world and begin to appear in the first year of life. However, they are uncommon in older persons and are probably absorbed. They are especially prominent in the aorta and other major arteries, more often on the posterior wall than the anterior wall. Grossly, the lesions may appear as flat or slightly elevated and yellow. They may be either in the form of small, multiple dots, about 1 mm in size, or in the form of elongated, beaded streaks. Microscopically, fatty streaks lying under the endo-thelium are composed of closely-packed foam cells, lipid-containing elongated smooth muscle cells and a few lymphoid cells. Small amount of extracellular lipid, collagen and proteoglycans are also present.

2. Gelatinous lesions. Gelatinous lesions develop in the intima of the aorta and other major arteries in the first few months of life. Like fatty streaks, they may also be precursors of plaques. They are round or oval, circumscribed grey elevations, about 1 cm in diameter.

Microscopically, gelatinous lesions are foci of increased ground substance in the intima with thinned overlying endothelium.

3. Atheromatous plaques. A fully developed atherosclerotic lesion is called atheromatous plaque, also called fibrous plaque, fibrofatty plaque or atheroma. Unlike fatty streaks, atheromatous plaques are selective in different geo-

graphic locations and races and are seen in advanced age. These lesions may develop from progression of early lesions of the atherosclerosis described above. Most often and most severely affected is the abdominal aorta, though smaller lesions, may be seen in descending thoracic aorta and aortic arch. The major branches of the aorta around the ostia are often severely involved, especially the iliac, femoral, carotid, coronary, and cerebral arteries.

Grossly, atheromatous plaques are white to yellowish-white lesions, varying in diameter from 1-2 cm and raised on the surface by a few millimeters to a centrimeter in thickness. Cut section of the plaque reveals the luminal surface as a firm, white fibrous cap and a central core composed of yellow to yellow-white, soft, porridge-like material and hence the name atheroma.

Microscopically, the appearance of plaque varies depending upon the age of the lesion. However, the following features are invariably present:

• The superficial luminal part of fibrous cap is covered by endothelium, and is composed of smooth muscle cells, dense connective tissue and extracellular matrix containing proteoglycans and collagen.

• The cellular area under the fibrous cap is comprised by a mixture of macrophages, foam cells, lymphocytes and a few smooth muscle cells which may contain lipid.

• The deeper central soft core consists of extracellular lipid material, cholesterol clefts, fibrin, necrotic debris and lipid-laden foam cells.

• In older and more advanced lesions, the collagen in the fibrous cap may be dense and hyalinised, smooth muscle cells may be atrophic and foam cells are fewer.

4. Complicated plaques. Various pathologic changes that occur in fully-developed atheromatous plaques are called the complicated lesions. These account for the most serious and aneurysmal dilatation. It is not uncommon to see more than one form of complication in a plaque.

i) Calcification. Calcification occurs more commonly in advanced atheromatous plaques, especially in the aorta and coronaries. The diseased intima cracks like an egg-shell when the vessel is incised and opened.

Microscopically, the calcium salts are deposited in the vicinity of necrotic area and in the soft lipid pool deep in the thickened intima. This form of atherosclerotic intimal calcification differs from Monckeberg's medial calcific arteriosclerosis that affects only the tunica media.

ii) Ulceration. The layers covering the soft pultaceous material of an atheroma may ulcerate as a result of haemodynamic forces or mechanical trauma. This results in discharge of emboli composed of lipid material and debris into the blood stream, leaving a shallow, ragged ulcer with yellow lipid debris in the base of the ulcer. Occasionally, atheromatous plaque in a

coronary artery may suddenly rupture into the arterial lumen forcibly and cause thromboembolic occlusion.

iii) Thrombosis. The ulcerated plaque and the areas of endothelial damage are vulnerable sites for formation of superimposed thrombi. These thrombi may get dislodged to become emboli and lodge elsewhere in the circulation, or may get organised and incorporated into the arterial wall as mural thrombi. Mural thrombi may become occlusive thrombi which may subsequently recanalise.

iv) Haemorrhage. Intimal haemorrhage may occur in an atheromatous plaque either from the blood in the vascular lumen through an ulcerated plaque, or from rupture of thin-walled capillaries that vascularise the atheroma from adventitial vasa vasorum. Haemorrhage is particularly a common complication in coronary arteries. The haematoma formed at the site contains numerous haemosiderin-laden macrophages.

v) Aneurysm formation. Though atherosclerosis is primarily an intimal disease, advanced lesions are associated with secondary changes in the media and adventitia. The changes in media include atrophy and thinning of the media and fragmentation of internal elastic lamina. The adventitia undergoes fibrosis and some inflammatory changes. These changes cause weakening in the arterial wall resulting in aneurysmal dilatation.

Clinical Effects

The clinical effects of atherosclerosis depend upon the size and type of arteries affected. In general, the clinical effects result from the following:

1. Slow luminal narrowing causing ischaemia and atrophy.
2. Sudden luminal occlusion causing infarction necrosis.
3. Propagation of plaque by formation of thrombi and emboli.
4. Formation of aneurysmal dilatation and eventual rupture.

Large arteries affected most often are the aorta, renal, mesenteric and carotids, whereas the medium- and small-sized arteries frequently involved are the coronaries, cerebrals and arteries of the lower limbs. Accordingly, the symptomatic atherosclerotic disease involves most often the heart, brain, kidneys, small intestine and lower extremities. The effects pertaining to these organs are described in relevant chapters later. Some of the important effects are listed below:

i) Aorta – Aneurysm formation, thrombosis and embolisation to other organs.

ii) Heart – Myocardial infarction, ischaemic heart disease.

iii)) Brain – Chronic ischaemic brain damage, cerebral infarction.

iv) Small intestine – Ischaemic bowel disease, infarction.

v) Lower extremities – Iintermittent claudication, gangrene.

HYPERTENSIVE VASCULAR DESIASE

An elevated arterial blood pressure is a major health problem, particularly in developed countries. A persistent and sustained high blood pressure has damaging effects on the heart, brain and kidneys (benign and malignant nephrosclerosis).

Definition and Classification

Arterial or systemic hypertension in a patient is defined clinically as *'borderline'* if the systolic blood pressure is 140 – 149 mm Hg, and diastolic pressure is 90 - 94 mm Hg, and *'hypertensive'*.

Table 1. Classification of Blood Pressure for Adults Aged ≥ 18 Years: JNC 7 vs JNC 6

JNC 7 Blood Pressure Category	JNC 6 Blood Pressure Categor y	SBP (mm Hg)	and/or	DBP (mm Hg)
Normal	Optimal	< 120	and	< 80
Prehypertension		120-139	or	80-89
	Normal	< 130	and	< 85
	High-normal	130-139	or	85-89
Hypertension:	Hypertension			
Stage 1	Stage 1	140-159	or	90-99
Stage 2		≥ 160	or	≥ 100
	Stage 2	160-179	or	100-109
	Stage 3	≥ 180	or	≥ 110

The diastolic pressure is often considered more significant. However, blood pressure varies with many factors such as age of the patient, exercise, emotional disturbances like fear and anxiety. Therefore, it is important to measure blood pressure at least twice during two separate examinations under least stressful conditions. A clinically useful classification of hypertension has been recently described by the Joint National Committee of the WHO/International Society of Hypertension. By means of these criteria, the prevalence of hypertension is observed in about 25% of population. Hypertension is generally classified into 2 types:

1. Primary or essential hypertension in which the cause of increase in blood pressure is unknown. Essential hypertension constitutes about 90-95% patients of hypertension.

2. Secondary hypertension, in which the increase in blood pressure is caused by diseases of the kidneys, endocrines or some other organs. Secondary hypertension comprises 5-10% cases of hypertension.

According to the clinical course, both essential and secondary hypertension may be benign or malignant.

• **Benign hypertension** is moderate elevation of blood pressure and the rise is slow over the years.

About 90-95% patients of hypertension have benign hypertension.

• **Malignant hypertension** is marked and rapid increase of blood pressure to 200/140 mm Hg or more and the patients have papilloedema, retinal haemorrhages and hypertensive encephalopathy. Less than 5% of hypertensive patients develop malignant hypertension and life expectancy after diagnosis in these patients is generally less than 2 years if not treated effectively.

Etiology and Pathogenesis

The etiology and pathogenesis of secondary hypertension that comprises less than 10% cases has been better understood, whereas the mechanism of essential hypertension that constitutes about 90% of cases remains largely obscure. In general, normal blood pressure is regulated by 2 haemodynamic forces – *cardiac output* and *total peripheral vascular resistance.* Factors which alter these two factors result in hypertension. The role of kidney in hypertension, particularly in secondary hypertension, by elaboration of renin and subsequent formation of angiotensin II, is well established (renin-angiotensin system).

With this background knowledge, we next turn to the mechanisms involved in the two forms of hypertension.

ESSENTIAL (PRIMARY) HYPERTENSION. By definition, the cause of essential hypertension is unknown but a number of factors are related to its development. These are as under:

1. Genetic factors. The role of heredity in the etiology of essential hypertension has long been suspected. The evidences in support are the familial aggregation, occurrence of hypertension in twins, epidemiologic data, experimental animal studies and identification of hypertension susceptibility gene (angiotensinogen gene).

2. Racial and environmental factors. Surveys in the US have revealed higher incidence of essential hypertension in blacks than in whites. A number of environmental factors have been implicated in the development of hypertension including salt intake, obesity, skilled occupation, higher living standards and patients in high stress.

3. Risk factors modifying the course of essential hypertension. There is sufficient evidence to show that the course of essential hypertension that begins in middle life is modified by a number of factors. These are as under:

i) Age. Younger the age at which hypertension is first noted but left untreated, lower the life expectancy.

ii) Sex. Females with hypertension appear to fare better than males.

iii) Atherosclerosis. Accelerated atherosclerosis invariably accompanies essential hypertension. This could be due to contributory role of other independent factors like cigarette smoking, elevated serum cholesterol, glucose intolerance and obesity.

iv) Other risk factors. Other factors which alter the prognosis in hypertension include: smoking, excess of alcohol intake, diabetes mellitus, persistently high diastolic pressure above 115 mm Hg and evidence of end-organ damage (i.e. heart, eyes, kidney and nervous system).

The *pathogenetic mechanism* in essential hypertension is explained by many theories. These are:

1. *High plasma level of catecholamines.*

2. Increase in blood volume i.e. arterial overfilling (volume hypertension) and arteriolar constriction (vasoconstrictor hypertension).

3. *Increased cardiac output.*

4. *Low-renin essential hypertension* found in approximately 20% patients due to altered responsiveness to renin release.

5. *High renin essential hypertension* seen in about 15% cases due to decreased adrenal responsiveness to angiotensin II.

SECONDARY HYPERTENSION. Mechanisms underlying hypertension with identifiable cause have been studied more extensively. Based on the etiology, these are described under four headings: renal hypertension, endocrine hypertension, hypertension associated with coarctation of aorta and neurogenic causes.

1. **Renal Hypertension**. Hypertension produced by renal diseases is called renal hypertension. Renal hypertension is subdivided into 2 groups:

i) Renal vascular hypertension e.g. in occlusion of a major renal artery, pre-eclampsia, eclampsia, polyarteritis nodosa and fibromuscular dysplasia of renal artery.

ii) Renal parenchymal hypertension e.g. in various types of glomerulonephritis, pyelonephritis, interstitial nephritis, diabetic nephropathy, amyloidosis, polycystic kidney disease and renin-producing tumours.

In either case, renal hypertension can be produced by one of the 3 inter-related pathogenetic mechanisms:

- activation of renin-angiotensin system,
- sodium and water retention, and
- decreased release of vasodepressor materials.

a) Activation of renin-angiotensin system. Renin is a proteolytic enzyme produced and stored in the granules of the juxtaglomerular cells surrounding the afferent arterioles of glomerulus. The release of renin is stimulated by renal ischaemia, sympathetic nervous system stimulation, depressed sodium concentration, fluid depletion and decreased potassium intake. Released renin is transported through blood stream to the liver where it acts upon substrate angiotensinogen, an a_2-globulin synthesised in the liver, to form angiotensin I, a decapeptide. Angiotensin I is converted into angiotensin II, an octapeptide, by the action of convertase in the lungs. Angiotensin II is the most potent naturally-

occurring vasoconstrictor substance and its pressor action is mainly attributed to peripheral arteriolar vasoconstriction. The other main effect of angiotensin II is to stimulate the adrenal cortex to secrete aldosterone that promotes reabsorption of sodium and water.

Thus, the renin-angiotensin system is concerned mainly with 3 functions:

i) Control of blood pressure by altering plasma concentration of angiotensin II and aldosterone.

ii) Regulation of sodium and water content,

iii)) Regulation of potassium balance.

b) Sodium and water retention. Blood volume and cardiac output, both of which have a bearing on blood pressure, are regulated by blood levels of sodium which is significant for maintaining extracellular fluid volume. Blood concentration of sodium is regulated by 3 mechanisms:

i) *Release of aldosterone* from activation of renin-angiotensin system, as already explained,

ii) *Reduction in GFR* due to reduced blood flow as occurs in reduced renal mass or renal artery stenosis. This results in proximal tubular reabsorption of sodium,

iii) *Release of atriopeptin hormone* from atria of the heart in response to volume expansion. These peptides cause increased GFR and inhibit sodium reabsorption.

c) Release of vasodepressor material. A number of vasodepressor materials and antihypertensives counterbalance the vasopressor effect of angiotensin II. These substances include: prostaglandins (PGE2, PGF2, PGA or medullin) released from interstitial cells of the medulla, urinary kallikrein-kinin system and platelet-activating factor.

2. **Endocrine hypertension**. A number of hormonal secretions may produce secondary hypertension. These are:

i) *Adrenal gland* – e.g. in primary aldosteronism, Cushing's syndrome, adrenal virilism and pheochromocytoma.

ii) *Parathyroid gland* – e.g. hypercalcaemia in hyperparathyroidism.

iii) *Oral contraceptives* – Oestrogen component in the oral contraceptives stimulates hepatic synthesis of renin substrate.

3. **Coarctation of aorta**. Coarctation of the aorta causes systolic hypertension in the upper part of the body due to constriction itself. Diastolic hypertension results from changes in circulation.

4. **Neurogenic**. Psychogenic, polyneuritis, increased intracranial pressure and section of spinal cord are all uncommon causes of secondary hypertension.

EFFECTS OF HYPERTENSION

Systemic hypertension causes major effects in three main organs – heart and its blood vessels, nervous system, and kidneys. The renal effects in the form of benign and malignant nephrosclerosis are discussed below, whereas hypertensive effects on other organs are described elsewhere in the respective chapters.

Benign Nephrosclerosis is the term used to describe the kidney of benign phase of hypertension. Mild benign nephrosclerosis is the most common form of renal disease in persons over 60 years of age but its severity increases in the presence of hypertension and diabetes mellitus.

Pathologic changes. Grossly, both the kidneys are affected equally and are reduced in size and weight, often weighing about 100 gm or less. The capsule is often adherent to the cortical surface. The surface of the kidney is finely granular and shows V-shaped areas of scarring. The cut surface shows firm kidney and narrowed cortex. *Microscopically*, there are primarily diffuse vascular changes which produce parenchymal changes secondarily as a result of ischaemia. The histologic changes are, thus, described as vascular and parenchymal:

i) Vascular changes: Changes in blood vessels involve arterioles and arteries up to the size of arcuate arteries. There are 2 types of changes in these blood vessels:

a) *Hyaline arteriolosclerosis* that results in homogeneous and eosinophilic thickening of the wall of small blood vessels.

b) *Intimal thickening* due to proliferation of smooth muscle cells in the intima.

ii) Parenchymal changes: As a consequence of ischaemia, there is variable degree of atrophy of parenchyma. This includes: glomerular shrinkage, deposition of collagen in Bowman's space, periglomerular fibrosis, tubular atrophy and fine interstitial fibrosis.

Clinical features. There is variable elevation of the blood pressure with headache, dizziness, palpitation and nervousness. Eye ground changes may be found but papilloedema is absent. Renal function tests and urine examination are normal in early stage. But in long-standing cases, there may be mild proteinuria with some hyaline or granular casts. Rarely, renal failure and uraemia may occur.

Malignant Nephrosclerosis is the form of renal disease that occurs in malignant or accelerated hypertension. Malignant nephrosclerosis is uncommon and usually occurs as a superimposed complication in 5% cases of preexisting benign essential hypertension or in those having secondary hypertension with identifiable cause such as in chronic renal diseases. However, the pure form of disease also occurs, particularly at younger age with preponderance in males.

Pathologic changes. *Grossly,* the appearance of the kidney varies. In a case of malignant hypertension superimposed on pre-existing benign nephrosclerosis, the kidneys are small in size, shrunken and reduced in weight and have finely granular surface. However, the kidneys of a patient who develops malignant hypertension in pure form are enlarged, oedematous and have petechial haemorrhages on the surface producing so called *'flea-bitten kidney'*. Cut surface shows red and yellow mottled appearance.

Microscopically, most commonly the changes are superimposed on benign nephrosclerosis. These changes are as under:

i) Vascular changes: These are more severe and involve the arterioles. The two characteristic vascular changes seen are as under:

a) *Necrotising arteriolitis* develops on hyaline arteriolosclerosis. The vessel wall shows fibrinoid necrosis, a few acute inflammatory cells and small haemorrhages.

b) *Hyperplastic intimal sclerosis* or *onionskin proliferation* is characterised by concentric laminae of proliferated smooth muscle cells, collagen and basement membranes.

ii) Ischaemic changes: The effects of vascular narrowing on the parenchyma include tubular loss, fine interstitial fibrosis and foci of infarction necrosis.

Clinical features. The patients of malignant nephrosclerosis have malignant or accelerated hypertension with blood pressure of 200/140 mm Hg or higher. Headache, dizziness and impaired vision are commonly found. The presence of papilloedema distinguishes malignant from benign phase of hypertension. The urine frequently shows haematuria and proteinuria. Renal function tests show deterioration during the course of the illness. Azotaemia (high BUN and serum creatinine) and uraemia develop soon if malignant hypertension is not treated aggressively. Approximately 90% of patients die within one year from causes such as uraemia, congestive heart failure and cerebrovascular accidents.

CEREBROVASCULAR DISEASES

Cerebrovascular diseases include a variety of medical conditions that affect the blood vessels of the brain and the cerebral circulation. Arteries supplying oxygen and nutrients to the brain are often damaged by atherosclerosis or arterial hypertension or deformed in these disorders. The most common presentations of cerebrovascular diseases are a stroke (ischemic and hemorrhagic), transitory ischemia of the brain, discirculatory encephalopathy and vertebro-basilar insufficiency.

TRANSITORY ISCHEMIA OF BRAIN, OR TRANSIENT ISCHEMIC ATTACK (TIA)

TIA (also called a mini-stroke) is a condition in which the blood flow to a region of the brain is blocked, but blood flow is quickly restored and the

brain tissue can fully recover. The symptoms are only transient, leaving no sequelae or long-term deficits. In order to diagnose this entity, all neurologic signs and symptoms must have been resolved within 24 hrs without evidence of brain infarction on brain imaging.

Morphologically TIA is characterized by vascular disturbances (spasm of arteriols, serum imbibitions of their walls, perivascular edema and single small haemorrhages) and local changes of brain tissue (edema, dystrophic changes of neurons).

Sometimes perivascular accumulation of haemosiderin is revealed at the place of former small haemorrhages.

STROKE

There are two main variants of strokes: ischemic and hemorrhagic. Ischemic stroke means decreased blood supply to the brain regions, while hemorrhagic stroke is bleeding into or around the brain.

Signs and symptoms of a stroke may include an inability to move or feel on one side of the body (hemiplegia), problems of speech understanding or speaking, dizziness, loss of vision, etc. Signs and symptoms often appear soon after the stroke has occurred. A hemorrhagic stroke may also be associated with a severe headache.

Ischemic stroke, the most common is caused by a blockage of a blood vessel in the brain usually due thrombosis or emboli from the proximal arteries or from the heart, that leads to the brain ischemia. The neurologic signs and symptoms last longer than 24 hours and the brain infarction is demonstrated by imaging techniques.

Morphologically ischemic stroke is characterized by cerebral infarction development or grey malacia of the brain matter.

Haemorrhagic stroke.

There are two main types of hemorrhagic stroke:

Intracerebral hemorrhage, which is basically bleeding within the brain itself (when an artery in the brain bursts, flooding the surrounding tissue with blood), due to either intraparenchymal hemorrhage (bleeding within the brain tissue) or intraventricular hemorrhage (bleeding within the brain's ventricular system).

Subarachnoid hemorrhage, which is basically bleeding that occurs outside of the brain tissue but still within the skull, and precisely between the arachnoid mater and pia mater (the delicate innermost layer of the three layers of the meninges that surround the brain).

The above two main types of hemorrhagic stroke are also two different forms of intracranial hemorrhage, which is the accumulation of blood anywhere within the cranial vault; but the other forms of intracranial hemor-

rhage, such as epidural hematoma (bleeding between the skull and the dura mater, which is the thick outermost layer of the meninges that surround the brain) and subdural hematoma (bleeding in the subdural space), are not considered "hemorrhagic strokes".

Hemorrhagic strokes may occur on the background of alterations to the blood vessels in the brain, such as hyalinosis, cerebral amyloid angiopathy, cerebral arteriovenous malformation and an intracranial aneurysm, which can cause intraparenchymal or subarachnoid hemorrhage.

In addition to neurological impairment, hemorrhagic strokes usually cause specific symptoms (for instance, subarachnoid hemorrhage classically causes a severe headache known as a thunderclap headache) or reveal evidence of a previous head injury.

Inflammation contributes to the secondary brain injury after hemorrhage.

The outcomes of stroke vary widely depending on size and location of the lesion. Disfunctions depend on the brain areas that have been damaged.

Some of the physical disabilities that can result from stroke include muscle weakness, numbness, pressure sores, pneumonia, incontinence, apraxia (inability to perform learned movements), difficulties to carry out the daily activities, appetite loss, speech loss, vision loss and pain.

Emotional problems following a stroke can be due to direct damage of emotional centers in the brain or from frustration and difficulty of adapting to new limitations.

If the stroke is severe enough, or in a certain location such as parts of the brainstem, coma or death can result.

VERTEBROBASILAR INSUFFICIENCY (VBI)

Vertebrobasilar insufficiency (VBI), or vertebral-basilar ischemia, also called beauty parlor syndrome (BPS), is a temporary set of symptoms due to decreased blood flow (ischemia) in the posterior circulation of the brain. The posterior circulation supplies blood to the medulla, cerebellum, pons, midbrain, thalamus, and occipital cortex (responsible for vision). Therefore, the symptoms due to VBI vary according to which portions of the brain experience significantly decreased blood flow. In the United States, 25% of strokes and transient ischemic attacks occur in the vertebrobasilar distribution. These must be separated from strokes arising from the anterior circulation, which involves the carotid arteries.

Main causes of vascular disorders in the VB-system are:

1. Occlusive damages (atherosclerotic stenosis and thrombosis, embolisms, arteriitis of different etiology, fibromuscular dysplasia and other);

2. Extravascular compressions (compression by osteophytes, articular processes, muscles, vessels, tumors, scars and other);

3. Deformation (pathological crimpiness, thrombosis);

4. Abnormalities (hypoplasia, abnormalities of beginning, localization, topography and other).

DYSCIRCULATORY ENCEPHALOPATHY (DEP)

Dyscirculatory encephalopathy is a slowly progressive brain dysfunction that has arisen as a result of diffuse and / or small-focal damage to the brain tissue in conditions of long-term insufficiency of the cerebral blood supply

Dyscirculatory encephalopathy is the most common diagnosis in clinical practice. The term was proposed by G.A. Maksudov and V.M. Kogan in 1958 (according to other sources - E. Schmidt and G. Maksudov in the 70-s of the last century), and is traditionally used in the CIS countries, despite the fact that is not represented in the ICD-10. In English literature, especially in the United States, this state corresponds as subcortical arteriosclerotic encephalopathy (SAE), Binswanger's encephalopathy, multi-infarct dementia (Binswanger's type), subcortical dementia, vascular dementia (Binswanger's type), subcortical ischemic vascular disease and others (chronic cerebrovascular insufficiency, chronic cerebrovascular insufficiency, ischemic disease of the brain, etc).The vast majority (96%) was chronic ischemic – DEP.

DEP is the result of a slowly progressive blood supply due to stenosis or obliteration of small intracranial atherosclerotic arteries. This process leads to the development of primary (acute, recurrent) and secondary changes in the brain substance.

On the main reasons there are the following types of discirculatory encephalopathy: 1) atherosclerotic (often suffer great vessels of the head), 2) hypertensive, 3) mixed, and 4) venous. In general, it could be a specific disease or a combination thereof (vegetative dystonia, rheumatism, vascular lesions with vasculitis and trauma, systemic hemodynamic disorders, blood disorders, etc.). Damage in the white matter of nerve fibers leads to dissociation of the functions of the cortex and underlying structures, which results in the clinical manifestations of DEP.

ISHAEMIC HEART DISEASE

Ischaemic heart disease (IHD) is defined as acute or chronic form of cardiac disability arising from imbalance between the myocardial supply and demand for oxygenated blood. Since narrowing or obstruction of the coronary arterial system is the most common cause of myocardial anoxia, the alternate term 'coronary artery disease (CAD)' is used synonymously with IHD. IHD or CAD is the leading cause of death in most industrialised countries (about one-third of all deaths) and somewhat low incidence is observed in the developing

countries. Men develop IHD earlier than women and death rates are also slightly higher for men than for women until the menopause.

Etiopathogenesis. IHD is invariably caused by disease affecting the coronary arteries, the most prevalent being atherosclerosis accounting for more than 90% cases, while other causes are responsible for less than 10% cases of IHD. Therefore, it is convenient to consider the etiology of IHD under three broad headings:

i) coronary atherosclerosis;

ii) superadded changes in coronary atherosclerosis; and

iii) non-atherosclerotic causes.

I. Coronary Atherosclerosis

Coronary atherosclerosis resulting in 'fixed' obstruction is the major cause of IHD in more than 90% cases. Here, a brief account of the pathology of lesions in atherosclerotic coronary artery disease is presented.

1. Distribution. Atherosclerotic lesions in coronary arteries are distributed in one or more of the three major coronary arterial trunks, the highest incidence being in the anterior descending branch of the left coronary, followed in decreasing frequency, by the right coronary artery and still less in circumflex branch of the left coronary. About one-third of cases have single-vessel disease, most often left anterior descending arterial involvement; another one-third have two-vessel disease, and the remainder have three major vessel disease.

2. Location. Almost all adults show atherosclerotic plaques scattered throughout the coronary arterial system. However, significant stenotic lesions that may produce chronic myocardial ischaemia show more than 75% (three-fourth) reduction in the cross-sectional area of a coronary artery or its branch. The area of severest involvement is about 3 to 4 cm from the coronary ostia, more often at or near the bifurcation of the arteries, suggesting the role of haemodynamic forces in atherogenesis.

3. Fixed atherosclerotic plaques. The atherosclerotic plaques in the coronaries are more often eccentrically located bulging into the lumen from one side. Occasionally, there may be concentric thickening of the wall of the artery. Atherosclerosis produces gradual luminal narrowing that may eventually lead to 'fixed' coronary obstruction. The general features of atheromas of coronary arteries are similar to those affecting elsewhere in the body and may develop similar complications like calcification, coronary thrombosis, ulceration, haemorrhage, rupture and aneurysm formation.

II. Superadded Changes in Coronary Atherosclerosis

The attacks of acute coronary syndromes, namely acute myocardial infarction, unstable angina and sudden ischaemic death, are precipitated by cer-

tain changes superimposed on a pre-existing fixed coronary atheromatous plaque. These are as under:

1. Acute changes in chronic atheromatous plaque.

Though chronic fixed obstructions are the most frequent cause of IHD, acute coronary episodes are often precipitated by sudden changes in chronic plaques such as plaque haemorrhage, fissuring, or ulceration that results in embolisation of atheromatous debris. Acute plaque changes are brought about by factors such as sudden coronary artery spasm, tachycardia, intraplaque haemorrhage and hypercholesterolaemia.

2. Coronary artery thrombosis. Transmural acute myocardial infarction is often precipitated by partial or complete coronary thrombosis. The initiation of thrombus occurs due to surface ulceration of fixed chronic atheromatous plaque, ultimately causing complete luminal occlusion. The lipid core of plaque, in particular, is highly thrombogenic. Small fragments of thrombotic material are then dislodged which are embolised to terminal coronary branches and cause microinfarcts of the myocardium.

3. Local platelet aggregation and coronary artery spasm. Some cases of acute coronary episodes are caused by local aggregates of platelets on the atheromatous plaque, short of forming a thrombus. The aggregated platelets release vasospasmic mediators such as thromboxane A_2 which may probably be responsible for coronary vasospasm in the already atherosclerotic vessel.

III. Non-Atherosclerotic Causes

A number of other lesions may cause IHD in less than 10% of cases. These are as under:

1. Vasospasm. It has been possible to document vasospasm of one of the major coronary arterial trunks in patients with no significant atherosclerotic coronary narrowing which may cause angina or myocardial infarction.

2. Stenosis of coronary ostia. Coronary ostial narrowing may result from extension of syphilitic aortitis or from aortic atherosclerotic plaques encroaching on the opening.

3. Arteritis. Various types of inflammatory involvements of coronary arteries or small branches like in rheumatic arteritis, polyarteriitis nodosa, thromboangiitis obliterans (Buerger's disease), Takayasu's disease, Kawasaki's disease, tuberculosis and other bacterial infections may contribute to myocardial damage.

4. Embolism. Rarely, emboli originating from elsewhere in the body may occlude the left coronary artery and its branches and produce IHD. The emboli may originate from bland thrombi, or from vegetations of bacterial endocarditis; rarely fat embolism and air embolism of coronary circulation may occur.

5. Thrombotic diseases. Another infrequent cause of coronary occlusion is from hypercoagulability of the blood such as in shock, polycythaemia vera, sickle cell anaemia and thrombotic thrombocytopenic purpura.

6. Trauma. Contusion of a coronary artery from penetrating injuries may produce thrombotic occlusion.

7. Aneurysms. Extension of dissecting aneurysm of the aorta into the coronary artery may produce thrombotic coronary occlusion. Rarely, congenital, mycotic and syphilitic aneurysms may occur in coronary arteries and produce similar occlusive effects.

8. Compression. Compression of a coronary from outside by a primary or secondary tumour of the heart may result in coronary occlusion.

EFFECTS OF MYOCARDIAL ISCHAEMIA

Development of lesions in the coronaries is not always accompanied by cardiac disease. Depending upon the suddenness of onset, duration, degree, location and extent of the area affected by myocardial ischaemia, there can be two types of ischaemic manifestations:

A. Myocardial infarction

B. Non-infarct effects of myocardial ischaemia which include the following:

1. Angina pectoris
2. Chronic ischaemic heart disease
3. Sudden cardiac death

Acute coronary syndromes include: acute myocardial infarction, unstable angina and sudden ischaemic death.

MYOCARDIAL INFARCTION

Myocardial infarction (MI) is the most important consequence of coronary artery disease. Many patients may die within the first few hours of the onset, while remainder suffer from effects of impaired cardiac function. A significant factor that may prevent or diminish the myocardial damage is the development of collateral circulation through anastomotic channels over a period of time. A regular and well-planned exercise programme is likely to encourage good collateral circulation.

Incidence. In industrialised countries, MI accounts for 10-25% of all deaths. Due to the dominant etiologic role of coronary atherosclerosis in MI, the incidence of MI correlates well with the incidence of atherosclerosis in a geographic area.

Age. MI may virtually occur at all ages, though the incidence is higher in the elderly. About 5% of heart attacks occur in young people under the age

of 40 years, particularly in those with major risk factors to develop atherosclerosis like hypertension, diabetes mellitus, cigarette smoking, familial hypercholesterolaemia etc.

Sex. Males throughout their life are at a significantly higher risk of developing MI as compared to females. Women during reproductive period have remarkably low incidence of MI, probably due to the protective influence of oestrogen. The use of oral contraceptives is associated with high risk of developing MI. After menopause, this sex difference gradually declines but the incidence of disease among women never reaches that among men of the same age.

Etiopathogenesis. The etiologic role of severe coronary atherosclerosis (more than 75% compromise of lumen) of one or more of the three major coronary arterial trunks in the pathogenesis of about 90% cases of acute MI is well documented by autopsy studies as well as by coronary angiographic studies. A few notable features in the etiology and pathogenesis of acute MI are considered below:

1. Mechanism of myocardial ischaemia. Myocardial ischaemia is brought about by one or more of the following mechanisms:

i) Diminised coronary blood flow e.g. in coronary artery disease, shock.

ii) Increased myocardial demand e.g. in exercise, emotions.

iii) Hypertrophy of the heart without simultaneous increase of coronary blood flow e.g. in hypertension, valvular heart disease.

2. Role of platelets. Rupture of an atherosclerotic plaque exposes the subendothelial collagen to platelets which undergo aggregation, activation and release reaction. These events contribute to the build-up of the platelet mass that may give rise to emboli or initiate thrombosis.

3. Complicated plaques. Two important complications in coronary atherosclerotic plaques which are frequently encountered are coronary thrombosis and haemorrhage:

i) Superimposed coronary thrombosis is seen in about half the cases of acute MI. Infusion of intracoronary fibrinolysins in the first few hours of development of acute MI in such cases restores blood flow in the blocked vessel in majority of cases.

ii) Intramural haemorrhage is found in about one-third cases of acute MI. Haemorrhage and thrombosis may occur together in some cases.

4. Non-atherosclerotic causes. About 10% cases of acute MI are caused by non-atherosclerotic factors such as coronary vasospasm, arteritis, coronary ostial stenosis, embolism, thrombotic diseases, trauma and outside compression as already described.

5. Transmural versus subendocardial infarcts. There are some differences in the pathogenesis of the transmural infarcts involving the full thickness of ventricular wall and the subendocardial (laminar) infarcts affecting the inner subendocardial one-third to half. These are as under:

i) Transmural (full thickness) infarcts are the most common type seen in 95% cases. Critical coronary narrowing (more than 75% compromised lumen) is of great significance in the causation of such infarcts. Atherosclerotic plaques with superimposed thrombosis and intramural haemorrhage are significant in about 90% cases, and non-atherosclerotic causes in the remaining 10% cases.

ii) Subendocardial (laminar) infarcts have their genesis in reduced coronary perfusion due to coronary atherosclerosis but without critical stenosis (not necessarily 75% compromised lumen), aortic stenosis or haemorrhagic shock. This is because subendocardial myocardium is normally least well perfused by coronaries and thus is more vulnerable to any reduction in the coronary flow. Superimposed coronary thrombosis is frequently encountered in these cases too, and hence the beneficial role of fibrinolytic treatment in such patients.

Types of infarcts. Infarcts have been classified in a number of ways by the physicians and the pathologists:

1. *According to the time of appearance*:

i) Primary MI continues 8 weeks from the onset of myocardium ischemia.

ii) Secondary MI develops in 4 weeks after primary one.

iii) Recurrent MI arises during 4 weeks after appearance of primary one.

2. According to tha anatomic region of the left ventricle involved, they are called anterior, posterior (inferior), lateral, septal and circumferential, and their combinations like anterolateral, posterolateral (or inferolateral) and anteroseptal.

3. According to the degree of thickness of the ventricular wall involved, infarcts are of four types:

i) full-thickness or transmural, when necrosis involves the entire thickness of the ventricular wall,

ii) subendocardial or laminar, when necrosis occupies the innner subendocardial half of the myocardium,

iii) subepicardial, when necrosis occupies the outer subepicardial half of the myocardium;

iv) Intramural, when they occupy the middle part of myocardium.

4. According to the age of infarcts, they are of two types:

i) Newly-formed infarcts are called acute, recent or fresh.

ii) Advanced infarcts are called old, healed or organized.

5. According to spreading of necrotic changes:

i) small focal,

ii) large focal,

iii)) transmural.

Location of infarcts. Infarcts are most frequently located in the left ventricle. Right ventricle is less susceptible to infarction due to its thin wall, having less metabolic requirements and is thus adequately nourished by the thebesian vessels. Atrial infarcts, whenever present, are more often in the right atrium, usually accompanying the infarct of the left ventricle. Left atrium is relatively protected from infarction because it is supplied by the oxygenated blood in the left atrial chamber.

TABLE 2. Contrasting Features of Subendocardial and Transmural Infarcts

	Feature	Transmural infarct	Subendocardial infarct
1.	Definition	Full-thickness, solid	Inner third to half, patchy
2.	Frequency	Most frequent (95%)	Less frequent
3.	Distribution	Specific area of coronary supply	Circumferential
4.	Pathogenesis	> 75% coronary stenosis	Hypoperfusion of myocardium
5.	Coronary thrombosis	Common	Rare
6.	Epicarditis	Common	None

The region of infarction depends upon the area of obstructed blood supply by one or more of the three coronary arterial trunks. Accordingly, there are three regions of myocardial infarction:

1. Stenosis of the left anterior descending coronary artery is the most common (40-50%). The region of infarction is the anterior part of the left ventricle including the apex and the anterior two-thirds of the interventricular septum.

2. Stenosis of the right coronary artery is the next most frequent (30-40%). It involves the posterior part of the left ventricle and the posterior one-third of the interventricular septum.

3. Stenosis of the left circumflex coronary artery is seen least frequently (15-20%). Its area of involvement is the lateral wall of the left ventricle.

Pathologic changes. The gross and microscopic changes in the myocardial infarction vary according to the age of the infarct.

Grossly, most infarcts occur singly and vary in size from 4 to 10 cm. As explained above, they are found most often in the left ventricle. Less often, there are multifocal lesions. The transmural infarcts, which by definition involve the entire thickness of the ventricular wall, usually have a thin rim of

preserved subendocardiai myocardium which is perfused directly by the blood in the ventricular chamber. The subendocardial infarcts which affect the inner subendocardial half of the myocardium produce less well-defined gross changes than the transmural infarcts. The sequence of macroscopic changes in all myocardial infarcts is as under:

1. In 6 to 12-hour old infarcts, no striking gross changes are discernible except that the affected myocardium is slightly paler and drier than normal. However, the early infarcts (3 to 6 hours old) can be detected by histochemical staining for dehydrogenases on unfixed slice of the heart. This consists of immersing a slice of unfixed heart in the solution of triphenyl tetrazolium chloride (TTC) which imparts red brown colour to the normal heart muscle, while the area of infarcted muscle fails to stain due to lack of dehydrogenases.

2. By about 24 hours, the infarct develops cyanotic, red-purple, blotchy areas of haemorrhage due to stagnation of blood.

3. During the next 48 to 72 hours, these changes become progressively more distinct.

4. By 4th day, the infarct develops a yellow border due to neutrophilic infiltration and thus becomes more well defined

5. By the end of first week, the entire infarct is bright yellow or yellow-green, soft and has thin hyperaemic border.

6. By 10 days, the periphery of the infarct appears reddish-purple due to growth of granulation tissue. With the passage of time, further healing takes place; the necrotic muscle is resorbed and the infarct shrinks and becomes pale grey.

7. By the end of 6 weeks, the infarcted area is replaced by a thin, grey-white, hard, shrunken fibrous scar which is well developed in about 2 to 3 months. However, the time taken by an infarct to heal by fibrous scar may vary depending upon the size of the infarct and adequacy of collateral circulation.

Microscopically, the changes are similar in both transmural and subendocardial infarcts. As elsewhere in the body, myocardial ischaemia induces ischaemic coagulative necrosis of the myocardium which eventually heals by fibrosis.

I. First week: The progression of changes takes place in the following way:

i) In the first 6 hours after infarction, usually no detectable histologic change is observed in routine light microscopy. However, some investigators have described stretching and waviness of the myocardial fibres within one hour of the onset of ischaemia.

ii) After 6 hours, there is appearance of some oedema fluid between the myocardial fibres. The muscle fibres at the margin of the infarct show vacuolar degeneration called myocytolysis.

iii) By 12 hours, coagulative necrosis of the myocardial fibres sets in and neutrophils begin to appear at the margin of the infarct. Coagulative necrosis of fibres is characterised by loss of striations and intense eosinophilic, hyaline appearance and may show nuclear changes like karyolysis, pyknosis and karyorrhexis. Haemorrhages and oedema are present in the interstitium.

iv) During the first 24 hours, coagulative necrosis progresses further as evidenced by shrunken eosinophilic cytoplasm and pyknosis of the nuclei. The neutrophilic infiltrate at the margins of the infarct is slight.

v) During the first 48 to 72 hours, coagulative necrosis is complete with loss of nuclei. The neutrophilic infiltrate is well developed and extends centrally into the interstitium.

vi) By 4th day, neutrophilic infiltrate is further pronounced with some of them undergoing degenerative changes.

vii) By the end of first week, the process of resorption of necrosed muscle fibres by macrophages begins. Simultaneously, there is onset of proliferation of capillaries and fibroblasts from the margins of the infarct.

TABLE 3. Sequential Pathologic Changes in Myocardial Infarction

Time	Gross changes	Light microscopy
First week		
0-6 hours	No change or pale; TTC test negative in infarcted area	No change; stretching and waviness of fibres
6-12 hours	-do-	Coagulative necrosis begins; neutrophilic infiltration begins; oedema and haemorrhages present
24 hours	Cyanotic red-purple area of haemorrhage	Coagulative necrosis progresses; marginal neutrophilic infiltrate
48-72 hours	Pale, hyperaemic	Coagulative necrosis complete, neutrophilic infiltrate well developed
4th day	Well-defined yellow border	Prominent neutrophilic infiltrate some undergoing degeneration
7th day	Bright yellow to yellow-green, soft	Beginning of resorption of necrosed fibres by macrophages, onset of fibrovascular response; neutrophils gradually disappear
Second week		
10th day	Red-purple periphery	Most of the necrosed muscle in a

		small infarct removed; fibrovascular reaction more prominent; pigmented macrophages, eosinophils, lymphocytes, plasma cells present
14th day	-------	Necrosed muscle mostly removed; neutrophils disappear; fibrocollagenic tissue at the periphery
Third week	-------	Necrosed muscle fibres from larger infarcts removed; more ingrowth of fibrocollagenic tissue
Fourth to sixth week	Thin, grey-white, hard, shrunken fibrous scar	Increased fibrocollagenic tissue, decreased vascularity; fewer pigmented macrophages, lymphocytes and plasma cells

Many of the neutrophils are necrosed and gradually disappear.

2. Second week: The changes are as under:

i) By 10th day, most of the necrosed muscle at the periphery of infarct is removed. The fibrovascular reaction at the margin of infarct is more prominent. Many pigmented macrophages containing yellow-brown lipofuscin (derived from breakdown of myocardial cells) and golden brown haemosiderin (derived from lysed erythrocytes in haemorrhagic areas) are seen. Also present are a few other inflammatory cells like eosinophils, lymphocytes and plasma cells.

ii) By the end of the 2nd week, most of the necrosed muscle in small infarcts is removed, neutrophils have almost disappeared, and newly laid collagen fibres replace the periphery of the infarct.

3. Third week: Necrosed muscle fibres from larger infarcts continue to be removed and replaced by ingrowth of newly formed collagen fibres. Pigmented macrophages as well as lymphocytes and plasma cells are prominent while eosinophils gradually disappear.

4. Fourth to sixth week: With further removal of necrotic tissue, there is increase in collagenous connective tissue, decreased vascularity and fewer pigmented macrophages, lymphocytes and plasma cells. Thus, at the end of 6 weeks, a contracted fibrocollagenic scar with diminished vascularity is formed. The pigmented macrophages may persist for a long duration in the scar, sometimes for years.

Changes in early infarcts. By special techniques like electron microscopy, chemical and histochemical studies, changes can be demonstrated in early infarcts before detectable light microscopic alterations appear. It has been shown by experimental studies on early infarcts that recovery is possible if blood flow is restored within 20 to 30 minutes of infarction after which the injury becomes irreversible.

1. Electron microscopic changes. Changes by EM examination are evident in less than half an hour on onset of infarction. These changes are:

i) Disappearance of perinuclear glycogen granules within 5 minutes of ischaemia.

ii) Swelling of mitochondria in 20 to 30 minutes.

iii) Disruption of sarcolemma.

iv) Nuclear alterations like peripheral clumping of nuclear chromatin.

2. Chemical and histochemical changes. Analysis of tissues from early infarcts by chemical and histochemical techniques has shown a number of findings. These are:

i) Glycogen depletion in myocardial fibres within 30 to 60 minutes of infarction.

ii) Increase in lactic acid in the myocardial fibres.

iii) Loss of K^+ from the ischaemic fibres.

iv) Increase of Na^+ in the ischaemic cells.

v) Influx of Ca^{++} into the cells causing irreversible cell injury.

Based on the above observations and on leakage of enzymes from the ischaemic myocardium, alterations in the concentrations of various enzymes are detected in the blood of these patients.

COMPLICATIONS. Following an attack of acute MI, only 10-20% cases do not develop major complications and recover. The remainder 80-90% cases develop one or more major complications, some of which are fatal. The immediate mortality from acute MI (sudden cardiac death) is about 25%. The important complications which may develop following acute MI are as follows:

1. Arrhythmias. Arrhythmias are the most common form of complications in acute MI. These occur due to ischaemic injury or irritation to the conduction system, resulting in abnormal rhythm. Other causes of arrhythmias include leakage of K^+ from ischaemic muscle cells and increased concentration of lactate and free fatty acids in the tissue fluid. Arrhythmias may be in the form of sinus tachycardia or sinus bradycardia, atrial fibrillation, premature systoles, and the most serious ventricular fibrillation responsible for many sudden cardiac deaths.

2. Congestive heart failure. About half the patients with MI develop CHF which may be in the form of right ventricular failure, left ventricular failure or both. CHF is responsible for about 40% of deaths from acute MI. If the patient survives, healing may restore normal cardiac function but in some CHF may persist and require regular treatment later.

3. Cardiogenic shock. About 10% of patients with acute MI develop cardiogenic shock characterised by hypotension with systolic blood pressure of 80 mmHg or less for many days. Shock may be accompanied by peripheral circulatory failure, oliguria and mental confusion.

4. Mural thrombosis and thromboembolism. The incidence of thromboembolism from intracardiac thrombi and from thrombosis in the leg veins is 15-45% in cases of acute MI and is the major cause of death in 12% cases. Mural thrombosis in the heart develops due to involvement of the endocardium and subendocardium in the infarct and due to slowing of the heart rate. Mural thrombi often form thromboemboli. Another source of thromboemboli is the venous thrombosis in the leg veins due to prolonged bed rest. Thromboemboli from either source may cause occlusion of the pulmonary, renal, mesenteric, splenic, pancreatic or cerebral arteries and cause infarcts in these organs.

5. Rupture. Rupture of heart occurs in upto 5% cases of acute MI causing death. Rupture occurs most often from the infarcted ventricular wall into the pericardial cavity causing haemopericardium and tamponade. Other sites of rupture are through interventricular septum and rupture of a papillary muscle in infarct of the left ventricle. Rupture at any of these sites occurs usually in the first week and is often fatal.

6. Cardiac aneurysm. Another 5% of patients of MI develop aneurysm, often of the left ventricle. It occurs in healed infarcts through thin, fibrous, non-elastic scar tissue. Cardiac aneurysms impair the function of the heart and are the common sites for mural thrombi. Rarely, calcification of the wall of aneurysm may occur.

7. Pericarditis. Sterile pericarditis appearing on about the second day is common over transmural infarcts. It is characterised by fibrinous pericarditis and may be associated with pericardial effusion. Often, it is of no functional significance and resolves spontaneously.

8. Post-myocardial infarction syndrome. About 3 to 4% of patients who suffered from acute MI develop post-myocardial infarction syndrome or Dressler's syndrome subsequently. It usually occurs 1 to 6 weeks after the attack of MI. It is characterised by pneumonitis. The symptoms are usually mild and disappear in a few weeks. The exact pathogenesis of this syndrome is not known. It may be due to autoimmune reaction as evidenced by circulating anti-heart antibodies in the serum of these patients. But these antibodies are also present in patients with MI who do not develop this syndrome.

B. NON-INFARCT EFFECTS OF MYOCARDIAL ISCHAEMIA

Myocardial ischaemia may produce effects other than infarction. These are: angina pectoris, chronic ischaemic heart disease, and sudden cardiac (coronary) death.

ANGINA PECTORIS is a clinical syndrome of IHD resulting from transient myocardial ischaemia. It is characterised by paroxysmal pain in the substernal or precordial region of the chest which is aggravated by an increase in

the demand of the heart and relieved by a decrease in the work of the heart. Often, the pain radiates to the left arm, neck, jaw or right arm.

There are 3 overlapping clinical patterns of angina pectoris with some differences in their pathogenesis:

i) Stable or typical angina,

ii) Prinzmetal's variant angina,

iii) Unstable or crescendo angina.

CHRONIC ISCHAEMIC HEART DISEASE, or Ischaemic Cardiomyopathy, or Myocardial sclerosis are the terms used for focal or diffuse fibrosis in the myocardium characteristically found in elderly patients of progressive IHD. Such small areas of fibrous scarring are commonly found in the heart of patients who have history of episodes of angina and attacks of MI some years back. The patients generally have gradually developing CHF due to decompensation over a period of years. Occasionally, serious cardiac arrhythmias or infarction may supervene and cause death.

Etiopathogenesis. In majority of cases, coronary atherosclerosis causes progressive ischaemic myocardial damage and replacement by myocardial sclerosis. A small percentage of cases may result from other causes such as emboli, coronary arteritis and myocarditis.

The mechanism of development of myocardial sclerosis can be explained by one of the following concepts:

i) Myocardial fibrosis represents healing of minute infarcts involving small scattered groups of myocardial fibres.

ii) An alternate concept of development of myocardial sclerosis is healing of minute areas of focal myocytolysis – the myocardial fibres in a small area undergo slow degeneration due to myocardial ischaemia. These fibres lose their myofibrils but nuclei remain intact. These foci are infiltrated by macrophages and eventually are replaced by proliferating fibroblasts and collagen.

Pathologic changes. Grossly, the heart may be normal in size or hypertrophied. The left ventricular wall generally shows foci of grey-white fibrosis in brown myocardium. Healed scars of previous MI may be present. Valves of the left heart may be distorted, thickened and show calcification. Coronary arteries invariably show moderate to severe atherosclerosis.

*Microscopically***,** the characteristic features are as follows:

i) There are scattered areas of diffuse myocardial fibrosis, especially around the small blood vessels in the interstitial tissue of the myocardium,

ii) Intervening single fibres and groups of myocardial fibres show variation in fibre size and foci of myocytolysis.

iii) Areas of brown atrophy of the myocardium may also be present.

iv) Coronary arteries show atherosclerotic plaques and may have complicated lesions in the form of superimposed thrombosis.

Sudden Cardiac (Coronary) Death is defined as sudden natural death from cardiac causes within 1 hour of the onset of acute cardiac symptoms. The most important cause is IHD; other less common causes are: coronary vasospasm, calcific aortic stenosis, myocarditis of various types, hypertrophic cardiomyopathy, mitral valve prolapse, endocarditis, and hereditary and acquired defects of the conduction system. The mechanism of sudden death by myocardial ischaemia is almost always by fatal arrhythmias, chiefly ventricular asystole or fibrillation.

Pathologic changes. At autopsy, such cases reveal most commonly critical atherosclerotic coronary narrowing (more than 75% compromised lumen) in one or more of the three major coronary arterial trunks with superimposed thrombosis or plaque-haemorrhage. Healed and new myocardial infarcts are found in many cases.

TABLE 4. Lesions in Coronary Artery in Various Forms of IHD

Types of IHD	Coronary lesion
1. Myocardial infarction	Plaque haemorrhage Fissuring and ulceration Complete mural thrombosis
2. Stable angina	Critical coronary narrowing (3/4th)
3. Unstable (pre-infarction) angina	Plaque rupture, haemorrhage ulceration, Mural thrombosis with thromboembolism
4. Chronic IHD	Chronic progressive coronary atherosclerosis
5. Sudden ischaemic death	Severe multivessel disease Acute changes in plaque Thrombosis with thromboembolism

RHEUMATIC (OR COLLAGEN-VASCULAR) DISEASES

A number of collagen diseases may result in chronic interstitial fibrosis and destruction of blood vessels. All rheumatic diseases are characterized by common features:

- systemic disorganization of connective tissue;
- impairment of microcirculatory bed vessels:
- impairment of immune homeostasis:
- chronic progressive wavy course of pathologic process:
- positive effect of corticosteroid therapy.

This group of diseases includes:

1. Rheumatism (Rheumatic fever). This infection-allergic disease damages mainly the heart and vessels. It may have different form and duration. Clinicomorhologic forms of rheumatism are polyarthritic, cardiovascular, cerebral, nodular.

2. Scleroderma (progressive systemic sclerosis).

3. Rheumatoid arthritis.

4. Systemic lupus erythematosus.

5. Dermatomyositis and polymyositis.

6. Sjogren's syndrome. Patients with Sjogren's syndrome often have rheumatoid arthritis and associated pulmonary changes. Involvement of the bronchial mucous gland by a process similar to that in the salivary glands can lead to inadequate bronchial clearance and repeated infections.

7. Wegener's granulomatosis.

All rheumatic diseases have common features:

- systemic disorganization of connective tissue,
- damage of microcirculatory bed vessels,
- impairment of immune homeostasis,
- progressive course of pathologic process,
- positive effect of corticosteroid therapy.

Microscopically, these granulomas have foci of fibrinoid necrosis and intense exudate of lymphocytes, plasma cells and macrophages with scattered multinucleate giant cells. Besides necrotising granulomas, there is associated vasculitis.

RHEUMATIC FEVER (RHEUMATISM)

Rheumatic fever (RF) is a systemic, post-streptococcal, non-suppurative inflammatory disease, principally affecting the heart, joints, central nervous system, skin and subcutaneous tissues. The chronic stage of RF involves all the layers of the heart (pancarditis) causing major cardiac sequelae referred to as rheumatic heart disease (RHD). In spite of its name suggesting an acute arthritis migrating from joint to joint, it is now well known that it

is the heart rather than the joints which is first affected. William Boyd years ago gave the dictum 'rheumatism licks the joint, but bites the whole heart'.

Incidence. The disease appears most commonly in children between the age of 5 to 15 years when the streptococcal infection is most frequent and intense. Both the sexes are affected equally, though some investigators have noted a slight female preponderance.

The geographic distribution, incidence and severity of RF and RHD are generally related to the frequency and severity of streptococcal pharyngeal infection. The disease is seen more commonly in poor socioeconomic strata of the society living in damp and overcrowded places which promote interpersonal spread of the streptococcal infection. Its incidence has declined in the developed countries as a result of improved living conditions and use of antibiotics in streptococcal infection. But it is still common in the developing countries of the world like in India, Pakistan, some Arab countries, parts of Africa and South America.

Etiopathogenesis. After a long controversy, the etiologic role of preceding throat infection with β-haemolytic streptococci of group A in RF is now generally accepted. However, the mechanism of lesions in the heart, joints and other tissues is not by direct infection but by induction of hypersensitivity or autoimmunity. Thus, there are 2 components in the etiology and pathogenesis of RF and RHD: the infective component and the autoimmune component.

A. The infective component. There is a body of clinical and epidemiological evidence to support the concept that RF occurs following infection of the throat and upper respiratory tract with β-haemolytic streptococci of Lancefield group A. These evidences are as under:

1. There is often a history of infection of the pharynx and upper respiratory tract with this microorganism about 2 to 3 weeks prior to the attack of RF. This period is usually the latent period required for sensitisation to the bacteria.

2. Subsequent attacks of streptococcal infection are generally associated with exacerbations of RF.

3. A higher incidence of RF has been observed after outbreaks and epidemics of streptococcal infection of throat in children from schools or in youngmen from training camps.

4. Administration of antibiotics leads to lowering of the incidence as well as severity of RF and its recurrences.

5. Cardiac lesions similar to those seen in RHD have been produced in experimental animals by induction of repeated infection with P-haemolytic streptococci of group A.

6. Patients with RF have elevated titres of antibodies to the antigens of β-haemolytic streptococci of group A such as anti-streptolysin O (ASO), anti-streptokinase, anti-streptohyaluronidase and anti DNAase B.

7. Socioeconomic factors like poverty, poor nutrition, density of population, overcrowding in quarters for sleeping etc are associated with spread of infection, lack of proper medical attention and hence higher incidence of RF.

8. The geographic distribution of the disease, as already pointed out, shows higher frequency and severity of the disease in the developing countries of the world where the living conditions are substandard and medical facilities are insufficient. Populations in these regions develop recurrent throat infections which remain untreated and have higher incidence of RF.

9. The role of climate in the development of RF has been reported by some workers. The incidence of the disease is higher in subtropical and tropical regions with cold, damp climate near the rivers and waterways which favour the spread of infection.

10. The individual susceptibility to RF and familial incidence have been reported. The factors contributing to proneness to develop RF include adverse social conditions, presence of streptococcal carrier at home and, as yet unclear role of hereditary defect.

Despite all these evidences, only a small proportion of patients with streptococcal pharyngeal infection develop RF – the attack rate is less than 3%. There is a suggestion that a concomitant virus enhances the effect of streptococci in individuals who develop RF. The microorganisms are not cultured from the lesions in the heart, joints and other tissues at the time RF appears 2 to 3 weeks after acute streptococcal infection.

B. The autoimmune component. Failure to grow microorganism from the active rheumatic lesions in different tissues has led to the concept that some antigenic products of streptococci in throat are absorbed through the blood vessels and lymphatics and are then distributed to different tissues. These streptococcal antigens incite autogenous tissues to form autoantibodies which react with specific tissue components to produce the lesions in RF. The following evidences are cited in support of the autoimmune concept:

1. Anti-heart antibodies formed as a result of autoimmune reaction to heart tissues have been demonstrated in patients of RF who develop cardiac lesions.

2. Experimental induction of rheumatic condition in rats by injecting mixture of killed streptococci and emulsions of target tissue (e.g. heart or connective tissue) has been possible. Autoantibodies against its own respective tissues are demonstrated in blood.

However, it has not been possible to characterise the specific streptococcal products nor is it clear which individual will develop RF and RHD following streptococcal pharyngeal infection.

Pathologic changes. RF is generally regarded as an autoimmune focal inflammatory disorder of the connective tissues throughout the body. The

cardiac lesions of RF in the form of pancarditis, particularly the valvular lesions, are its major manifestations. However, supportive connective tissues at other sites like the synovial membrane, periarticular tissue, skin and subcutaneous tissue, arterial wall, lungs, pleura and the CNS are all affected (extracardiac lesions).

A. CARDIAC LESIONS

The cardiac manifestations of RF are in the form of focal inflammatory involvement of the interstitial tissue of all the three layers of the heart, the so-called pancarditis. The pathognomonic feature of pancarditis in RF is the presence of distinctive Aschoff nodules or Aschoff bodies.

TABLE 5. Classification of Cardiovascular form of Rheumatic Fever

	Endocarditis	**Myocarditis**	**Pericarditis**
Forms	Vasculitis	Nodular productive (granulomatous)	Serous
	Acute warty endocarditis	Diffusive exudative	Serous-fibrinous
	Fibroplastic	Spotted interstitial myocarditis	Fibrinous
	Reverse warty		

The Aschoff nodules or bodies. The Aschoff nodules or the Aschoff bodies are spheroidal or fusiform distinct microscopic structures occurring in the interstitium of the heart in RF. They are especially found in the vicinity of small blood vessels in the myocardium and endocardium and occasionally in the pericardium and the adventitia of the proximal part of the aorta. Lesions similar to the Aschoff nodules may be found in the extra-cardiac tissues.

Evolution of fully-developed Aschoff bodies involves 3 stages all of which may be found in the same heart at different stages of development. These are as follows:

1. Early (exudative or degenerative) stage. The earliest sign of injury in the heart in RF is apparent by about 4th week of illness. Initially, there is oedema of the connective tissue and increase in acid mucopolysaccharide in the ground substance. This results in separation of the collagen fibres by accumulating ground substance. Eventually, the collagen fibres are fragmented and disintegrated and the affected focus takes the appearance and staining characteristics of fibrin. This change is referred to as fibrinoid degeneration.

2. Intermediate (proliferative or granulomatous) stage. It is this stage of the Aschoff body which is pathognomonic of rheumatic conditions. This stage is apparent in 4th to 13th week of illness. The early stage of fibrinoid

change is followed by proliferation of cells resulting in formation of lymphocytes, plasma cells, a few neutrophils and the characteristic cardiac histiocytes (Anitschkow cells) at the margin of the lesion. Cardiac histiocytes or Anitschkow cells are present in small numbers in normal heart but their number is increased in the Aschoff bodies. These are large mononuclear cells having central round nuclei and contain moderate amount of amphophilic cytoplasm. The nuclei are vesicular and contain prominent central chromatin mass which in longitudinal section appears serrated or caterpillar-like, while in cross-section the chromatin mass appears as a small rounded body in the centre of the vesicular nucleus, just like an owl's eye. Some of these modified cardiac histiocytes become multinucleate cells containing 1 to 4 nuclei and are called Aschoff cells.

The origin and nature of the Anitschkow cells have long been debated. They are considered by most workers as modified cardiac histiocytes. However, others consider Anitschkow cells as derivatives of striated heart muscle cells or of non-striated smooth muscle cells present in the endocardium. Still others have suggested the genesis of these cells from proliferation of diseased lymphatic vessels in RF.

3. Late (healing or fibrous) stage. The stage of healing by fibrosis of the Aschoff nodule occurs in about 12 to 16 weeks after the illness. The nodule becomes oval or fusiform in shape, about 200 μm wide and 600 μm long. The Anitschkow cells in the nodule become spindle-shaped with diminished cytoplasm and the nuclei stain solidly rather than showing vesicular character. These cells tend to be arranged in a palisaded manner. With passage of months and years, the Aschoff body becomes less cellular and the collagenous tissue is increased. Eventually, it is replaced by a small fibrocollagenous scar with little cellularity, frequently located perivascularly.

RHEUMATIC PANCARDITIS. Although all the three layers of the heart are affected in RF, the intensity of their involvement is variable.

RHEUMATIC ENDOCARDITIS. Endocardial lesions of RF may involve the valvular and mural endocardium, causing rheumatic valvulitis and mural endocarditis, respectively. Rheumatic valvulitis is chiefly responsible for the major cardiac manifestations in chronic RHD.

RHEUMATIC VALVULITIS. Grossly, the valves in acute RF show thickening and loss of translucency of the valve leaflets or cusps. This is followed by the formation of characteristic, small (1 to 3 mm in diameter), rnulitple, warty vegetations or verrucae, chiefly along the line of closure of the leaflets and cusps. These tiny vegetations are almost continuous so that the free margin of the cusps or leaflets appears as a rough and irregular ridge. The vegetations in RF appear grey-brown, translucent and are firmly attached so that

they are not likely to get detached to form emboli, unlike the friable vegetations of infective endocarditis.

Though all the four heart valves are affected, their frequency and severity of involvement varies: mitral valve alone being the most common site, followed in decreasing order of frequency, by combined mitral and aortic valve. The tricuspid and pulmonary valves usually show infrequent and slight involvement. The higher incidence of vegetations on left side of the heart is possibly because of the greater mechanical stresses on the valves of the left heart, especially along the line of closure of the valve cusps. The occurrence of vegetations on the atrial surfaces of the atrioventricular valves (mitral and tricuspid) and on the ventricular surface of the semilunar valves (aortic and pulmonary) further lends support to the role of mechanical pressure on the valves in the pathogenesis of vegetations.

The chronic stage of RHD is characterised by permanent deformity of one or more valves, especially the mitral and aortic. The frequency of deformity of various valves is as under: mitral alone in 65-70% of cases, mitral and aortic combined in about 25% cases, and rarely tricuspid and pulmonary valves are involved. The macroscopic appearance of chronic healed valves in RHD is the most characteristic 'fish mouth' or 'button hole' stenosis of the mitral valve. Mitral stenosis and insufficiency are commonly combined in chronic RHD; calcific aortic stenosis may also be found. These healed chronic valvular lesions in RHD occur due to diffuse fibrocollagenous thickening and calcification of the valve cusps or leaflets which cause adhesions between the lateral portions, especially in the region of the commissures. Thickening, shortening and fusion of the chordae tendineae further contribute to the chronic valvular lesions. Microscopically, the inflammatory changes begin in the region of the valve rings (where the leaflets are attached to the fibrous annulus) and then extend throughout the entire leaflet, whereas vegetations are usually located on the free margin of the leaflets and cusps.

i) In the early (acute) stage, the histological changes are oedema of the valve leaflet, presence of increased number of capillaries and infiltration with lymphocytes, plasma cells, histiocytes with many Anitschkow cells and a few polymorphs. Occasionally, Aschoff bodies with central foci of fibrinoid necrosis and surrounded by palisade of cardiac histiocytes are seen, but more often the cellular infiltration is diffuse in acute stage of RF. Vegetations present at the free margins of cusps appear as eosinophilic, tiny structures mainly consisting of fibrin with superimposed platelet-thrombi and do not contain bacteria.

ii) In the healed (chronic) stage, the vegetations have undergone organisation. The valves show diffuse thickening as a result of fibrous tissue with hyalinisation, and often calcification. Vascularisation of the valve cusps

may still be evident in the form of thick-walled blood vessels with narrowed lumina. Typical Aschoff bodies are rarely seen in the valves at this stage.

Rheumatic mural endocarditis. Mural endocardium may also show features of rheumatic carditis though the changes are less conspicuous as compared to valvular changes.

Grossly, the lesions are seen most commonly as MacCallum's patch which is the region of endocardial surface in the posterior wall of the left atrium just above the posterior leaflet of the mitral valve. MacCallum's patch appears as a map-like area of thickened, roughened and wrinkled part of the endocardium.

Microscopically, the appearance of MacCallum's patch is similar to that seen in rheumatic valvulitis. The affected area shows oedema, fibrinoid change in the collagen, and cellular infiltrate of lymphocytes, plasma cells and macrophages with many Anitschkow cells. Typical Aschoff bodies may sometimes be found.

RHEUMATIC MYOCARDITIS. Grossly, in the early (acute) stage, the myocardium, especially of the left ventricle, is soft and flabby. In the intermediate stage, the interstitial tissue of the myocardium shows small foci of necrosis. Later, tiny pale foci of the Aschoff bodies may be visible throughout the myocardium.

Microscopically, the most characteristic feature of rheumatic myocarditis is the presence of distinctive Aschoff bodies. These diagnostic nodules are scattered throughout the interstitial tissue of the myocardium and are most frequent in the interventricular septum, left ventricle and left atrium. Derangements of the conduction system may, thus, be present. The Aschoff bodies are best identified in the intermediate stage when they appear as granulomas with central fibrinoid necrosis and are surrounded by palisade of Anitschkow cells and multinucleate Aschoff cells. There is infiltration by lymphocytes, plasma cells and some neutrophils. In the late stage, the Aschoff bodies are gradually replaced by small fibrous scars in the vicinity of blood vessels and the inflammatory infiltrate subsides. Presence of active Aschoff bodies along with old healed lesions is indicative of rheumatic activity.

RHEUMATIC PERICARDITIS. Inflammatory involvement of the pericardium commonly accompanies RHD.

Grossly, the usual finding is fibrinous pericarditis in which there is loss of normal shiny pericardial surface due to deposition of fibrin on its surface and accumulation of slight amount of fibrinous exudate in the pericardial sac. If the parietal pericardium is pulled off from the visceral pericardium, the two separated surfaces are shaggy due to thick fibrin covering them. This appearance is often likened to 'bread and butter appearance' i.e. resembling the

buttered surfaces of two slices in a sandwich when they are gently pulled apart. If fibrinous pericarditis fails to resolve and, instead, undergoes organisation, the two layers of the pericardium form fibrous adhesions resulting in chronic adhesive pericarditis. **Microscopically,** fibrin is identified on the surfaces. The subserosal connective tissue is infiltrated by lymphocytes, plasma cells, histiocytes and a few neutrophils. Characteristic Aschoff bodies may be seen which later undergo organisation and fibrosis. Organisation of the exudate causes fibrous adhesions between the visceral and parietal surfaces of the pericardial sac and obliterates the pericardial cavity.

B. EXTRA-CARDIAC LESIONS

Patients of the syndrome of acute rheumatism develop lesions in connective tissue elsewhere in the body, chiefly the joints, subcutaneous tissue, arteries, brain and lungs.

POLYARTHRITIS. Acute and painful inflammation of the synovial membranes of some of the joints, especially the larger joints of the limbs, is seen in about 90% cases of RF in adults and less often in children. As pain and swelling subside in one joint, others tend to get involved, producing the characteristic 'migratory polyarthritis' involving two or more joints at a time.

Histologically, the changes are transitory. The synovial membrane and the periarticular connective tissue show hyperaemia, oedema, fibrinoid change and neutrophilic infiltration. Sometimes, focal lesions resembling Aschoff bodies are observed. A serous effusion into the joint cavity is commonly present.

SUBCUTANEOUS NODULES. The subcutaneous nodules of RF occur more often in children than in adult. These nodules are small (0.5 to 2 cm in diameter), spherical or ovoid and painless. They are attached to deeper structures like tendons, ligaments, fascia or periosteum and therefore often remain unnoticed by the patient. Characteristic locations are extensor surfaces of the wrists, elbows, ankles and knees.

Histologically, the subcutaneous nodules of RF are representative of giant Aschoff bodies of the heart. They consist of 3 distinct zones: a central area with fibrinoid changes, surrounded by a zone of histiocytes and fibroblasts forming a palisade arrangement, and the outermost zone of connective tissue which is infiltrated by nonspecific chronic inflammatory cells and proliferating blood vessels.

It may be mentioned here that histologically similar but clinically different subcutaneous lesions appear in rheumatoid arthritis; they are larger, painful and tender and persist for months to years.

ERYTHEMA MARGINATUM. This nonpruritic erythematous rash is characteristic of RF. The lesions occur mainly on the trunk and proximal parts of the extremities. The erythematous area develops central clearing and has slightly elevated red margins. The erythema is transient and migratory.

RHEUMATIC ARTERITIS. Arteritis in RF involves not only the coronary arteries and aorta but also occurs in arteries of various other organs such as renal, mesenteric and cerebral arteries. The lesions in the coronaries are seen mainly in the small intramyocardial branches.

Histologically, the lesions may be like those of hypersensitivity angiitis, or sometimes may resemble polyarteritis nodosa. Occasionally, foci of fibrinoid necrosis or ill-formed Aschoff bodies may be present close to the vessel wall.

CHOREA MINOR. Chorea minor or Sydenham's chorea or Saint Virus' dance is a delayed manifestation of RF as a result of involvement of the central nervous system. The condition is characterised by disordered and involuntary jerky movements of the trunk and the extremities accompanied by some degree of emotional instability. The condition occurs more often in younger age, particularly in girls.

Histologically, the lesions are located in the cerebral hemispheres, brainstem and the basal ganglia. They consist of small haemorrhages, oedema and perivascular infiltration of lymphocytes. There may be endarteritis obliterans and thrombosis of cortical and meningeal vessels.

RHEUMATIC PNEUMONITIS AND PLEURITIS. Involvement of the lungs and pleura occurs rarely in RF. Pleuritis is often accompanied with serofibrinous pleural effusion but definite Aschoff bodies are not present. In rheumatic pneumonitis, the lungs are large, firm and rubbery.

Histologically, the changes are oedema, capillary haemorrhages and focal areas of fibrinous exudate in the alveoli. Aschoff bodies are generally not found.

The major causes of death in RHD are cardiac failure, bacterial endocarditis and embolism:

1. Cardiac failure is the most common cause of from RHD. In young patients, cardiac failure occurs due to the chronic valvular deformities, while in patients coronary artery disease may be superim on old RHD.

2. Bacterial endocarditis of both acute and subacul may supervene due to inadequate use of antibiotics.

3. Embolism in RHD originates most commonly mural thrombi in the left atrium and its appendages, in association with mitral stenosis. The organs most frequently affected are the brain, kidneys, spleen and lungs.

4. Sudden death may occur in RHD as a result of ball thrombus in the left atrium or due to acute coronary insufficiency in association with aortic stenosis.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. Though the most prominent manifestation of RA is inflammatory arthritis of the peripheral joints, usually with a symmetrical distribution,

its systemic manifestations include haematologic, pulmonary, neurological and cardiovascular abnormalities.

RA is a common disease having peak incidence in 3rd to 4th decades of life, with 3-5 times higher preponderance in females. The condition has high association with FILA-DR4 and HLA-DR1 and familial aggregation. The onset of disease is insidious, beginning with prodrome of fatigue, weakness, joint stiffness, vague arthralgias and myalgias. This is followed by pain and swelling of joints usually in symmetrical fashion, especially involving joints of hands, wrists and feet. Unlike migratory polyarthritis of rheumatic fever, RA usually persists in the involved joint. Approximately 20% of patients develop rheumatoid nodules located over the extensor surfaces of the elbows and fingers.

About 80% of cases are seropositive for *rheumatoid factor (RF).* However, RF titres are elevated in certain unrelated diseases too such as in: viral hepatitis, cirrhosis, sarcoidosis and leprosy. Advanced cases show characteristic radiologic abnormalities such as narrowing of joint space and ulnar deviation of the fingers and radial deviation of the wrist. Other laboratory findings include mild normocytic and normochromic anaemia, elevated ESR, mild leucocytosis and hypergammaglobulinaemia. Extra-articular manifestations infrequently produce symptoms, but when present complicate the diagnosis.

Etiopathogenesis. The exact etiology and pathogenesis of RA are not known. At different times, various factors have been implicated which include: endocrine imbalance, climate, hypersensitivity reactions, infections, postinfectious immunologic reactions, autoimmunity, heredity and psychophysiologic disorders. However, present concept on etiology and pathogenesis proposes that RA occurs in an *immunogenetically predisposed individual to the effect of microbial agents acting as trigger antigen.* More recently, the role of *superantigens* which are produced by several microorganisms with capacity to bind to HLA-DR molecules has been proposed.

I. Immunologic derangements. A number of observations in patients and experimental animals indicate the role of immune processes, particularly autoimmune phenomenon, in the development of RA. These include the following:

1. Detection of circulating autoantibody called rheumatoid factor (RF) against Fc portion of autologous IgG in about 80% cases of RA. RF antibodies are heterogeneous and consist of IgM, IgG and IgA.

2. The presence of antigen-antibody complexes (IgG-RF complexes) in the circulation as well as in the synovial fluid.

3. The presence of other autoantibodies such as antinuclear factor (ANF), antibodies to collagen type II, and antibodies to cytoskeleton.

4. Antigenicity of proteoglycans of human articular cartilage.

5. The presence of γ-globulin, particularly IgG and IgM, in the synovial fluid.

6. Association of RA with amyloidosis.

7. Activation of cell-mediated immunity as evidenced by presence of numerous inflammatory cells in the synovium, chiefly CD4+ T lymphocytes and some macrophages.

II. Trigger events. Though the above hypothesis of a possible role of autoimmunity in the etiology and pathogenesis of RA is generally widely accepted, controversy continues as regards the trigger events which initiate the destruction of articular cartilage. Various possibilities which have been suggested are as follows:

1. The existence of an infectious agent such as mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus (CMV) or rubella virus, either locally in the synovial fluid or systemic infection some time prior to the attack of RA.

2. The possible role of HLA-DR4 and HLA-DR1 in initiation of immunologic damage.

The various mediators which are potentially damaging to the cartilage and subjacent bone are elaborated by *neutrophils* (e.g. reactive free radicals, proteases, PGE2 and leukotrienes); *synoviocytes* (e.g. colla-genase, PGE2 and IL-1), *lymphocytes* (e.g. lymphokines such as IL-2, γ-interferon, macrophage inhibitory and activating factors) and *macrophages* (e.g. monokines such as interleukin-1 and tumour necrosis factor).

Pathologic Changes. The predominant pathologic lesions are found in the joints and tendons, and less often, extra-articular lesions are encountered.

Articular Lesions. RA involves first the small joints of hands and feet and then symmetrically affects the joints of wrists, elbows, ankles and knees. The proximal interphalangeal and metacarpo-phalangeal joints are affected most severely. Frequently cervical spine is involved but lumbar spine is spared.

Histologically, the characteristic feature is diffuse proliferative synovitis with formation of pannus. The microscopic changes are as under:

1. Numerous folds of large villi of synovium.

2. Marked thickening of the synovial membrane due to oedema, congestion and multilayering of synoviocytes.

3. Intense inflammatory cell infiltrate in the synovial membrane with predominence of lymphocytes, plasma cells and some macrophages, at places forming lymphoid follicles.

4. Foci of fibrinoid necrosis and fibrin deposition.

The pannus progressively destroys the underlying cartilage and subchondral bone. This invasion of pannus results in demineralisation and cystic resorption of underlying bone. Later, fibrous adhesions or even bony ankylosis may unite the two opposing joint surfaces. In addition, persistent inflammation causes weakening and even rupture of the tendons.

Extra-Articular Lesions. Nonspecific inflammatory changes are seen in the blood vessels (acute vasculitis), lungs, pleura, pericardium, myocardium, lymph nodes, peripheral nerves and eyes. But one of the characteristic extra-articular manifestation of RA is occurrence of rheumatoid nodules in the skin.

Rheumatoid nodules are particularly found in the subcutaneous tissue over pressure points such as the elbows, occiput and sacrum. The center of these nodules consists of an area of fibrinoid necrosis and cellular debris, surrounded by several layers of palisading large epithelioid cells, and peripherally there are numerous lymphocytes, plasma cells and macrophages. Similar nodules may be found in the lung parenchyma, pleura, heart valves, myocardium and other internal organs.

There are some variants of RA:

1. Juvenile RA found in adolescent patients under 16 years of age is characterised by acute onset of fever and predominant involvement of knees and ankles. Pathologic changes are similar but RF is rarely present.

2. Felty's syndrome consists of polyarticular RA associated with splenomegaly and hypersplenism and consequent haematologic derangements.

3. Ankylosing spondylitis or rheumatoid spondylitis is rheumatoid involvement of the spine, particularly sacro-iliac joints, in young male patients. The condition has a strong HLA-B27 association and may have associated inflammatory diseases such as inflammatory bowel disease, anterior uveitis and Reiter's syndrome.

Pulmonary involvement in rheumatoid arthritis may result in pleural effusion, interstitial pneumonitis, necrobiotic nodules and rheumatoid pneumoconiosis (Caplan's syndrome). The parenchymatous lesions in rheumatoid arthritis are most commonly seen in the lower lobe. Necrobiotic nodules are the most specific manifestations of rheumatoid disease and closely resemble the subcutaneous nodules commonly found in rheumatoid arthritis.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE), or Libman – Sak`s disease, is a chronic disease of connective tissue with expressive autoimmunization and predominant damage of skin, vessels and kidney. Mostly young women suffer (90%) from SLE.

SLE is the classical example of systemic autoimmune or collagen diseases. The disease derives its name “lupus” from the Latin word meaning “wolf” since initially this disease was believed to affect skin only and eat away skin like a wolf. However, now 2 forms of lupus erythematosus are described:

1. Systemic or disseminated form is characterised by acute and chronic inflammatory lesions widely scattered in the body and there is presence of various nuclear and cytoplasmic autoantibodies in the plasma.

2. Discoid form is characterised by chronic and localised skin lesions involving the bridge of nose and adjacent cheeks without any systemic manifestations. Rarely, discoid form may develop into disseminated form.

Etiology. The exact etiology of SLE is not known. However, autoantibodies against nuclear and cytoplasmic components of the cells are demonstrable in plasma by immunofluorescence tests in almost all cases of SLE. There is impairment in regulation of both humoral and cell-mediated immunity. Humoral reaction develops due to appearance of autoantibodies to different nuclear and cytoplasm components (to DNA, RNA, nucleoproteins, erythrocytes, lymphocytes and thrombocytes) and formation of large amount of immune complexes. It leads to fibrinoid necrosis resulting from delayed hypersensitivity reaction.

Some of the important antinuclear antibodies (ANAs) against different nuclear antigens are:

i) antibodies to double-stranded or single-stranded DNA;

ii) antibodies to histones;

iii) antibodies to non-histone proteins bound to RNA; and

iv) antibodies to nucleolar antigens.

Out of these ANAs, antibodies to double-stranded DNA are pathognomonic of SLE.

The source of these autoantibodies as well as hypergammaglobulinaemia in SLE is the polyclonal activation of B cells brought about by following derangements:

1. Immunologic factors. These include:

i) an inherited defect in B cells;

ii) stimulation of B cells by microorganisms;

iii)) T helper cell hyperactivity; and

iv) T suppressor cell defect.

2. Genetic factors. Genetic predisposition to develop autoantibodies to nuclear and cytoplasmic antigens in SLE is due to the immunoregulatory function of class II HLA genes implicated in the pathogenesis of SLE.

3. Other factors. Various other factors express the genetic susceptibility of an individual to develop clinical disease. These factors are:

i) certain drugs e.g. penicillamine D;

ii) certain viral infections e.g. EBV infection; and

iii)) certain hormones e.g. oestrogen.

Pathogenesis. The autoantibodies formed by any of the mechanisms explained above are the mediators of tissue injury in SLE. Two types of immunologic tissue injury can occur in SLE:

1. Type III hypersensitivity is characterised by antigen-antibody complex (commonly DNA-anti-DNA antibody; sometimes Ig-anti-lg antibody

complex) which is deposited at sites such as renal glomeruli, walls of small blood vessels etc.

2. Type II hypersensitivity is characterised by formation of autoantibodies against blood cells (red blood cells, platelets, leucocytes) and results in haematologic derangement in SLE.

LE cell phenomenon. This was the first diagnostic laboratory test described for SLE. The test is based on the principle that ANAs cannot penetrate the intact cells and thus cell nuclei should be exposed to bind them with the ANAs. The binding of exposed nucleus with ANAs results in homogeneous mass of nuclear chromatin material which is called LE body or haematoxylin body.

LE cell is a phagocytic leucocyte, commonly polymorphonuclear neutrophil, and sometimes a monocyte, which engulfs the homogeneous nuclear material of the injured cell. For demonstration of LE cell phenomenon in vitro, the blood sample is traumatized to expose the nuclei of blood leucocytes to ANAs. This results in binding of denatured and damaged nucleus with ANAs. The ANA-coated denatured nucleus is chemotactic for phagocytic cells.

• If this mass is engulfed by a neutrophil, displacing the nucleus of neutrophil to the rim of the cell, it is called LE cell.

• If the mass, more often an intact lymphocyte, is phagocytosed by a monocyte, it is called Tart cell.

LE cell test is positive in 70% cases of SLE while newer and more sensitive immunofluorescence tests for autoantibodies are positive in almost 100% cases of SLE. A few other conditions may also show positive LE test e.g., rheumatoid arthritis, lupoid hepatitis, penicillin sensitivity etc.

Pathologic changes. The manifestations of SLE are widespread in different visceral organs as well as show erythematous cutaneous eruptions. The principal lesions are renal, vascular, cutaneous and cardiac; other organs and tissues involved are serosal linings (pleuritis, pericarditis); joints (synovitis); spleen (vasculitis); liver (portal triaditis); lungs (interstitial pneumonitis, fibrosing alveolitis) and CNS (vasculitis).

Histologically, the characteristic lesion in SLE is fibrinoid necrosis which may be seen in the connective tissue, beneath the endothelium in small blood vessels, under the mesothelial lining of pleura and pericardium, under the endothelium in endocardium, or under the synovial lining cells of joints.

Visceral manifestations of SLE are different. In 25% of cases heart damage is described with lesion of all there layers. In some patients abacterial endocarditis develops. There are butterfly rashes on the skin of face, glomerulonephritis with proteinuria and hematuria.

Renal manifestations of systemic lupus erythematosus (SLE) are termed lupus nephritis. The incidence of renal involvement in SLE ranges

from 40 to 75%. The two cardinal clinical manifestations of lupus nephritis are proteinuria and haematuria. In addition, hypertension and casts of different types such as red cell casts, fatty casts and leucocyte casts in the urinary sediment are found.

Pathologic Changes, According to the WHO, six patterns of mutually-merging renal lesions are seen in lupus nephritis:

Class I: Minimal lesions. On light microscopy, these cases do not show any abnormality. But examination by electron microscopy and immunofluorescence microscopy shows deposits within the mesangium which consist of IgG and **C3.**

Class II: Mesangial lupus nephritis. These cases have mild clinical manifestations. By light micros copy, there is increase in the number of mesangial cells and of mesangial matrix. Ultrastructural and immunofluorescence studies reveal granular mesangial deposits of IgG and C3; sometimes IgA and IgM are also present in the deposits.

Class III: Focal segmental lupus nephritis. This is characterised by focal and segmental proliferation of endothelial and mesangial cells, together with infiltrarion by macrophages and sometimes neutrophils.

Haematoxylin bodies of Gross may be present. Subendothelial and subepithelial deposits of IgG, often with IgM or IgA and C3, are seen.

Class IV: Diffuse proliferative lupus nephritis. In this type, all the morphologic manifestations of lupus are present in most advanced form. This is the most severe and the most common form of lupus nephritis. There is diffuse proliferation of endothelial, mesangial, and sometimes epithelial cells, involving most or all glomeruli. Electron microscopy shows large electron-dense deposits in the mesangium and in the subendothelial region which on immuno-fluorescence are positive for IgG; sometimes also for IgA or IgM, and C3.

Class V: Membranous lupus nephritis. These lesions resemble those of idiopathic membranous GN. These consist of diffuse thickening of glomerular capillary wall on light microscopy and show subendothelial deposits of immune complexes containing IgG, IgM and C3 on ultrastructural studies.

Class VI: Sclerosing lupus nephritis. This is end-stage kidney of SLE, akin to chronic GN. Most glomeruli are sclerosed and hyalinised and there may be remnants of preceding lesions.

SLE, like most other autoimmune diseases, is more common in women in their 2nd to 3rd decades of life. SLE is a multisystem disease and thus a wide variety of clinical features may be present. A typical full-fledged case of SLE has the following characteristics:

- butterfly-like erythematous rash on skin of face;
- fever;
- painful joints;
- chest pain (due to pleuritis and pericarditis);

• renal involvement (proteinuria, haematuria, casts);

• haematologic derangements (haemolytic anaemia, thrombocytopenia, leucopenia); and

• neurologic disorders (seizures, psychosis).

The disease usually runs a long course of flare-ups and remissions; renal failure is the most frequent cause of death.

Patients with systemic lupus erythematosus (SLE) commonly develop some form of lung disease during the course. The most common manifestation of SLE is pleurisy with small amount of pleural effusion that may contain LE cells. Other pulmonary lesions in SLE are interstitial pneumonitis, pulmonary haemorrhage and vasculitis.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Just like SLE, scleroderma was initially described as a skin disease characterised by progressive fibrosis. But now, 2 main types are recognised:

1. Diffuse scleroderma in which the skin shows widespread involvement and may progress to involve visceral structures.

2. CREST syndrome of progressive systemic sclerosis characterised by Calcinosis (C), Raynaud's phenomenon (R), Esophageal hypomotility (E) Sclerodactyly (S) and Telangiectasia (T).

Etiopathogenesis. The etiology of this disease is not known. However, antinuclear antibodies are detected in majority of cases of systemic sclerosis. Immunologic mechanisms have been implicated in the pathogenesis of lesions in systemic sclerosis which finally cause activation of fibroblasts. The immune mechanisms leading to stimulation of fibroblasts may act in the following ways:

1. Elaboration of cytokines such as by fibroblast growth factor and chemotactic factors by activated T cells and macrophages.

2. Endothelial cell injury due to cytotoxic damage to endothelium from autoantibodies or antigen-antibody complexes. This results in aggregation and activation of platelets which increases vascular permeability and stimulates fibroblastic proliferation.

Pathological changes. Disseminated visceral involvement as well as cutaneous lesions are seen in systemic sclerosis.

1. Skin changes. Skin is involved diffusely, beginning distally from fingers and extending proximally to arms, shoulders, neck and face. In advanced stage, the fingers become claw-like and face mask-like.

Microscopically, changes are progressive from early to late stage.

• Early stage shows oedema and degeneration of collagen. The small-sized blood vessels are occluded and there is perivascular infiltrate of mononuclear cells.

• Late stage reveals thin and flat epidermis. Dermis is largely replaced by compact collagen and there is hyaline thickening of walls of dermal blood vessels. In advanced cases subcutaneous calcification may occur.

2. Kidney changes. Involvement of kidneys is seen in majority of cases of systemic sclerosis. The lesions are prominent in the walls of interlobular arteries which develop changes resembling malignant hypertension. There is thickening of tunica intima due to concentric proliferation of intimal cells and fibrinoid necrosis of vessel wall.

3. Smooth muscle of GIT. Muscularis of the alimentary tract, particularly oesophagus, is progressively atrophied and replaced by fibrous tissue.

4. Skeletal muscle. The interstitium of skeletal muscle shows progressive fibrosis and degeneration of muscle fibres with associated inflammatory changes.

5. Cardiac muscle. Involvement of interstitium of the heart may result in heart failure.

6. Lungs. Diffuse fibrosis may lead to contraction of the lung substance. There may be epithelium-lined honeycombed cysts of bronchioles. The lungs are involved in 80% cases of scleroderma. Interstitial pulmonary fibrosis is the most common form of pulmonary involvement. The disease usually involves the lower lobes and subpleural regions of the lungs and may lead to honeycombing of the lung. There is increased risk of development of cancer of the lung in pulmonary fibrosis in scleroderma.

7. Small arteries. The lesions in small arteries show endarteritis due to intimal proliferation and may be the cause for Raynaud's phenomenon.

Systemic sclerosis is more common in middle-aged women. The clinical manifestations include claw-like flexion deformity of hands; Raynaud's phenomenon; oesophageal fibrosis causing dysphagia and hypomotility; malabsorption syndrome; respiratory distress; malignant hypertension; pulmonary hypertension; and biliary cirrhosis.

POLYMYOSITIS-DERMATOMYOSITIS

As the name suggests, this disease is a combination of symmetric muscle weakness and skin rash.

Etiopathogenesis. The exact cause of the disease is unknown. However, antinuclear antibodies are detected in *25%* of cases. Thus, an immunologic hypothesis has been proposed. The affected muscles are infiltrated by sensitised T lymphocytes of both T helper and T suppressor type which are considered to bring about inflammatory destruction of muscle. Viral etiology due to infection with coxsackie B virus has also been suggested.

Pathologic changes. The skeletal muscles usually affected are of pelvis, shoulders, neck, chest and diaphragm. Interstitial pneumonitis and interstitial fibrosis commonly accompany dermatomyositis and polymyositis.

Histologically, vacuolisation and fragmentation of muscle fibres and numerous inflammatory cells are present. In late stage, muscle fibres are replaced by fat and fibrous tissue.

It is a multisystem disease characterised by muscle weakness, mainly proximal; skin rash, typically with heliotropic erythema and periorbital oedema; dysphagia due to involvement of pharyngeal muscles; respiratory dysfunction; and association with deep-seated malignancies.

SJOGREN'S SYNDROME

Sjogren's syndrome is characterised by the triad of dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and rheumatoid arthritis. The combination of the former two symptoms is called sicca syndrome.

Etiopathogenesis. Immune mechanisms have been implicated in the etiopathogenesis of lesions in Sjogren's syndrome. Antinuclear antibodies are found in about 90% of cases; test for rheumatoid factor is positive in 25% of cases. The lesions in lacrimal and salivary glands are mediated by T lymphocytes, B cells and plasma cells.

Pathologic changes. In early stage, the lacrimal and salivary glands show periductal infiltration by lymphocytes and plasma cells, which at times may form lymphoid follicles (pseudolymphoma). In late stage, glandular parenchyma is replaced by fat and fibrous tissue. The ducts are also fibrosed and hyalinised.

The disease is common in women in 4th to 6th decades of life.

REITER'S SYNDROME

This syndrome is characterised by triad of arthritis, conjunctivitis and urethritis. There may be mucocutaneous lesions on palms, soles, oral mucosa and genitalia. Antinuclear antibodies and RA factor are usually negative.

MIXED CONNECTIVE TISSUE DISEASE

This designation is applied to a syndrome having features of 3 collagen diseases – SLE, progressive systemic sclerosis, and dermatomyositis. High titers of antinuclear antibodies are detected. The clinical features are varied and consist of manifestations of diseases included. However, renal involvement is generally not seen and prognosis is good due to response to corticosteroid therapy.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is an inflammatory lesion having 4 components — granulomas of the upper respiratory tract, granulomas of the lungs, systemic vasculitis and focal necrotising glomerulonephritis. *Localised or limited form* of the disease occurs in the lungs without involvement of other organs. Pulmonary involvement is in the form of single or multiple granulomas.

Microscopically, these granulomas have foci of fibrinoid necrosis and intense exudate of lymphocytes, plasma cells and macrophages with scattered multinucleate giant cells. Besides necrotising granulomas, there is associated vasculitis.

PATHOLOGY OF THE RESPIRATORY SYSTEM

LUNGS

Anatomy. The normal *adult right lung* weighs 375 to 550 gm (average 450 gm) and is divided by two fissures into three lobes - the upper, middle and lower lobes. The weight of the normal *adult left lung* is 325 to 450 gm (average 400 gm) and has one fissure dividing it into two lobes - the upper and lower lobes, while the middle lobe is represented by the lingula. The airways of the lungs arise from the trachea by its division into right and left main bronchi which continue to divide and subdivide further so as to terminate into the alveolar sacs. The right main bronchus is more vertical so that aspirated foreign material tends to pass down to the right lung rather than to the left. The trachea, major bronchi and their branchings possess cartilage, smooth muscle and mucous glands in their walls, while the bronchioles have smooth muscle but lack cartilage as well as the mucous glands. Between the tracheal bifurcation and the smallest bronchi, about 8 divisions take place. The *bronchioles* so formed further undergo 3 to 4 divisions leading to the *terminal bronchioles* which are less than 2 mm in diameter. The part of the lung tissue distal to a terminal bronchiole is called an *acinus.* A cluster of about 5 acini supplied by terminal bronchioles and enclosed by visible fibrous septa is termed as the *pulmonary lobule.* An **acinus** consists of 3 parts:

1. Several (usually 3 to 5 generations) *respiratory bronchioles* originate from a terminal bronchiole.

2. Each respiratory bronchiole divides into several *alveolar ducts.*

3. Each alveolar duct opens into many *alveolar sacs (alveoli)* which are blind ends of the respiratory passages.

The lungs have double blood supply -oxygenated blood from the bronchial arteries and venous blood from the pulmonary arteries, and there is mixing of the blood to some extent. In case of blockage of one side of circulation, the supply from the other can maintain the vitality of pulmonary parenchyma. The bronchial veins drain the blood supplied by the bronchial arteries. The lungs have abundant intercommunicating lymphatics on the surface which drain into the subpleural plexus. Hilar and tracheobronchial lymph nodes receive the lymph and drain into the thoracic duct.

Histology. The bronchi and their subdivisions up to bronchioles are lined by pseudostratified columnar ciliated epithelial cells, also called *respiratory epithelium.* These cells are admixed with mucus-secreting goblet cells which decrease in number as the bronchioles are approached. The mucosa of bronchi but not of the bronchioles contains numerous submucosal mucous glands and neuro-endocrine cells which are bronchial counterparts of the argentaffin cells of the alimentary tract. The structure of bronchioles differs from that of bronchi and its subdivisions as well as from alveoli. They are lined by a single layer of pseudostratified columnar ciliated epithelium but no mucous cells and hence, unlike the bronchi, contain no mucus secretion on the surface. They contain some nonciliated Clara cells which secrete protein rich in lysozyme and immunoglobulins but unlike the alveoli contain no surfactant.

The **alveolar walls or alveolar septa** are the sites of exchange between the blood and air and have the following microscopic features:

1. The *capillary endothelium* lines the anastomotic capillaries in the alveolar walls.

2. The capillary endothelium and the alveolar lining epithelial cells are separated by the *capillary basement membrane and some interstitial tissue.* The interstitial tissue consists of scanty amount of collagen, fibroblasts, fine elastic fibres, smooth muscle cells, a few mast cells and mononuclear cells.

3. The *alveolar epithelium* consists of 2 types of cells: *type I* or *membranous pneumocytes* are the most numerous covering about 95% of alveolar surface, and *type II* or

granular pneumocytes project into the alveoli and are covered by microvilli. Type II pneumocytes are essentially reserve cells which undergo hyperplasia when type I pneumocytes are injured and are the source of pulmonary surfactant rich in lecithin. The main functions of coating of surfactant are to lower the surface tension of the alveolar lining cells and in maintaining the stability of the alveoli.

4. The *alveolar macrophages* belonging to mononuclear-phagocyte system are present either free in the alveolar spaces or are attached to the alveolar cells.

5. The *pores of Kohn* are the sites of alveolar connections between the adjacent alveoli and allow the passage of bacteria and exudate.

The three important groups of diseases of the respiratory tract are: infections, injury due to inhaled pollutants and cardiorespiratory diseases.

PULMONARY INFECTIONS

Acute and chronic pulmonary infections are common at all ages and are a frequent cause of death. They are generally caused by a wide variety of microorganisms such as bacteria, viruses, fungi and mycoplasma.

PNEUMONIAS

Pneumonia is defined as acute inflammation of the lung parenchyma distal to the terminal bronchioles which consist of the respiratory bronchiole, alveolar ducts, alveolar sacs and alveoli. The terms 'pneumonia' and 'pneumonitis' are often used synonymously for inflammation of the lungs, while 'consolidation' (meaning solidification) is the term used for macroscopic and radiologic appearance of the lungs in pneumonia.

Pathogenesis. The microorganisms gain entry into the lungs by one of the following four routes:

1. *Inhalation* of the microbes present in the air.
2. *Aspiration* of organisms from the nasopharynx or oropharynx.
3. *Haematogenous spread* from a distant focus of infection.
4. *Direct spread* from an adjoining site of infection. The normal lung is free of bacteria because of the presence of a number of lung defense mechanisms at different levels such as nasopharyngeal filtering action, mucociliary action of the lower respiratory airways, the presence of phagocytosing alveolar macrophages and immunoglobulins. Failure of these defense mechanisms and presence of certain predisposing factors result in pneumonias. These conditions are as under:

1. Altered consciousness. The oropharyngeal contents may be aspirated in states causing unconsciousness e.g. in coma, cranial trauma, seizures, cerebrovascular accidents, drug overdose, alcoholism etc.

2. Depressed cough and glottic reflexes. Depression of effective cough may allow aspiration of gastric contents e.g. in old age, pain from trauma or thoraco-abdominal surgery, neuromuscular disease, weakness due

to malnutrition, kyphoscoliosis, severe obstructive pulmonary diseases, endotracheal intubation and tracheostomy.

3. Impaired mucociliary transport. The normal protection offered by mucus-covered ciliated epithelium in the airways from the larynx to the terminal bronchioles is impaired or destroyed in many conditions favouring passage of bacteria into the lung parenchyma. These conditions are cigarette smoking, viral respiratory infections, immotile cilia syndrome, inhalation of hot or corrosive gases and old age.

4. Impaired alveolar macrophage function. Pneumonias may occur when alveolar macrophage function is impaired e.g. by cigarette smoke, hypoxia, starvation, anaemia, pulmonary oedema and viral respiratory infections.

5. Endobronchial obstruction. The effective clearance mechanism is interfered with in endobronchial obstruction from tumour, foreign body, cystic fibrosis and chronic bronchitis.

6. Leucocyte dysfunctions. Disorders of lymphocytes including congenital and acquired immunodeficiencies (eg. AIDS, immunosuppressive therapy) and granulocyte abnormalities may predispose to pneumonia.

Classification. On the basis of the anatomic part of the lung parenchyma involved, pneumonias are traditionally classified into 3 main types:

1. Lobar pneumonia,
2. Bronchopneumonia (or Lobular pneumonia),
3. Interstitial pneumonia.

BACTERIAL PNEUMONIA

Bacterial infection of the lung parenchyma is the most common cause of pneumonia or consolidation of one or both the lungs. Two kinds of acute bacterial pneumonias are distinguished – lobar pneumonia and broncho-(lobular-) pneumonia, each with distinct etiologic agent and morphologic changes.

LOBAR PNEUMONIA

Lobar pneumonia is an acute bacterial infection of a part of a lobe, the entire lobe, or even two lobes of one or both the lungs.

Etiology. Based on the etiologic microbial agent causing lobar pneumonia, the following types are described:

1. Pneumococcal pneumonia: More than 90% of all lobar pneumonias are caused by *Streptococcus pneumoniae,* a lancet-shaped diplococcus. Out of various types, type *3 S. pneumoniae* causes particularly virulent form of lobar pneumonia. Pneumococcal pneumonia in majority of cases is community-acquired infection.

2. Staphylococcal pneumonia: *Staphylococcus aureus* causes pneumonia by haematogenous spread of infection from another focus or after viral infections.

3. Streptococcal pneumonia: β-haemolytic streptococci may rarely cause pneumonia such as in children after measles or influenza, in severely debilitated elderly patients and in diabetics.

4. Pneumonia by gram-negative aerobic bacteria: Less common causes of lobar pneumonia are gram-negative bacteria like *Haemophilus influenzae, Klebsiella pneumoniae (Friedlander's bacillus), Pseudomonas, Proteus* and *Escherichia coli, H. influenzae* commonly causes pneumonia in children below 3 years of age after a preceding viral infection.

Pathologic changes. Laennec's original description divides lobar pneumonia into 4 sequential pathologic phases:

– *stage of congestion* (initial phase),

– *red hepatisation* (early consolidation),

– *grey hepatisation* (late consolidation) and

– *resolution.*

However, these classic stages seen in untreated cases are found much less often nowadays due to administration of antibiotics and improved medical care.

In lobar pneumonia, as the name suggests, part of a lobe, a whole lobe, or two lobes are involved, sometimes bilaterally. The lower lobes are affected most commonly. The sequence of pathologic changes described below represents the inflammatory response of lungs in bacterial infection.

1. Stage of congestion: initial phase. The initial phase represents the early acute inflammatory response to bacterial infection and lasts for 1 to 2 days.

Grossly, the affected lobe is enlarged, heavy, dark red and congested. Cut surface exudes blood-stained frothy fluid.

Histologically, typical features of acute inflammatory response to the organisms are seen. These are:

i) Dilatation and congestion of the capillaries in the alveolar walls.

ii) Pale eosinophilic oedema fluid in the air spaces.

iii)) A few red cells and neutrophils in the intra-alveolar fluid.

iv) Numerous bacteria demonstrated in the alveolar fluid by Gram's staining.

2. Red hepatisation: early consolidation. This phase lasts for 2 to 4 days. The term hepatisation in pneumonia refers to liver-like consistency of the affected lobe on cut section.

Grossly, the affected lobe is red, firm and consolidated. The cut surface of the involved lobe is airless, red-pink, dry, granular and has liver-like consistency. The stage of red hepatisation is accompanied by serofibrinous pleurisy.

Histologically, the following features are observed:

i) The oedema fluid of the preceding stage is replaced by strands of fibrin.

ii) There is marked cellular exudate of neutrophils and extravasation of red cells.

iii)) Many neutrophils show ingested bacteria.

iv) The alveolar septa are less prominent than in the first stage due to cellular exudation.

3. Grey hepatisation: late consolidation. This phase lasts for 4 to 8 days.

Grossly, the affected lobe is firm and heavy. The cut surface is dry, granular and grey in appearance with liver-like consistency. The change in colour from red to grey begins at the hilum and spreads towards the periphery. Fibrinous pleurisy is prominent. *Histologically,* the following changes are present:

i) The fibrin strands are dense and more numerous,

ii) The cellular exudate of neutrophils is reduced due to disintegration of many inflammatory cells as evidenced by their pyknotic nuclei. The red cells are also fewer. The macrophages begin to appear in the exudate.

iii) The cellular exudate is often separated from the septal walls by a thin clear space,

iv) The organisms are less numerous and appear as degenerated forms.

4. Resolution*:* This stage begins by 8th to 9th day if no chemotherapy is administered and is completed in 1 to 3 weeks. However, antibiotic therapy induces resolution on about 3rd day. Resolution proceeds in a progressive manner.

Grossly, the previously solid fibrinous constituent is liquefied by enzymatic action, eventually restoring the normal aeration in the affected lobe. The process of softening begins centrally and spreads to the periphery. The cut surface is grey-red or dirty brown and frothy, yellow, creamy fluid can be expressed on pressing. The pleural reaction may also show resolution but may undergo organisation leading to fibrous obliteration of pleural cavity.

Histologically, the following features are noted:

i) Macrophages are the predominant cells in the alveolar spaces, while neutrophils diminish in number. Many of the macrophages contain engulfed neutrophils and debris.

ii) Granular and fragmented strands of fibrin in the alveolar spaces are seen due to progressive enzymatic digestion.

iii) Alveolar capillaries are engorged,

iv) There is progressive removal of fluid content as well as cellular exudate from the air spaces, partly by expectoration but mainly by lymphatics, resulting in restoration of normal lung parenchyma with areation.

Complications. Since the advent of antibiotics, serious complications of lobar pneumonia are uncommon. However, they may develop in neglected cases and in patients with impaired immunologic defenses. These are as under:

1. Organisation. In about 3% of cases, resolution of the exudate does not occur but instead it is organised. There is ingrowth of fibroblasts from the

alveolar septa resulting in fibrosed, tough, airless leathery lung tissue. This type of post-pneumonic fibrosis is called *carnification.*

2. Pleural effusion. About 5% of treated cases of lobar pneumonia develop inflammation of the pleura with effusion. The pleural effusion usually resolves but sometimes may undergo organisation with fibrous adhesions between visceral and parietal pleura.

3. Empyema. Less than 1% of treated cases of lobar pneumonia develop encysted pus in the pleural cavity termed empyema.

4. Lung abscess. A rare complication of lobar pneumonia is formation of lung abscess, especially when there is secondary infection by other organisms.

5. Metastatic infection. Occasionally, infection in the lungs and pleural cavity in lobar pneumonia may extend into the pericardium and the heart causing purulent pericarditis, bacterial endocarditis and myocarditis. Other forms of metastatic infection encountered rarely in lobar pneumonias are otitis media, mastoiditis, meningitis, brain abscess and purulent arthritis.

BRONCHOPNEUMONIA (LOBULAR PNEUMONIA)

Bronchopneumonia or lobular pneumonia is infection of the terminal bronchioles that extends into the surrounding alveoli resulting in patchy consolidation of the lung. The condition is particularly frequent at extremes of life (i.e. in infancy and old age), as a terminal event in chronic debilitating diseases and as a secondary infection following viral respiratory infections such as influenza, measles etc.

Etiology. The common organisms responsible for bronchopneumonia are staphylococci, streptococci, pneumococci, *Klebsiella pneumoniae, Haemophilus influenzae,* and gram-negative bacilli like *Pseudomonas* and coliform bacteria.

Pathologic changes. *Grossly,* bronct monia is identified by patchy areas of red or grey consolidation affecting one or more lobes, frequently found bilaterally and more often involving the lower zones of the lungs due to gravitation of the secretions. On cut surface, these patchy consolidated lesions are dry, granular, firm, red or grey in colour, 3 to 4 cm in diameter, slightly elevated over the surface and are often centred around a bronchiole. These patchy areas are best picked up by passing the fingertips on the cut surface.

Histologically, the following features are observed:

i) Acute bronchiolitis.

ii) Suppufative exudate, consisting chiefly of neutrophils, in the peribronchiolar alveoli,

iii) Thickening of the alveolar septa by congested capillaries and leucocytic infiltration,

iv) Less involved alveoli contain oedema fluid.

Complications. The complications of lobar pneumonia may occur in bronchopneumonia as well. However, complete resolution of bronchopneumonia is uncommon. There is generally some degree of destruction of the bronchioles resulting in foci of bronchiolar fibrosis that may eventually cause bronchiectasis.

VIRAL AND MYCOPLASMAL PNEUMONIA (PRIMARY ATYPICAL PNEUMONIA)

Viral and mycoplasmal pneumonia is characterised by patchy inflammatory changes, largely confined to interstitial tissue of the lungs, without any alveolar exudate. Other terms used for these respiratory tract infections are *interstitial pneumonitis,* reflecting the interstitial location of the inflammation, and *'primary atypical pneumonia',* atypicality being the absence of alveolar exudate commonly present in other pneumonias. Interstitial pneumonitis may occur in all ages. Most of the cases are mild and transient; exceptionally it may be severe and fulminant.

Etiology. Interstitial pneumonitis is caused by a wide variety of agents, the most common being *respiratory syncytial virus* (RSV). Others are *Mycoplasma pneumoniae* and many viruses such as influenza and parainfluenza viruses, adenoviruses, rhinoviruses, coxsackieviruses and cytomegaloviruses (CMV). Occasionally, psittacosis *(Chlamydia)* and Q fever *(Coxiella)* are associated with interstitial pneumonitis. Infections of the respiratory tract with these organisms are quite common. In most cases, the infection remains confined to the upper respiratory tract presenting as common cold. Occasionally, it may extend lower down to involve the interstitium of the lungs. The circumstances favouring such extension of infection are malnutrition, chronic debilitating diseases and alcoholism.

Pathologic changes. Irrespective of the etiologic agent, the pathologic changes are similar in all cases.

Grossly, depending upon the severity of infection, the involvement may be patchy to massive and widespread consolidation of one or both the lungs. The lungs are heavy, congested and subcrepitant. Sectioned surface of the lung exudes small amount of frothy or bloody fluid. The pleural reaction is usually infrequent and mild.

Histologically, hallmark of viral pneumonias is the interstitial nature of the inflammatory reaction. The microscopic features are as under:

i) Interstitial inflammation: There is thickening of alveolar walls due to congestion, oedema and mononuclear inflammatory infiltrate comprised by lymphocytes, macrophages and some plasma cells.

ii) Necrotising bronchiolitis: This is characterised by foci of necrosis of the bronchiolar epithelium, inspissated secretions in the lumina and mononuclear infiltrate in the walls and lumina.

iii) Reactive changes: The lining epithelial cells of the bronchioles and alveoli proliferate in the presence of virus and may form multinucleate giant cells and syncytia in the bronchiolar and alveolar walls. Occasionally, viral inclusions (intranuclear and/or intracytoplasmic) are found, especially in pneumonitis caused by CMY.

iv) Alveolar changes: In severe cases, the alveolar lumina may contain oedema fluid, fibrin, scanty inflammatory exudate and coating of alveolar walls by pink, hyaline membrane similar to the one seen in respiratory distress syndrome. Alveolar changes are prominent if bacterial infection supervenes.

Complications. The major complication of interstitial pneumonitis is superimposed bacterial infection and its complications. Most cases of interstitial pneumonitis recover completely. In more severe cases, there may be interstitial fibrosis and permanent damage.

Clinical features. Majority of cases of interstitial pneumonitis initially have upper respiratory symptoms with fever, headache and muscle aches. A few days later appears dry, hacking, non-productive cough with retrosternal burning due to tracheitis and bronchitis. Chest radiograph may show patchy or diffuse consolidation. Cold agglutinin titres in the serum are elevated in almost half the cases of mycoplasmal pneumonia, 20% cases of adenovirus infection but absent in other forms of viral pneumonia. Isolation of the etiologic agent, otherwise, is difficult.

OTHER TYPES OF PNEUMONIAS

Some other types of pneumonias caused by *infective agents* (such as *Pneumocystis carinii* pneumonia and *Legionella* pneumonia) and certain *non-infective varieties* (e.g. aspiration pneumonia, hypostatic pneumonia and lipid pneumonia) are described here.

I. PNEUMOCYSTIS CARINII PNEUMONIA

Pneumocystis carinii, a protozoon widespread in the environment, causes pneumonia by inhalation of the organisms as an opportunistic infection in neonates and immunosuppressed people. Almost 100% cases of AIDS develop opportunistic infection, most commonly *Pneumocystis carinii* pneumonia. Other immunosuppressed groups are patients on chemotherapy for organ transplant and tumours, malnutrition, agamma-globulinaemia etc.

Pathologic changes. *Grossly,* the affected parts of lung are consolidated, dry and grey.

Microscopically$_t$ the features are as under:

i) Interstitial pneumonitis with thickening and mononuclear infiltration of the alveolar walls.

ii) Alveolar lumina contain pink frothy fluid.

iii) By Gomori's methenamine-silver (GMS) stain, the characteristic oval or crescentic cysts, about 5 μm in diameter and surrounded by numerous tiny black dot-like trophozoites of P. carinii are demonstrable in the frothy fluid.

iv) No significant inflammatory exudate is seen in the air spaces.

Clinical features. There is rapid onset of dyspnoea, tachycardia, cyanosis and non-productive cough. If untreated, it causes death in one or two weeks. Chest radiograph shows diffuse alveolar and interstitial infiltrate.

II. LEGIONELLA PNEUMONIA

Legionella pneumonia or legionnaire's disease is an epidemic illness caused by gram-negative bacilli, *Legionella pneumophila* that thrives in aquatic environment. It was first recognised following investigation into high mortality among those attending American Legion Convention in Philadelphia in July 1976. The epidemic occurs in summer months by spread of organisms through contaminated drinking water or in air-conditioning cooling towers. Impaired host defenses in the form of immunodeficiency, corticosteroid therapy, old age and cigarette smoking play important roles.

Pathologic changes. Grossly, there are changes of widespread bronchopneumonia involving many lobes and there may be consolidation of the entire lung. Pleural effusion is frequently present.

Histologically, the changes are not distinctive. The features commonly seen are:

i) Intra-alveolar exudate, initially of neutrophils but later composed mainly of macrophages.

ii) Alveolar septa show foci of hyperplasia of the lining epithelium and thrombosis of vessels in the septa.

iii) The organisms may be demonstrated in the macrophages by special stains or by immunofluorescent techniques.

Clinical features. The disease begins with malaise, headache and muscle aches followed by high fever, chills, cough and tachypnoea. Systemic manifestations unrelated to pathologic changes in the lungs are seen due to bacteraemia and include abdominal pain, watery diarrhoea, proteinuria and mild hepatic dysfunction.

III. ASPIRATION (INHALATION) PNEUMONIA

Aspiration or inhalation pneumonia results from inhaling different agents into the lungs. These substances include food, gastric contents, foreign body and infected material from oral cavity. A number of factors predispose to inhalation pneumonia which include: unconsciousness, drunkenness, neurological disorders affecting swallowing, drowning, necrotic oropharyngeal tumours, in premature infants and congenital tracheo-oesophageal fistula. Some patients die immediately from asphyxiation or laryngospasm without developing pneumonia.

Pathologic changes. Pathologic changes vary depending upon the particulate matter aspirated but in general right lung is affected more often due to direct path from the main bronchus:

1. Aspiration of small amount of **sterile foreign matter** such as acidic gastric contents produce *chemical pneumonitis.* It is characterised by haemorrhagic pulmonary oedema with presence of particles in the bronchioles. Patients rapidly develop cyanosis, dyspnoea, shock and bloody sputum and are often likely to die of cardiac failure. If the patient survives the acute episode, secondary bacterial infection is likely to occur.

2. Non-sterile aspirate causes widespread *bronchopneumonia* with multiple areas of necrosis and suppuration. A granulomatous reaction with foreign body giant cells may surround the aspirated vegetable matter.

IV. HYPOSTATIC PNEUMONIA

Hypostatic pneumonia is the term used for the collection of oedema fluid and secretions in the dependent parts of the lungs in severely debilitated, bed-ridden patients. The accumulated fluid in the basal zone and posterior part of lungs gets infected by bacteria from the upper respiratory tract and sets in bacterial pneumonia. Hypostatic pneumonia is a common terminal event in the old, feeble, comatose patients.

V. LIPID PNEUMONIA

Another variety of noninfective pneumonia is lipid pneumonia. It is of 2 types: exogenous and endogenous.

1. Exogenous lipid pneumonia. This is caused by aspiration of a variety of oily materials. These are: inhalation of oily nasal drops, regurgitation of oily medicines from stomach (e.g. liquid paraffin), administration of oily vitamin preparation to reluctant children or to debilitated old patients.

2. Endogenous lipid pneumonia. Endogenous origin of lipids causing pneumonic consolidation is more common. The sources of origin are tissue breakdown following obstruction to airways e.g. obstruction by bronchogenic cancer, tuberculosis and bronchiectasis.

Pathologic changes. *Grossly,* the exogenous type affects the right lung more frequently due to direct path from the main bronchus. Quite often, the lesions are bilateral. The affected part of the lungs is consolidated. Cut surface is characteristically 'golden yellow'.

Microscopically, the features are as under:

i) The lipid is finely dispersed in the cytoplasm of macrophages forming foamy macrophages within the alveolar spaces.

ii) There may be formation of cholesterol clefts due to liberation of cholesterol and other lipids.

iii) Formation of granulomas with foreign body giant cells may be seen around the large lipid droplets.

LUNG ABSCESS

Lung abscess is a localised area of necrosis of lung tissue with suppuration. It is of 2 types:

• *Primary lung abscess* that develops in an otherwise normal lung. The commonest cause is aspiration of infected material.

• *Secondary lung abscess* that develops as a complication of some other disease of the lung or from another site.

Etiopathogenesis. The microorganisms commonly isolated from the lungs in lung abscess are streptococci, staphylococci and various gram-negative organisms. These are introduced into the lungs from one of the following mechanisms:

1. Aspiration of infected foreign material. A number of foreign materials such as food, decaying teeth, gastric contents, severely infected gingivae and teeth, and necrotic tissue from lesions in the mouth, upper respiratory tract or nasopharynx may be aspirated. This occurs particularly in favourable circumstances such as during sleep, unconsciousness, anaesthesia, general debility and acute alcoholism.

2. Preceding bacterial infection. Preceding bronchopneumonia in a debilitated patient may develop into lung abscess. Other infective conditions like tuberculosis, bronchiectasis and mycotic infections may occasionally result in formation of lung abscess.

3. Bronchial obstruction. An abscess may form distal to an obstructed bronchus such as from bronchial tumour or from impacted foreign body.

4. Septic embolism. Infected emboli originating from pyaemia, thrombophlebitis or from vegetative bacterial endocarditis may be disseminated in the venous circulation and reach the right side of the heart from where they are lodged in the lung and result in multiple abscesses.

5. Miscellaneous. Rare causes of lung abscesses include:

i) Infection in pulmonary infarcts.

ii) Amoebic abscesses due to infection with *Entamoeba histolytica.*

iii) Trauma to the lungs.

iv) Direct extension from a suppurative focus in the mediastinum, oesophagus, subphrenic area or spine.

Pathologic changes. Abscesses due to aspiration are more likely to be in right lung due to more vertical main bronchus and are frequently single. They are commonly located in the lower part of the right upper lobe or apex of right lower lobe. Abscesses developing from preceding pneumonia and septic or pyaemic abscesses are often multiple and scattered throughout the lung.

Grossly, abscesses may be of variable size from a few millimeters to large cavities, 5 to 6 cm in diameter. The cavity often contains exudate. An acute lung abscess is initially surrounded by acute pneumonia and has poor-

ly-defined ragged wall. With passage of time, the abscess becomes chronic and develops fibrous wall.

Histologically, the characteristic feature is the destruction of lung parenchyma with suppurative exudate in the lung cavity. The cavity is initially surrounded by acute inflammation in the wall but later there is replacement by exudate of lymphocytes, plasma cells and macrophages. In more chronic cases, there is considerable fibroblastic proliferation forming a fibrocollagenic wall.

Clinical features. The clinical manifestations are fever, malaise, loss of weight, cough, purulent expectoration and haemoptysis in half the cases. Clubbing of the fingers and toes appears in about 20% of patients. Secondary amyloidosis may occur in chronic longstanding cases.

FUNGAL INFECTIONS OF LUNG

Fungal infections of the lung are more common than tuberculosis in the United States of America. These infections in healthy individuals are rarely serious but in immunosuppressed individuals may prove fatal. Some of the common examples of fungal infections of the lung are briefly outlined below:

1. Histoplasmosis. It is caused by oval organism, *Histoplasma capsulatum,* by inhalation of infected dust or bird droppings. The condition may remain asymptomatic or may produce lesions similar to the Ghon's complex.

2. Coccidiodomycosis. Coccidiodomycosis is caused by *Coccidioides immitis* which are spherical spores. The infection in human beings is acquired by close contact with infected dogs. The lesions consist of peripheral parenchymal granuloma in the lung.

3. Cryptococcosis. It is caused by *Cryptococcus neoformans* which is round yeast having a halo around it due to shrinkage in tissue sections. The infection occurs from infection by inhalation of pigeon droppings. The lesions in the body may range from a small parenchymal granuloma in the lung to cryptococcal meningitis.

4. Blastomycosis. It is an uncommon condition caused by *Blastomyces dermatitidis.* The lesions result from inhalation of spores in the ground. Pathological features may present as Ghon's complex-like lesion, as a pneumonic consolidation, and as multiple skin nodules.

5. Aspergillosis. Aspergillosis is the most common fungal infection of the lung caused by *Aspergillus fumigatus.* The fungus exists as thin septate hyphae with dichotomous branching and grows best in cool, wet climate. The infection may result in *allergic bronchopulmonary aspergillosis, aspergilloma* and *necrotising bronchitis.* Immunocompromised persons develop more serious manifestations of aspergillus infection, especially in leukaemic patients on cytotoxic drug therapy. Extensive haematogenous spread of asper-

gillus infection may result in widespread changes in lung tissue due to arterial occlusion, thrombosis and infarction.

6. Mucormycosis. Mucormycosis or phycomycosis is caused by *Mucor* and *Rhizopus.* The infection in the lung occurs in a similar way as in aspergillosis.The pulmonary lesions are especially common in patients of *diabetic ketoacidosis.*

7. Candidiasis. Candidiasis or moniliasis caused by *Candida albicans* is a normal commensal in oral cavity, gut and vagina but attains pathologic form in immunocompromised host. Angio-invasive growth of the organism may occur in the airways.

PULMONARY TUBERCULOSIS

The classical and most common example of chronic infection of the lungs is pulmonary tuberculosis. Pulmonary lesions caused by *Mycobacterium tuberculosis* and other mycobacteria will be discussed later.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) or chronic obstructive airways disease (COAD) are commonly-used clinical terms for a group of pathological conditions in which there is chronic, partial or complete, obstruction to the airflow at any level from trachea to the smallest airways resulting in functional disability of the lungs. The obstructive pulmonary disease must be distinguished from restrictive pulmonary disease. The following 4 entities are included in COPD:

I. Chronic bronchitis
II. Emphysema
III. Bronchial asthma
IV. Bronchiectasis

Chronic bronchitis and emphysema are quite common and often occur together. More recently, small airways disease involving inflammation of small bronchi and bronchioles (bronchiolitis) has been added to the group of COPD.

CHRONIC BRONCHITIS

Chronic bronchitis is a common condition defined clinically as persistent cough with expectoration on most days for at least three months of the year for two or more consecutive years. The cough is caused by oversecretion of mucus. In spite of its name, chronic inflammation of the bronchi is not a prominent feature. The condition is more common in middle-aged males than females; approximately 20% of adult men and 5% of adult women have chronic bronchitis, but only a minority of them develop serious disa-

bling COPD or cor pulmonale. Quite frequently, chronic bronchitis is associated with emphysema.

Etiopathogenesis. The two most important etiologic factors responsible for majority of cases of chronic bronchitis are: cigarette smoking and atmospheric pollution. Other contributory factors are occupation, infection, familial and genetic factors.

1. Smoking. The most commonly identified factor implicated in causation of chronic bronchitis and in emphysema is heavy smoking. Heavy cigarette smokers have 4 to 10 times higher proneness to develop chronic bronchitis. Prolonged cigarette smoking appears to act on the lungs in a number of ways:

i) It impairs ciliary movement,

ii) It inhibits the function of alveolar macrophages.

iii)) It leads to hypertrophy and hyperplasia of mucus-secreting glands.

iv) It causes considerable obstruction of small airways,

v) It stimulates the vagus and causes broncho-constriction.

2. Atmospheric pollution. The incidence of chronic bronchitis is higher in industrialised urban areas where air is polluted. Some of the atmospheric pollutants which increase the risk of developing chronic bronchitis are sulfur dioxide, nitrogen dioxide, particulate dust and toxic fumes.

3. Occupation. Workers engaged in certain occupations such as in cotton mills (byssinosis), plastic factories etc are exposed to various organic or inorganic dusts which contribute to disabling chronic bronchitis in such individuals.

4. Infection. Bacterial, viral and mycoplasmal infections do not initiate chronic bronchitis but usually occur secondary to bronchitis. Cigarette smoke, however, predisposes to infection responsible for acute exacerbation in chronic bronchitis.

5. Familial and genetic factors. There appears to be a poorly-defined familial tendency and genetic predisposition to develop disabling chronic bronchitis. However, it is more likely that nonsmoker family members who remain in the air-pollution of home are significantly exposed to smoke (passive smoking) and hence have increased blood levels of carbon monoxide.

Pathologic changes. *Grossly,* the bronchial wall is thickened, hyperaemic and oedematous. Lumina of the bronchi and bronchioles may contain mucus plugs and purulent exudate. *Microscopically,* the characteristic features are as follows:

1. The cartilage-containing large airways have hypertrophy and hyperplasia of submucosal mucous glands. The increase in thickness can be quantitatively assessed by *Reid index* which is the ratio between thickness of the submucosal glands to that of the bronchial wall. The bronchial epithelium may show squamous metaplasia and dysplasia.

2. The non-cartilage containing small airways show goblet cell hyperplasia and intraluminal and peribronchial fibrosis.

Clinical features. There is considerable overlap of clinical features of chronic bronchitis and pulmonary emphysema as quite often the two coexist. Some important features of 'predominant bronchitis' are:

1. Persistent cough with copious expectoration of long duration; initially beginning in a heavy smoker with 'morning catarrh' or 'throat clearing' which worsens in winter.
2. Recurrent respiratory infections are common.
3. Dyspnoea is generally not prominent at rest but is more on exertion.
4. Patients are called 'blue bloaters' due to cyanosis and oedema.
5. Features of right heart failure (cor pulmonale) are common.
6. Chest X-ray shows enlarged heart with prominent vessels.

EMPHYSEMA

The WHO has defined pulmonary emphysema as combination of permanent dilatation of air spaces distal to the terminal bronchioles and the destruction of the walls of dilated air spaces. *Thus, emphysema is defined morphologically, while chronic bronchitis is defined clinically.* Since the two conditions coexist frequently and show considerable overlap in their clinical features, it is usual to label patients as 'predominant emphysema' and 'predominant bronchitis'.

Classification. As mentioned in the beginning of this chapter, a lobule is composed of about 5 acini distal to a terminal bronchiole and that an acinus consists of 3 to 5 generations of respiratory bronchioles and a variable number of alveolar ducts and alveolar sacs. By strictly adhering to the WHO definition of pulmonary emphysema, it is classified, according to the portion of the acinus involved, into *5 types:*

- centri-acinar,
- panacinar (panlobular),
- para-septal (distal acinar),
- irregular (para-cicatricial),
- and mixed (unclassified) emphysema.

A number of other conditions to which the term 'emphysema' is losely applied are, in fact, examples of 'over inflation.

Etiopathogenesis. The commonest form of COPD is the combination of chronic bronchitis and pulmonary emphysema. Chronic bronchitis, however, does not always lead to emphysema nor all cases of emphysema have changes of chronic bronchitis. The association of the two conditions is principally linked to the common etiologic factors; most importantly, *tobacco smoke* and *air pollutants.* Other less significant contributory factors are occupational exposure, infection and somewhat poorly-understood familial and genetic influences. All these factors have already been discussed above.

However, the pathogenesis of the most significant event in emphysema, the *destruction of the alveolar walls,* is not linked to bronchial changes but is closely related to deficiency of serum alpha-1-antitrypsin (al-protease inhibitor) commonly termed *protease-antiprotease hypothesis* detailed below.

Protease-antiprotease hypothesis. Alpha-1-antitrypsin, also called α1-protease inhibitor, is a glycoprotein that forms the normal constituent of the α1-globulin fraction of the plasma proteins on serum electrophoresis. The single gene locus that codes for α-1-antitrypsin is located on the long arm of chromosome 14 that codes for immunoglobulin light chains as well. It is normally synthesised in the liver and is distributed in the circulating blood, tissue fluids and macrophages. The normal function of α1-antitrypsin is to inhibit proteases and hence its name α1-protease inhibitor. The proteases (mainly elastases) are derived from neutrophils.

Neutrophil elastase has the capability of digesting lung parenchyma but is inhibited from doing so by anti-elastase (i.e. by α1-antitrypsin).

Deficiency of the enzyme α1-antitrypsin develops in homozygous state due to genetically abnormal locus for protease inhibitor (Pi). The normal phenotype of individuals in homozygote is called PiMM, while the most common abnormal phenotype in classic al-antitrypsin deficiency in homozygous state is PiZZ. The heterozygote pattern of PiMZ is not sufficient to produce clinical deficiency, but heterozygote individuals who smoke heavily have higher risk of developing emphysema.

The α1-antitrypsin deficiency develops in adults and causes pulmonary emphysema in smokers as well as in non-smokers, though the smokers become symptomatic about 15 years earlier than non-smokers. The other organ showing effects of α1-antitrypsin deficiency is liver which may develop obstructive jaundice early in infancy, and cirrhosis and hepatoma late in adulthood.

The mechanism of alveolar wall destruction in emphysema by elastolytic action is based on the imbalance between proteases (chiefly *elastase)* and anti-proteases (chiefly *anti-elastase):*

• By decreased anti-elastase activity i.e. deficiency of α-1 antitrypsin.

• By increased activity of elastase i.e. increased neutrophilic infiltration in the lungs causing excessive elaboration of neutrophil elastase.

There are enough evidences to suggest that smoking promotes emphysema by both decreasing the amount of anti-elastase as well as by increasing the elastolytic protease in the lungs. These are as under:

1. Oxidant in cigarette smoke has inhibitory influence on α1-antitrypsin thus lowering the level of anti-elastase activity.

2. Smokers have up to ten times more phagocytes and neutrophils in their lungs than nonsmokers. Thus they have very high elastase activity.

Pathologic changes. Emphysema can be diagnosed with certainty only by gross and histologic examination of sections of whole lung. The lungs should be perfused with formalin under pressure in inflated state to grade the severity of emphysema with naked eye.

Grossly, the lungs are voluminous, pale with little blood. The edges of the lungs are rounded. Mild cases show dilatation of air spaces visible with hand lens. Advanced cases show subpleural bullae and blebs bulging outwards from the surface of the lungs with rib markings between them. The *bullae* are air-filled cyst-like or bubble-like structures, larger than 1 cm in diameter. They are formed by the rupture of adjacent air spaces while *blebs* are the result of rupture of alveoli directly into the subpleural interstitial tissue and are the common cause of spontaneous pneumothorax.

Microscopically, depending upon the type of emphysema, there is dilatation of air spaces and destruction of septal walls of part of acinus involved i.e. respiratory bronchioles, alveolar ducts and alveolar sacs. Changes of bronchitis may be present. Bullae and blebs when present show fibrosis and chronic inflammation of the walls.

MORPHOLOGY OF INDIVIDUAL TYPES OF EMPHYSEMA

1. CENTRIACINAR (CENTRILOBULAR) EMPHYSEMA. Centriacinar or centrilobular emphysema is one of the common types. It is characterised by initial involvement of respiratory bronchioles i.e. the central or proximal part of the acinus. This is the type of emphysema that usually coexists with chronic bronchitis and occurs predominantly in smokers and in coal miners' pneumoconiosis.

Grossly, the lesions are more common and more severe in the upper lobes of the lungs. The characteristic appearance is obvious in cut surface of the lung. It shows distended air spaces in the centre of the lobules surrounded by a rim of normal lung parenchyma in the same lobule. The lobules are separated from each other by fine fibrous tissue septa. Large amount of black pigment is often present in the walls of emphysematous spaces. In more severe cases, distal parts of acini are also involved and the appearance may closely resemble panacinar emphysema.

Microscoptcally, there is distension and destruction of the respiratory bronchiole in the centre of lobules, surrounded peripherally by normal uninvolved alveoli. The terminal bronchioles supplying the acini show chronic inflammation and are narrowed.

2. PANACINAR (PANLOBULAR) EMPHYSEMA. Panacinar or panlobular emphysema is the other common type. In this type, all portions of the acinus are affected but not of the entire lung. Panacinar emphysema is most often associat-

ed with α1-antitrypsin deficiency in middle-aged smokers and is the one that produces the most characteristic anatomical changes in the lung in emphysema.

Grossly, in contrast to centriacinar emphysema, the panacinar emphysema involves lower zone of lungs more frequently and more severely than the upper zone. The involvement may be confined to a few lobules, or may be more widespread affecting a lobe or part of a lobe of the lung. The lungs are enlarged and over inflated.

Microscopically, usually all the alveoli within a lobule are affected to the same degree. All portions of acini are distended – respiratory bronchioles, alveolar ducts and alveoli, are all dilated and their walls stretched and thin. Ruptured alveolar walls and spurs of broken septa are seen between the adjacent alveoli. The capillaries are stretched and thinned. Special stains show loss of elastic tissue. Inflammatory changes are usually absent.

3. PARASEPTAL (DISTAL ACINAR) EMPHYSEMA. This type of emphysema involves distal part of acinus while the proximal part is normal. Paraseptal or distal acinar emphysema is localised along the pleura and along the perilobular septa. The involvement is seen adjacent to the areas of fibrosis and atelectasis and involves upper part of lungs more severely than the lower. This form of emphysema is seldom associated with COPD but is the common cause of spontaneous pneumothorax in young adults. Grossly, the subpleural portion of the lung shows air-filled cysts, 0.5 to 2 cm in diameter.

4. IRREGULAR (PARA-CICATRICIAL) emphysema. This is the most common form of emphysema, seen surrounding scars from any cause. The involvement is irregular as regards the portion of acinus involved as well as within the lung as a whole. During life, irregular emphysema is often asymptomatic and may be only an incidental autopsy finding.

5. MIXED (UNCLASSIFIED) EMPHYSEMA. Quite often, the same lung may show more than one type of emphysema. It is usually due to more severe involvement resulting in loss of clearcut distinction between one type of emphysema and the other. Thus, the lungs of an elderly smoker at autopsy may show continuation of centriacinar emphysema in the upper lobes, pana-cinar in the lower lobes, and paraseptal emphysema in the subpleural region.

MORPHOLOGY OF TYPES OF OVERINFLATION

Under this heading are covered a group of lung conditions of heterogeneous etiology characterised by overinflation of the parts of acini but without significant destruction of the walls and are sometimes loosely termed emphysema.

1. Compensatory overinflation (compensatory emphysema). When part of a lung or a lobe of lung is surgically removed, the residual lung parenchyma undergoes compensatory hyperinflation so as to fill the pleural cavity. Histologic examination shows dilatation of alveoli but no destruction of sep-

tal walls and hence the term compensatory overinflation is preferable over 'compensatory emphysema'.

2. Senile hyperinflation (aging lung, senile emphysema). In old people, the lungs become voluminous due to loss of elastic tissue, thinning and atrophy of the alveolar ducts and alveoli. The alveoli are thin-walled and distended throughout the lungs but there is no significant destruction of the septal walls and, therefore, preferable designation is 'senile hyperinflation' over 'senile emphysema.'

3. Obstructive overinflation (infantile lobar emphysema). Partial obstruction to the bronchial tree such as by a tumour or a foreign body causes over inflation of the region supplied by obstructed bronchus. Infantile lobar emphysema is a variant of obstructive over inflation occurring in infants in the first few days of life who develop respiratory distress or who have congenital hypoplasia of bronchial cartilage. In all such cases, air enters the lungs during inspiration but cannot leave on expiration resulting in ballooning up of the affected part of the lung.

4. Unilateral translucent lung (unilateral emphysema). This is a form of overinflation in which one lung or one of its lobes or segments of a lobe are radiolucent. The condition occurs in adults and there is generally a history of serious pulmonary infection in childhood, probably bronchiolitis obliterans. The affected lung is grossly overinflated. Microscopy shows overinflated alveoli and there is histologic evidence of preceding widespread bronchiolitis obliterans.

5. Interstitial emphysema (surgical emphysema). The entry of air into the connective tissue framework of the lung is called interstitial or surgical emphysema. The usual sources of entry of air into stroma of the lung are rupture of alveoli or of larger airways. The causes are as under:

i) Violent coughing with bronchiolar obstruction e.g. in children with whooping cough, bronchitis, in patients with obstruction to the airways by foreign bodies, blood clots and exposure to irritant gases.

ii) Rupture of the oesophagus, trauma to the lung, or major bronchus and trachea.

iii) Entry of air through surgical incision.

iv) Fractured rib puncturing the lung parenchyma.

v) Sudden change in atmospheric pressure e.g. in decompression sickness.

The condition may affect patients of all ages. On rupture of alveoli, the leaked air enters the fibrous connective tissue of the alveolar walls from where it extends into the fibrous septa of the lung, into the mediastinum, the pleura, and even the subcutaneous tissues. Escape of air into the pleural cavity may cause pneumothorax. Collection of small quantities of air is generally harmless and is

resorbed. However, extensive accumulation of air in surgical emphysema may produce impaired blood flow in the lungs. *Pneumo-mediastinum* may produce symptoms resembling myocardial infarction.

Histologically, the alveoli are distended but septal walls are not damaged; therefore it is not true emphysema. There are clear spaces of leaked out air in connective tissue septa.

BRONCHIAL ASTHMA

Asthma is a disease of airways that is characterised by increased responsiveness of the tracheobronchial tree to a variety of stimuli resulting in widespread spasmodic narrowing of the air passages which may be relieved spontaneously or by therapy. Asthma is an episodic disease manifested clinically by paroxysms of dyspnoea, cough and wheezing. However, a severe and unremitting form of the disease termed *status asthmaticus* may prove fatal.

Bronchial asthma is common and prevalent worldwide; in the United States about 4% of population is reported to suffer from this disease. It occurs at all ages but nearly 50% of cases develop it before the age of 10 years. In adults, both sexes are affected equally but in children there is 2 : 1 male-female ratio.

Etiopathogenesis and types. Based on the stimuli initiating bronchial asthma, two broad etiologic types are traditionally described: *extrinsic (allergic, atopic)* and *intrinsic (idiosyncratic, non-atopic) asthma. A* third type is a *mixed pattern* in which the features do not fit clearly into either of the two main types.

1. Extrinsic (atopic, allergic) asthma. This is the most common type of asthma. It usually begins in childhood or in early adult life. Most patients of this type of asthma have personal and/or family history of preceding allergic diseases such as rhinitis, urticaria or infantile eczema. Hypersensitivity to various extrinsic antigenic substances or 'allergens' is usually present in these cases. Most of these allergens cause ill-effects by inhalation e.g. house dust, pollens, animal danders, moulds etc. Occupational asthma stimulated by fumes, gases and organic and chemical dusts is a variant of extrinsic asthma. There are increased levels of IgE in the serum and positive skin test with the specific offending inhaled antigen representing an IgE-mediated type I hypersensitivity reaction which includes an 'acute immediate response' and a late phase reaction':

• The *acute immediate response* is initiated by IgE-sensitised mast cells (tissue counterparts of circulating basophils) on the mucosal surface. Mast cells on degranulation release mediators like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils. The net effects of these mediators are broncho-constriction, oedema, mucus hypersecretion and accumulation of eosinophils and neutrophils.

• The *late phase reaction* follows the acute immediate response and is responsible for the prolonged manifestations of asthma. It is caused by excessive mobilisation of blood leucocytes that include basophils besides eosinophils and neutrophils. These result in further release of mediators which accentuate the above-mentioned effects. In addition, inflammatory injury is caused by neutrophils and by major basic protein (MBP) of eosinophils.

2. Intrinsic (idiosyncratic, non atopic) asthma. This type of asthma develops later in adult life with negative personal or family history of allergy, negative skin test and normal serum levels of IgE. Most of these patients develop typical symptom-complex after an upper respiratory tract infection by viruses. Associated nasal polypi and chronic bronchitis are commonly present. There are no recognisable allergens but about 10% of patients become hypersensitive to drugs, most notably to small doses of aspirin (aspirin-sensitive asthma).

3. Mixed type. Many patients do not clearly fit into either of the above two categories and have mixed features of both. Those patients who develop asthma in early life have strong allergic component, while those who develop the disease late tend to be non-allergic. Either type of asthma can be precipitated by cold, exercise and emotional stress.

Pathologic changes. The pathologic changes are similar in both major types of asthma. The pathologic material examined is generally autopsy of lungs in patients dying of status asthmaticus but the changes are expected to be similar in non-fatal cases.

Grossly, the lungs are overdistended due to over-inflation. The cut surface shows characteristic occlusion of the bronchi and bronchioles by viscid mucus plugs.

Microscopically, the following changes are observed:

1. The mucus plugs contain normal or degenerated respiratory epithelium forming twisted strips called *Curschmann's spirals*.

2. The sputum usually contains numerous eosinophils and diamond-shaped crystals derived from eosinophils called *Charcot-Leyden crystals*.

3. The bronchial wall shows thickened basement membrane of the bronchial epithelium, submucosal oedema and inflammatory exudate consisting of lymphocytes and plasma cells with prominence of eosinophils. There is hypertrophy of submucosal glands as well as of the bronchial smooth muscle.

4. Changes of bronchitis and emphysema may supervene, especially in intrinsic asthma.

Clinical features. Asthmatic patients suffer from episodes of acute exacerbations interspersed with symptom-free periods. Characteristic clinical features are paroxysms of dyspnoea, cough and wheezing. Most attacks typically last for a few minutes to hours. When attacks occur continuously it may

result in more serious condition called *status asthmaticus*. The clinical diagnosis is supported by demonstration of circulation eosinophilia and sputum demonstration of Curschmann's spirals and Charcot-Leyden crystals. More chronic cases may develop cor pulmonale.

BRONCHIECTASIS

Bronchiectasis is defined as abnormal and irreversible dilatation of the bronchi and bronchioles (greater than 2 mm in diameter) developing secondary to inflammatory weakening of the bronchial walls. The most characteristic clinical manifestation of bronchiectasis is persistent cough with expectoration of copious amounts of foul-smelling, purulent sputum. Post-infectious cases commonly develop in childhood and in early adult life.

Etiopathogenesis. The origin of inflammatory destructive process of bronchial walls is nearly always a result of two basic mechanisms: obstruction and infection.

• *Endobronchial obstruction* by foreign body, neoplastic growth or enlarged lymph nodes causes resorption of air distal to the obstruction with consequent atelectasis and retention of secretions.

• *Infection* may be secondary to local obstruction and impaired systemic defense mechanism promoting bacterial growth, or infection may be a primary event i.e. bronchiectasis developing in suppurative necrotising pneumonia.

These 2 mechanisms - endobronchial obstruction and infection, are seen in a number of clinical settings. These are as under:

1. Hereditary and congenital factors. Several hereditary and congenital factors may result secondarily in diffuse bronchiectasis. These include:

i) *Congenital bronchiectasis* caused by developmental defect of the bronchial system.

ii) *Cystic fibrosis,* a generalised defect of exocrine gland secretions, results in obstruction, infection and bronchiectasis.

iii) *Hereditary immune deficiency diseases* are often associated with high incidence of bronchiectasis.

iv) Immotile cilia syndrome that includes Kartagener's syndrome (bronchiectasis, situs inversus and sinusitis) is characterised by ultrastructural changes in the microtubules causing immotility of cilia of the respiratory tract epithelium, sperms and other cells. Males in this syndrome are often infertile.

v) *Atopic bronchial asthma* patients have often positive family history of allergic diseases and may rarely develop diffuse bronchiectasis.

2. Obstruction. Post-obstructive bronchiectasis, unlike the congenital-hereditary forms, is of the localised variety, usually confined to one part of the bronchial system. The causes of endobronchial obstruction include foreign bodies, endobronchial tumours, compression by enlarged hilar lymph

nodes and post-inflammatory scarring (e.g. in healed tuberculosis) all of which favour the development of post-obstructive bronchiectasis.

3. Secondary complication. Necrotising pneumonias such as in staphylococcal suppurative pneumonia and *tuberculosis* may develop bronchiectasis as a complication.

Pathologic changes. The disease characteristically affects distal bronchi and bronchioles beyond the segrnental bronchi.

Macroscapicaly the lungs may be involved diffusely or segmentally. Bilateral involvement of lower lobes occurs most frequently. More vertical air passages of left lower lobe are more often involved than the right. The pleura is usually fibrotic and thickened with adhesions to the chest wall. Cut surface of the affected lobes, generally the lower zones, shows characteristic honeycombed appearance. The bronchi are extensively dilated nearly to the pleura, their walls are thickened and the lumina are filled with mucus or mucopus. The intervening lung parenchyma is reduced and fibrotic. The dilated airways, depending upon their gross or bronchographic appearance, have been subclassified into the following different types:

i) *Cylindrical:* the most common type characterised by tube-like bronchial dilatation.

ii) *Fusiform:* having spindle-shaped bronchial dilatation.

iii) *Saccular:* having rounded sac-like bronchial distension,

iv) *Varicose:* having irregular bronchial enlargements.

Microscopically, fully-developed cases show the following histologic features.

i) The bronchial epithelium may be normal, ulcerated or may show squamous metaplasia.

ii) The bronchial wall shows infiltration by acute and chronic inflammatory cells and destruction of normal muscle and elastic tissue with replacement by fibrosis.

iii) The intervening lung parenchyma shows fibrosis, while the surrounding lung tissue shows changes of interstitial pneumonia.

iv) The pleura in the affected area is adherent and shows bands of fibrous tissue between the bronchus and the pleura.

CHRONIC RESTRICTIVE PULMONARY DISEASE

The second large group of diffuse lung disease is 'chronic restrictive pulmonary disease' characterised by reduced expansion of lung parenchyma with decreased total lung capacity. This group of diseases must be distinguished from the foregoing COPD. Restrictive lung disease includes 2 types of conditions:

A. Restriction due to chest wall disorder. These causes are:

1. Kyphoscoliosis
2. Poliomyelitis
3. Severe obesity
4. Pleural diseases.

B. Restriction due to interstitial and infiltrative diseases. These are diseases characterised by non-infectious involvement of the interstitial connective tissue of lung parenchyma. The term 'infiltrative' is used here to denote the radiologic appearance of lungs in chest radiographs which show ground-glass shadows due to diffuse infiltration by small nodules or irregular lines. The conditions included in this group are as under:

I. Pneumoconiosis,
II. Immunologic lung diseases,
III. Collagen-vascular diseases,
IV. Idiopathic pulmonary fibrosis,
V. Sarcoidosis.

The pathogenesis of the interstitial lung disease is explained by inflammatory reaction causing initial alveolitis in response to various stimuli. In alveolitis, there is accumulation of lymphocytes, macrophages, neutrophils and eosinophils, all of which result in inflammatory destruction of the pulmonary parenchyma followed by fibrosis. Eventually, there is widespread destruction of alveolar capillary walls resulting in end-stage lung or 'honeycomb lung'.

The *major clinical manifestations* of restrictive lung diseases are dyspnoea, tachypnoea and cyanosis, but no wheezing so characteristic of COPD.

I. PNEUMOCONIOSES

Pneumoconiosis is the term used for lung diseases caused by inhalation of dust, mostly at work. These diseases are, therefore, also called 'dust diseases' or 'occupational lung diseases'.

The type of lung disease varies according to the nature of inhaled dust. Some dusts are inert and cause no reaction and no damage at all, while others cause immunologic damage and predispose to tuberculosis or to neoplasia. The factors which determine the extent of damage caused by inhaled dusts are:

1) size and shape of the particles;
2) their solubility and physic-chemical composition;
3) the amount of dust retained in the lungs;
4) the additional effect of other irritants such as tobacco smoke; and
5) host factors such as efficiency of clearance mechanism and immune status of the host.

In general, most of the inhaled dust particles larger than 5 μm reach the terminal airways where they are ingested by alveolar macrophages. Most of these too are eliminated by expectoration but the remaining accumulate in alveolar tissue. Of particular interest are the particles smaller than 1μm which are deposited in the alveoli most efficiently. Most of the dust-laden macrophages accumulated in the alveoli die leaving the dust, around which fibrous tissue is formed. Some macrophages enter the lymphatics and reach regional lymph nodes. The tissue response to inhaled dust may be one of the following three types:

- *Fibrous nodules* e.g. in coal-workers' pneumoconiosis and silicosis.
- *Interstitial fibrosis* e.g. in asbestosis.
- *Hypersensitivity reaction* e.g. in berylliosis.

COAL-WORKERS' PNEUMOCONIOSIS

This is the commonest form of pneumoconiosis and is defined as the lung disease resulting from inhalation of coal dust particles, especially in coal miners engaged in handling soft bituminous coal for a number of years, often 20 to 30 years. It exists in 2 forms – a milder form of the disease called *simple coal workers' pneumoconiosis* and an advanced form termed *progressive massive fibrosis* (complicated coal-miners pneumoconiosis). *Anthracosis,* on the other hand, is not a lung disease in true sense but is the common, benign and asymptomatic accumulation of carbon dust in the lungs of most urban dwellers due to atmospheric pollution and cigarette smoke. Anthracotic pigment is deposited in the macrophages in the alveoli and around the respiratory bronchioles and into the draining lymph nodes but does not produce any respiratory difficulty or radiologic changes.

Pathogenesis. Pathogenetically, it appears that anthracosis, simple coal-workers pneumoconiosis and progressive massive fibrosis are different stages in the evolution of fully-developed coal-workers' pneumoconiosis. However, progressive massive fibrosis develops in a small proportion of cases (2-8%) of simple coal-workers pneumoconiosis. A number of predisposing factors have been implicated in this transformation. These are:

1. Older age of the miners.
2. Severity of coal dust burden engulfed by macrophages.
3. Prolonged exposure (20 to 30 years) to coal dust.
4. Concomitant tuberculosis.
5. Additional role of silica dust.
6. Immunological factors.

The last named i.e. immunological mechanisms, are currently widely favoured in the pathogenesis of progressive massive fibrosis. These may act

by humoral mechanism as evidenced by elevated levels of anti-nuclear antibodies and rheumatoid factor. Alternatively, these may act via cell-mediated mechanisms by elaboration of macrophage-derived fibroblast growth factor, or the fibrosis may be reparative response to tissue injury caused by lysosomal enzymes and toxic free-radicals.

Pathologic changes. In life, the pathologic changes in lung in coal-workers' pneumoconiosis are graded by radiologic appearance according to the size and extent of opacities. The pathologic findings at autopsy of lungs in the major forms of coal workers' pneumoconiosis are considered below under 3 headings: simple coal-workers' pneumoconiosis, progressive massive fibrosis and rheumatoid pneumoconiosis (Caplan's syndrome).

Simple "coal-workers" pneumoconiosis. **Grossly**, the lung parenchyma shows small, black focal lesions, measuring less than 5 mm in diameter and evenly distributed throughout the lung but have a tendency to be more numerous in the upper lobes. These are termed *coal macules,* and if palpable are called *nodules.* The air spaces around coal macules are dilated with little destruction of alveolar walls. Though some workers have called it centri lobular emphysema of coalminers, others prefer not to consider it emphysema because there is no significant destruction of alveolar walls. Similar blackish pigmentations are found on the pleural surface and in the regional lymph nodes.

Histologically, the following features are seen:

1. Coal macules are composed of aggregates of dust-laden macrophages. These are present in the alveoli and in the bronchiolar and alveolar walls.
2. There is some increase in the network of reticulin and collagen in the coal macules.
3. Respiratory bronchioles and alveoli surrounding the macules are distended without significant destruction of the alveolar walls.

PROGRESSIVE MASSIVE FIBROSIS

Grossly, besides the coal macules and nodules of simple pneumoconiosis, there are larger, hard, black scattered areas measuring more than 2 cm in diameter and sometimes massive. They are usually bilateral and located more often in the upper parts of the lungs posteriorly. Sometimes, these masses break down centrally due to ischaemic necrosis or due to tuberculosis forming cavities filled with black semifluid resembling India ink. The pleura and the regional lymph nodes are also blackened and fibrotic.

Histologically, the following features are present:

1. The fibrous lesions are composed almost entirely of dense collagen and carbon pigment.

2. The wall of respiratory bronchioles and pulmonary vessels included in the massive scars are thickened and their lumina obliterated.

3. There is scanty inflammatory infiltrate of lymphocytes and plasma cells around the areas of massive scars.

4. The alveoli surrounding the scars are markedly dilated.

Progressive massive fibrosis probably has immunological pathogenetic basis as described above.

RHEUMATOID PNEUMOCONIOSIS (CAPLAN'S SYNDROME)

The development or rheumatoid arthritis in a few cases of coal-workers' pneumoconiosis, silicosis or absestosis is termed rheumatoid pneumoconiosis or Caplan's syndrome.

Grossly, the lungs have rounded, firm nodules with central necrosis, cavitation or calcification.

Histologically, the lung lesions are modified rheumatoid nodules with central zone of dust-laden fibrinoid necrosis enclosed by palisading fibroblasts and mononuclear cells.

The lung lesions in Caplan's syndrome have immunological basis for their origin as evidenced by detection of rheumatoid factor and antinuclear antibodies.

SILICOSIS

Historically, silicosis used to be called 'knife grinders' lung. Silicosis is caused by prolonged inhalation of silicon dioxide, commonly called silica. Silica constitutes about one-fourth of earth's crust. Therefore, a number of occupations engaged in silceous rocks or sand and products manufactured from them are at increased risk.

These include miners (e.g. of granite, sandstone, slate, coal, gold, tin and copper), quarry workers, tunnellers, sandblasters, grinders, ceramic workers, foundry workers and those involved in the manufacture of abrasives containing silica. Peculiar to India are the occupational exposure to pencil, slate and agate grinding industry carrying high risk of silicosis (agate = sort of very hard stone containing silica). According to a recent ICMR report, it is estimated that about 3 million workers in India are at high potential risk of silica exposure employed in a variety of occupations including construction workers. An infrequent acute form of silicosis called accelerated silicosis produces irregular fibrosis adjoining the alveoli which is filled with lipoproteinaceous exudate and resembles alveolar proteinosis. However, if not specified, silicosis refers to the common chronic form of the disease characterised by formation of small collagenous silicotic nodules.

Pathogenesis. Silicosis appears after prolonged exposure to silica dust, often a few decades. Besides, it depends upon a number of other factors such

as total dose, duration of exposure, the type of silica inhaled and individual host factors. The mechanisms involved in the formation of silicotic nodules are not clearly understood. The following sequence of events has been proposed and schematically:

1. Silica particles between 0.5 to 5 (im size on reaching the alveoli are taken by the macrophages which undergo necrosis. New macrophages engulf the debris and thus a repetitive cycle of *phagocytosis and necrosis* is set up.

2. Some silica-laden macrophages are carried to the respiratory bronchioles, alveoli and in the interstitial tissue. Some of the silica dust is transported to the subpleural and interlobar lymphatics and into the regional lymph nodes. The *cellular aggregates* containing silica become associated with lymphocytes, plasma cells, mast cells and fibroblasts.

3. Silica dust *isfibrogenic*. Crystalline form, particularly quartz, is more fibrogenic than non-crystalline form of silica.

4. As noted above, silica is *cytotoxic* and kills the macrophages which engulf it. The released silica dust activates viable macrophages leading to secretion of macrophage-derived growth factors such as interleukin-1 that favour fibroblast proliferation and collagen synthesis.

5. Simultaneously, there is *activation of T and B lymphocytes.* This results in increased serum levels of immunoglobulins (IgG and IgM), antinuclear antibodies, rheumatoid factor and circulating immune complexes as well as proliferation of T cells.

Pathologic changes. *Grossly,* the chronic silicotic lung is studded with well-circumscribed, hard, fibrotic nodules, 1 to 5 mm in diameters. They are scattered throughout the lung parenchyma but are initially more often located in the upper zones of the lungs. These nodular lesions frequently have simultaneous deposition of coal-dust and may develop calcification. The pleura is grossly thickened and adherent to the chest wall. There may be similar fibrotic nodules on the pleura and within the regional lymph nodes. The nodular lesions are detectable as egg-shell shadows in chest X-rays. The lesions may undergo ischaemic necrosis and develop cavitation, or be complicated by tuberculosis and rheumatoid pneumoconiosis.

Histologicaly, the following features are observed:

1. The silicotic nodules are located in the region of respiratory bronchioles, adjacent alveoli, pulmonary arteries, in the pleura and the regional lymph nodes.

2. The silicotic nodules consist of central hyalinised material with scanty cellularity and some amount of dust. The hyalinised centre is surrounded by concentric laminations of collagen which is further enclosed by more cellular connective tissue, dust-filled macrophages and a few lymphocytes and plasma cells. Some of these nodules may have calcium deposits.

3. The collagenous nodules have cleft-like spaces between the lamellae of collagen which when examined polariscopically may demonstrate numerous birefringent particles of silica.

4. The severe and progressive form of the disease may result in coalescence of adjacent nodules and cause complicated silicosis similar to progressive massive fibrosis of coal-workers' pneumoconiosis.

5. The intervening lung parenchyma may show hyperinflation or emphysema.

6. Cavitation when present may be due to ischaemic necrosis in the nodules, or may reveal changes of tuberculosis or rheumatoid pneumoconiosis (Caplan's syndrome), discussed already.

ASBESTOS DISEASE

Asbestos as a mineral is known to mankind for more than 4000 years but its harmful effects have come to light during the last few decades. Asbestos is a Greek word meaning 'unquenchable'. In general, if *coal is lot of dust and little fibrosis, asbestos is little dust and lot of fibrosis.* Prolonged exposure for a number of years to asbestos dust produces three types of severe diseases: *asbestosis of lungs, pleural disease and tumours.* In nature, asbestos exists as long thin fibrils which are fire-resistant and can be spun into yarns and fabrics suitable for thermal and electrical insulation and has many applications in industries. Particularly at risk are workers engaged in mining, fabrication and manufacture of a number of products from asbestos such as asbestos pipes, tiles, roofs, textiles, insulating boards, sewer and water conduits, brake lining, clutch castings etc. There are two major geometric forms of asbestos:

• *Serpentine* consisting of curly and flexible fibres. It includes the most common chemical form *chrysotile* (white asbestos) comprising more than 90% of commercially used asbestos.

• *Amphibole* consists of straight, stiff and rigid fibres. It includes the less common chemical forms *crocidolite* (blue asbestos), *amosite* (brown asbestos), *tremolite, anthophyllite* and *actinolyte.* However, the group of amphibole, though less common, is more important since it is associated with induction of malignant pleural tumours, particularly in association with crocidolite.

Pathogenesis. Overexposure to asbestos for more than a decade may produce asbestosis of the lung, pleural lesions and certain tumours. How asbestos causes all these lesions is not clearly understood but the following mechanisms have been suggested:

1. The inhaled asbestos fibres are *phagocytosed by alveolar macrophages* from where they reach the interstitium. Some of the engulfed dust is transported via lymphatics to the pleura and regional lymph nodes.

2. The asbestos-laden macrophages release *chemo-attractants* for neutrophils and for more macrophages, thus inciting cellular reaction around them.

3. Asbestos fibres are coated with glycoprotein and endogenous haemosiderin to produce characteristic beaded or dumbbell-shaped *asbestos bodies.*

4. All types of asbestos are *fibrogenic* and result in interstitial fibrosis. Fibroblastic proliferation may occur via macrophage-derived growth factor such as interleukin-1. Alternatively, fibrosis may occur as a reparative response to tissue injury by lysosomal enzymes released from macrophages and neutrophils or by toxic free radicals.

5. A few *immunological abnormalities* such as antinuclear antibodies and rheumatoid factor have been found in cases of asbestosis but their role in the genesis of disease is not clear.

6. Asbestos fibres are *carcinogenic,* the most carcinogenic being crocidolite. There is high incidence of bronchogenic carcinoma in asbestosis which is explained on the basis of the role of asbestos fibres as tumour promoters or by causing cell death of the airways so that it is exposed to the carcinogenic effect of cigarette smoke. The development of pleural mesothelioma in these cases is probably by carrying of asbestos fibres via lymphatics to the pleura.

Pathologic changes. As stated already, over-exposure to asbestos is associated with 3 types of lesions: asbestosis, pleural disease and certain tumours.

ASBESTOSIS. The gross pulmonary fibrosis caused by asbestos exposure and histologic demonstration of asbestos bodies on asbestos fibres is termed asbestosis.

Grossly, the affected lungs are small and firm with cartilage-like thickening of the pleura. The sectioned surface shows variable degree of pulmonary fibrosis, especially in the subpleural areas and in the bases of lungs. The advanced cases may show cystic changes.

Histologically, the following changes are observed:

1. There is non-specific interstitial fibrosis.

2. There is presence of characteristic *asbestos bodies* in the involved areas. These are asbestos fibres coated with glycoprotein and haemosiderin and appear beaded or dumbbell-shaped. The coating stains positively for Prussian blue reaction.

3. There may be changes of emphysema in the pulmonary parenchyma between the areas of interstitial fibrosis.

4. The involvement of hilar lymph nodes in asbestosis is not as significant as in silicosis.

PLEURAL DISEASE in asbestos exposure may produce one of the following 3 types of lesions:

1. Pleural Effusion. It develops in about 5% of asbestos workers and is usually serious type. Pleural effusion is generally accompanied by sub pleural asbestosis.

2. Visceral pleural fibrosis. Quite often, asbestosis is associated with dense fibrous thickening of the visceral pleura encasing the lung.

3. Pleural plaques, Fibrocalcific pleural plaques are the most common lesions associated with asbestos exposure.

Grossly, the lesions appear as circumscribed, flat, small (upto 1 cm in diameter), firm or hard, bilateral nodules. They are seen more often on the postero-lateral part of parietal pleura and on the pleural surface of the diaphragm.

Microscopically, they consist of hyalinised collagenous tissue which may be calcified so that they are visible on chest X-ray. Asbestos bodies are generally not found within the plaques.

TUMOURS. Asbestos exposure predisposes to a number of cancers, most importantly bronchogenic carcinoma and malignant mesothelioma. A few others are: carcinomas of oesophagus, stomach, colon, kidneys and larynx and various lymphoid malignancies.

1. Bronchogenic carcinoma is the most common malignancy in asbestos workers. Its incidence is 5 times higher in non-smoker asbestos workers than the non-smoker general population and 10 times higher in smoker asbestos workers than the other smokers.

2. Malignant mesothelioma is an uncommon tumour but association with asbestos exposure is present in 30 to 80% of cases with mesothelioma. The exposure need not be heavy because mesothelioma is known to develop in people living near asbestos plants or in wives of asbestos workers.

BERYLLIOSIS

Berylliosis is caused by heavy exposure to dust or fumes of metallic beryllium or its salts. Beryllium was used in the past in fluorescent tubes and light bulbs but currently it is principally used in nuclear and aerospace industries and in the manufacture of electrical and electronic equipments. Two forms of pulmonary berylliosis are recognized – *acute* and *chronic*.

ACUTE BERYLLIOSIS. Acute berylliosis occurs in individuals who are unusually sensitive to it and are heavily exposed to it for 2 to 4 weeks. The pulmonary reaction is in the form of an exudative chemical pneumonitis in which the alveoli are filled with protein-rich fluid with formation of hyaline membrane. The patient develops sudden dyspnoea, hyperapnoea and substernal pain. Most patients recover completely.

CHRONIC BERYLLIOSIS. Chronic berylliosis develops in individuals who are sensitised to it for a number of years, often after a delay of 20 or more years. The disease is a cell-mediated hypersensitivity reaction in which the metal beryllium acts as a hapten. The condition is characterised by development of non-caseating epithelioid granulomas like those of sarcoidosis. These granulomas are diffusely scattered throughout the lung parenchyma. The granulomas have giant cells which frequently contain 3 types of inclusions:

1. Birefringent crystals.
2. Concentrically-laminated haematoxyphilic Schaumann or conchoid bodies.
3. Acidophilic stellate-shaped asteroid bodies. These inclusions are described in giant cells of granulomas in sarcoidosis too. Similar sarcoid-like granulomas can occur in other organs such as in the liver, kidneys, spleen or lymph nodes in chronic berylliosis.

PAEDIATRIC LUNG DISEASE

A number of congenital anomalies (e.g. agenesis, hypoplasia, heterotopic tissue, vascular anomalies, tracheal and bronchial anomalies, congenital pulmonary over-inflation or lobar emphysema, congenital cysts and bronchopulmonary sequestration) and certain neonatal acquired lung diseases, (broncho-pulmonary dysplasia, meconium aspiration syndrome, persistent foetal circulation, atelactasis, collapse and bronchiolitis) have been described. A few important conditions will be discussed here.

Congenital Cysts

Developmental defects involving deficiency of bronchial or bronchiolar cartilage, elastic tissue and muscle result in congenital cystic disease of lungs. A single large cyst of this type occupying almost a lobe is called *pneumatocele*. Multiple small cysts are more common and give sponge-like appearance to the lung. The cysts are thin-walled and dilated and generally lined by flattened ciliated epithelium overlying a thin layer of supportive connective tissue. These cysts may contain air or may get infected and become abscesses. Cysts may rupture into bronchi producing haemoptysis, or into the pleural cavity giving rise to pneumothorax.

Bronchopulmonary Sequestration

Sequestration is the presence of lobes or segments of lung tissue which are not connected to the airway system. The blood supply of the sequestered area is not from the pulmonary arteries but from the aorta or its branches. Sequestration may be intralobar or extra-lobar.

• **Intralobar sequestration** is the sequestered bronchopulmonary mass within the pleural covering of the affected lung.

• **Extralobar sequestration** is the sequestered mass of lung tissue lying outside the pleural investing layer such as in the base of left lung or below the diaphragm. The extralobar sequestration is predominantly seen in infants and children and is often associated with other congenital malformations.

Neonatal Respiratory Distress Syndrome (Hyaline Membrane Disease)

Neonatal respiratory distress syndrome (RDS) or hyaline membrane disease characterised by formation of pulmonary hyaline membrane is the most common and serious form of disease of the newborn infants. The condition begins with dyspnoea a few hours after birth with tachypnoea, hypoxia and cyanosis and in severe cases death occurs in a few hours. The milder cases, however, recover with adequate oxygen therapy by ventilator-assist methods in a few days. The mortality rate is high (20 to 30%) and is still higher in babies under 1 kg of body weight. Some who recover develop bronchopulmonary dysplasia later on.

Etiology. The neonatal RDS is primarily initiated by hypoxia, either shortly before birth or immediately afterward. The following clinical settings are commonly associated with neonatal RDS:

1. Preterm infants.
2. Infants born to diabetic mothers.
3. Delivery by caesarean section.
4. Infants born to mothers with previous premature infants.
5. Excessive sedation of the mother causing depression in respiration of the infant.
6. Birth asphyxia from various causes such as coils of umbilical cord around the neck.
7. Male preponderance (1.5 to 2 times) over female babies due to early maturation of female lungs.

Besides all these factors causing respiratory distress, a number of cases of neonatal RDS remain idiopathic.

Pathogenesis. The basic defect in neonatal RDS is a deficiency of pulmonary surfactant, normally synthesised by type II alveolar cells. The production of surfactant is normally increased shortly before birth but in

prematurity and in neonatal hypoxia from any of the foregoing causes, its synthesis is decreased. The main function of alveolar surfactant being lowering of alveolar surface tension, its deficiency leads to increased alveolar surface tension which in turn causes atelectasis. Atelectasis of the lungs results in hypoventilation, pulmonary hypoperfusion, ischaemic damage to capillary endothelium and necrosis of the alveolar cells, exudation of plasma proteins including fibrinogen into the alveoli and eventually formation of hyaline membrane containing largely fibrin.

Pathologic changes. The pathologic changes of hyaline membrane disease are seldom seen in stillbirths or in those who die soon after birth.

Grossly, the lungs are normal in size and reddish purple in colour. They are solid and airless so that they sink in water.

1. The presence of collapsed alveoli (atelectasis) alternating with dilated alveoli.

2. Formation of characteristic eosinophilic hyaline membranes lining the respiratory bronchioles, alveolar ducts and the proximal alveoli. The membrane is largely composed of fibrin admixed with cell debris derived from necrotic alveolar cells.

3. Vascular congestion, focal haemorrhages and dilatation of septal lymphatics.

4. Absence of inflammatory reaction.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia occurs as a complication in infants treated for neonatal RDS with oxygen and assisted ventilation. The toxicity of oxygen and barotrauma from high pressure of oxygen give rise to subacute or chronic fibrosing condition of the lungs termed bronchopulmonary dysplasia. The condition is clinically characterised by persistence of respiratory distress for up to 3 to 6 months.

Pathologically, there is organisation of hyaline membranes resulting in fibrous thickening of the alveolar walls, bronchiolitis, peribronchial fibrosis, and development of emphysema due to alveolar dilatation. Many bronchioles show squamous metaplasia.

ATELECTASIS AND COLLAPSE

Atelectasis in the newborn or *primary atelectasis* is defined as incomplete expansion of a lung or part of a lung, while pulmonary collapse or *secondary atelectasis* is the term used for reduction in lung size of a previously expanded and well-aerated lung. Obviously, the former occurs in newborn whereas the latter may occur at any age.

ATELECTASIS. Stillborn infants have total atelectasis, while the newborn infants with weak respiratory action develop incomplete expansion of the lungs and clinical atelectasis. The common causes are prematurity, cerebral birth injury, CNS malformations and intrauterine hypoxia.

Grossly, the lungs are small, dark blue, fleshy and non-crepitant

Microscopically, the alveolar spaces in the affected area are small with thick interalveolar septa. The alveolar spaces contain proteinaceous fluid with a few epithelial squames and meconium. Scattered aerated areas of the lung are hyperinflated causing interstitial emphysema and pneumothorax.

COLLAPSE. Pulmonary collapse or secondary atelectasis in children and adults may occur from various causes such as compression, obstruction, contraction and lack of pulmonary surfactant. Accordingly, collapse may be of the following types:

1. Compressive collapse. Pressure from outside causes compressive collapse e.g. by massive pleural effusion, haemothorax, pneumothorax, intrathoracic tumour, high diaphragm and spinal deformities. Compressive collapse involves subpleural regions and affects lower lobes more than the central areas.

2. Obstructive/absorptive collapse. Obstruction of a bronchus or many bronchioles causes absorption of oxygen in the affected alveoli followed by collapse e.g. by viscid mucus secretions in bronchial asthma, chronic bronchitis, bronchiectasis, bronchial tumours and aspiration of foreign bodies. Obstructive collapse is generally less severe than the compressive collapse and is patchy.

3. Contraction collapse. This type occurs due to localised fibrosis in lung causing contraction followed by collapse.

BRONCHIOLITIS AND BRONCHIOLITIS OBLITERANS

Bronchiolitis and bronchiolitis obliterans are the inflammatory conditions affecting the small airways occurring predominantly in older paediatric age group and in quite elderly persons. A number of etiologic factors have been stated to cause this condition. These include viral infection (frequently adenovirus and respiratory syncytial virus), bacterial infection, fungal infection, inhalation of toxic gases (e.g. in silo-fillers' disease) and aspiration of gastric contents.

Microscopically, the lumina of affected bronchioles are narrow and occluded by fibrous plugs. The bronchiolar walls are inflamed and are infiltrated by lymphocytes and plasma cells. There are changes of interstitial pneumonitis and fibrosis in the alveoli around the affected bronchioles.

PULMONARY VASCULAR DISEASE

As stated before, diseases of the heart affect the lungs and diseases of the lungs affect the heart. This is because of the peculiar characteristics of pulmonary vasculature. The pressure in the pulmonary arteries is much lower than in the systemic arteries. The pulmonary arterial system is thinner than the systemic arterial system. They are thin elastic vessels which can be easily distinguished from thick-walled bronchial arteries supplying the large airways and the pleura.

General diseases of vascular origin occurring in the lungs such as pulmonary oedema, pulmonary congestion, pulmonary embolism and pulmonary infarction have all been already described in the section of General Pathology. Here, two specific forms of pulmonary vascular diseases – adult respiratory distress syndrome and pulmonary hypertension, will be discussed.

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

Adult respiratory distress syndrome (ARDS) is known by various synonyms such as shock-lung syndrome, diffuse alveolar damage (DAD), acute alveolar injury, traumatic wet lungs and post-traumatic respiratory insufficiency. ARDS is a syndrome caused by diffuse alveolar capillary damage and clinically characterised by sudden and severe respiratory distress, tachypnoea, tachycardia, cyanosis and severe hypoxaemia that fails to respond to oxygen therapy and assisted ventilation unlike neonatal RDS described above. The condition was first recognised during World War II in survivors of non-thoracic injuries with shock. The chest radiographs of these patients show diffuse bilateral alveolar infiltrates which may progress.

Etiology. Diffuse alveolar damage in ARDS may occur from a number of causes. These are:

1. Shock due to sepsis, trauma, burns,
2. Diffuse pulmonary infections, chiefly viral pneumonia,
3. Pancreatitis,
4. Oxygen toxicity,
5. Inhalation of toxins and irritants e.g. smoke, war gases, nitrogen dioxide, metal fumes etc.
6. Narcotic overdose,
7. Drugs e.g. salicylates, colchicines,
8. Aspiration pneumonia's,
9. Fat embolism,
10. Radiation.

Pathogenesis. The basic initiating event in the pathogenesis of ARDS is diffuse damage to the alveolocapillary wall by one of the injurious factors listed above. The mechanism of damage depends upon the etiologic agent – it

may be by oxygen-derived free radicals, by intravascular aggregation of neutrophils, or by liberation of mediators of inflammation. Injury to the capillary endothelium leads to increased vascular permeability. Injury to epithelial cells, especially to type 1 alveolar cells, causes necrosis of these cells. The net effect of injury to both capillary endothelium and alveolar epithelium is interstitial and intra-alveolar oedema, congestion, fibrin deposition and formation of hyaline membranes as seen in neonatal RDS. As a result of lining of the alveoli with hyaline membranes, there is loss of surfactant causing collapse with pulmonary oedema called 'stiff lung'. There is an attempt at regeneration of alveolar cells by proliferation of type II alveolar cells. A stiff lung of ARDS may undergo complete recovery or may undergo organisation resulting in proliferation of interstitial cells leading to interstitial fibrosis or even death.

Pathologic changes. *Grossly,* the lungs are characteristically stiff, congested and heavy.

Microscopically, the following features are evident:

1. Interstitial and intra-alveolar oedema.
2. Necrosis of alveolar epithelial cells with formation of hyaline membranes. The hyaline membranes are structurally similar to those of neonatal RDS i.e. they are chiefly composed of fibrin admixed with necrotic epithelial cells.
3. Congestion and intra-alveolar haemorrhages.
4. Changes of bronchopneumonia.
5. In organising stage, there may be interstitial fibrosis and regenerating flat alveolar epithelial cells lining the denuded alveoli.

PULMONARY HYPERTENSION

Normally, the blood pressure in the pulmonary arterial circulation is much lower than the systemic blood pressure; it does not exceed 30/15 mmHg even during exercise (normally, blood pressure in the pulmonary veins is between 3 and 8 mmHg). Pulmonary hypertension is defined as a systolic blood pressure in the pulmonary arterial circulation above 30 mmHg. Pulmonary hypertension is broadly classified into 2 groups: primary (idiopathic) and secondary; the latter being more common.

PRIMARY (IDIOPATHIC) PULMONARY HYPERTENSION

Primary or idiopathic pulmonary hypertension is an uncommon condition of unknown cause. The diagnosis can be established only after a thorough search for the usual causes of secondary pulmonary hypertension (discussed below). The patients are usually young females between the age of 20 and 40 years, or children around 5 years of age.

Etiopathogenesis. Though the etiology of primary pulmonary hypertension is unknown, a number of etiologic factors have been suggested to explain its pathogenesis:

1. A *neurohumoral vasoconstrictor mechanism* may be involved leading to chronic vasoconstriction that induces pulmonary hypertension.

2. The occurrence of disease in young females has prompted a suggestion that *unrecognised thromboemboli* or *amniotic fluid emboli* during pregnancy may play a role.

3. There is a suggestion that primary pulmonary hypertension may be a form of *collagen vascular disease.* This is supported by occurrence of Raynaud's phenomenon preceding the onset of this disease by a number of years in many patients, and association of the disease with SLE, scleroderma and rheumatoid arthritis.

4. *Pulmonary veno-occlusive disease* characterised by fibrous obliteration of small pulmonary veins is believed to be responsible for some cases of primary pulmonary hypertension, especially in children. Generally, this is considered to be a consequence of thrombosis or vasculitis.

5. *Ingestion of substances* like 'bush tea', oral contraceptives and appetite depressant agents like aminorex are believed to be related to primary pulmonary hypertension.

6. *Familial occurrence* has been reported in a number of cases.

SECONDARY PULMONARY HYPERTENSION

When pulmonary hypertension occurs secondary to a recognised lesion in the heart or lungs, it is termed as secondary pulmonary hypertension. It is the more common type and may be encountered at any age, but more frequently over the age of 50 years.

Etiopathogenesis. Based on the underlying mechanism, causes of secondary pulmonary hypertension are divided into the following 3 groups:

A. Passive pulmonary hypertension. This is the commonest and is produced by diseases raising pressure in the pulmonary veins. These diseases are:

1. Mitral stenosis.

2. Chronic left ventricular failure (e.g. in severe systemic hypertension, aortic stenosis, myocardial fibrosis).

B. Hyperkinetic (Reactive) pulmonary hypertension.

In this group are included causes in which the blood enters the pulmonary arteries in greater volume or at a higher pressure. These causes are:

1. Patent ductus arteriosus.

2. Atrial or ventricular septal defects.

C. Vaso-occlusive pulmonary hypertension. All such conditions which produce progressive diminution of the vascular bed in the lungs are included in this group. Vaso-occlusive causes may be further subdivided into 3 types:

1. *Obstructive type,* in which there is block in the pulmonary circulation e.g.

i) Multiple emboli or thrombi

ii) Sickle cell disease

iii)) Schistosomiasis

2. *Obliterative type,* in which there is reduction of pulmonary vascular bed by chronic parenchymal lung diseases e.g.

i) Chronic emphysema

ii) Chronic bronchitis

iii)) Bronchiectasis

iv) Pulmonary tuberculosis

v) Pneumoconiosis

3. *Vasoconstrictive type,* in which there is widespread and sustained hypoxic vasoconstriction and alveolar hyperventilation leading to pulmonary hypertension e.g.

i) In residents at high altitude

ii) Pathologic obesity (Pickwickian disease)

iii) Upper airway disease such as tonsillar hypertrophy

iv) Neuromuscular diseases such as poliomyelitis

v) Severe kyphoscoliosis.

Pathologic changes. Irrespective of the type of pulmonary hypertension (primary or secondary), chronic cases invariably lead to cor pulmonale. The pathologic changes are confined to the right side of the heart and pulmonary arterial tree in the lungs. There is hypertrophy of the right ventricle and dilatation of the right atriurn. The vascular changes are similar in primary and secondary types and involve the entire arterial tree from the main pulmonary arteries down to the arterioles. These changes are as under:

1. Arterioles and small pulmonary arteries: These branches show most conspicuous changes. These are:

i) Medial hypertrophy.

ii) Thickening and reduplication of elastic laminae,

iii) Plexiform pulmonary arteriopathy in which there is intraluminal tuft of capillary formation in dilated thin-walled arterial branches. These lesions are not so marked in secondary pulmonary hypertension.

2. Medium-sized pulmonary arteries:

i) Medial hypertrophy, which is not so marked in secondary pulmonary hypertension.

ii) Concentric intimal thickening.

iii) Adventitial fibrosis.

iv) Thickening and reduplication of elastic laminae.

3. Large pulmonary arteries:

i) Atheromatous deposits.

IMMUNOLOGIC LUNG DISEASE

Immunologic mechanisms play an important role in a number of lung diseases. These include the following important examples:

1. Bronchial asthma
2. Hypersensitivity (allergic) pneumonitis
3. Pulmonary eosinophilia
4. Goodpasture's syndrome
5. Pulmonary alveolar proteinosis

BRONCHIAL ASTHMA

Though bronchial asthma is included in immunologic lung diseases, immunologic reactions are one of the mechanisms involved in its pathogenesis.

HYPERSENSITIVITY (ALLERGIC) PNEUMONITIS

Hypersensitivity pneumonitis are a group of immunologically-mediated interstitial lung diseases occurring in workers inhaling a variety of organic (biologic) antigenic materials. The condition may have an *acute* onset due to isolated exposure or may be *chronic* due to repeated low-dose exposure.

Etiopathogenesis. The immunologic mechanisms underlying hypersensitivity pneumonitis from any of these causes appear to be either type III immune-complex disease or type IV delayed-hypersensitivity reaction.

1. Farmers' lung is the classic example resulting from exposure to thermophilic actinomycetes generated by humid and warm mouldy hay.

2. Bagassosis occurs in individuals engaged in manufacture of paper and cardboard from sugarcane bagasse. Spores of thermophilic actinomycetes grow rapidly in mouldy sugarcane bagasse which are inhaled.

3. Byssinosis is an occupational lung disease occurring in workers exposed to fibres of cotton, flex and hemp for a number of years. The role of immunologic mechanisms in byssinosis is not as clear as in exposure to other organic dusts.

4. Bird-breeders (Bird-fanciers) lung occurs in pigeon breeders, parrot breeders, chicken farmers and bird-fanciers who are exposed to bird-droppings and danders from their feathers.

5. Mushroom-workers lung is found in mushroom cultivators exposed to mushroom compost dust.

6. Malt-workers lung is seen in distillery and brewery workers who are exposed to mouldy barley and malt dust.

7. Maple-bark disease occurs in those involved in stripping of maple bark and inhale mouldy maple bark (maple tree is grown in northern hemisphere for timber and its leaf is the emblem of Canada).

8. Silo-fillers' disease occurs in individuals who enter the *silo* (silo is an airtight store-house of fodder for farm animals) in which toxic fumes of nitric oxide and nitrogen dioxide are formed due to fermentation of silage. The condition is generally rapidly fatal; less often it may lead to interstitial lung disease.

Pathologic changes. The pathologic changes primarily involve the alveoli in contrast to bronchiolar involvement in asthma. The changes vary depending upon whether the biopsy is examined in early stage or in late stage.

• *In early stage,* the alveolar walls are diffusely infiltrated with lymphocytes, plasma cells and macrophages. A proportion of cases show granulomas consisting of histiocytes and giant cells of foreign body or Langhans type.

• *In chronic cases,* the lungs show interstitial fibrosis with some inflammatory infiltrate. Honey-combing of the lung may be present.

PULMONARY EOSINOPHILIA

Pulmonary eosinophilia, eosinophilic pneumonias or pulmonary infiltration with eosinophilia (PIE) syndrome are a group of immunologically-mediated lung diseases characterised by combination of 2 features:

1. Infiltration of the lungs in chest radiographs; and
2. Elevated eosinophil count in the peripheral blood.

Etiopathogenesis. PIE syndrome has a number of diverse causes and pathogenesis. These are as under:

1. Loeffler's syndrome is characterised by eosinophilia in the blood and typical wandering radiologic shadows, appearing in some part of the lung for a few days and then disappearing so as to appear somewhere else in the lung. The condition is generally self-limiting and mild, associated with slight fever and a few respiratory symptoms. The etiology is unknown.

2. Tropical pulmonary eosinophilia is caused by the passage of larvae of worms through the lungs e.g. in filariasis, ascariasis, strongyloidosis, toxocariasis and ancylostomiasis.

3. Secondary chronic pulmonary eosinophilia occurs secondary to adverse drug reactions; infection with fungi, bacteria, and helminths; allergic broncho-pulmonary aspergillosis and in association with asthma.

4. Idiopathic chronic eosinophilic pneumonia is characterised by prominent focal areas of consolidation of the lung. The condition is clinically diagnosed by excluding other known causes of pulmonary eosinophilia.

5. Hypereosinophilic syndrome is occurrence of eosinophilia of over 1500/μl for more than 6 months without any identifiable cause and without eosinophilic infiltrates in the lungs and other organs.

Pathologic changes. The lesions in the lungs are similar in all cases.

Grossly, the lungs usually show patchy consolidation.

Microscopically, there is thickening of the alveolar walls by oedema and exudate, chiefly of eosinophils, and some lymphocytes and plasma cells. The alveolar lumina also contain eosinophils. Occasionally, small granulornas may be present.

GOODPASTURE'S SYNDROME

Goodpasture's syndrome is combination of necrotising haemorrhagic interstitial pneumonitis and rapidly progressive glomerulonephritis.

Etiopathogenesis. The condition results from immunologic damage produced by anti-basement membrane antibodies formed against antigens common to the glomerular and pulmonary basement membranes. The trigger for initiation of this autoimmune response is not clear; it could be virus infection, exposure to hydrocarbons and smoking.

Pathologic changes. *Grossly,* the lungs are heavy with red-brown areas of consolidation.

Microscopically, the features vary according to the stage of the disease:

• *In acute stage,* there are focal areas of haemorrhages in the alveoli and focal necrosis in the alveolar walls.

• *In more chronic cases,* there is organisation of the haemorrhage leading to interstitial fibrosis and filling of alveoli with haemosiderin-laden macrophages.

PULMONARY ALVEOLAR PROTEINOSIS

Pulmonary alveolar proteinosis is a rare chronic disease in which the distal airspaces of the lungs are filled with granular, PAS-positive, eosinophilic material with abundant lipid in it. The condition can occur at any age from infancy to old age.

Etiopathogenesis. The etiology and pathogenesis of alveolar proteinosis are unknown. A number of possibilities have been suggested:

• Since the alveolar material is combination of lipid and protein, it is not simply an overproduction of surfactant.

• Alveolar proteinosis may have an occupational etiology as seen in patients heavily exposed to silica.

• It may have an etiologic association with haematologic malignancies.

• There may be defective alveolar clearance of debris.

Pathologic changes. *Grossly,* usually both lungs are involved, particularly the lower lobes. The lungs are heavier with areas of consolidation. Sectioned surface exudes abundant turbid fluid.

Histologically, the hallmark of the condition is presence of homogeneous, granular, eosinophilic material which stains brightly with PAS. Often, the material contains cholesterol clefts. There is no significant inflammatory infiltrate in the affected alveoli. Biochemically, the material consists of serum proteins of low molecular weight, cholesterol and phospholipids similar to surfactant. Electron microscopy reveals that the material consists of necrotic alveolar macrophages and desquamated alveolar epithelial cells.

COLLAGEN-VASCULAR DISEASE (SEE ABOVE)

Microscopically, these granulomas have foci of fibrinoid necrosis and intense exudate of lymphocytes, plasma cells and macrophages with scattered multinucleate giant cells. Besides necrotising granulomas, there is associated vasculitis.

IDIOPATHIC PULMONARY FIBROSIS

Diffuse interstitial fibrosis can occur as a result of a number of pathologic entities such as pneumoconiosis, hypersensitivity pneumonitis and collagen-vascular disease. However, in half the cases of diffuse interstitial fibrosis, no apparent cause or underlying disease is identifiable. Such cases are included under the entity *'idiopathic pulmonary fibrosis'* in the United States and *'cryptogenicfibrosing alveolitis'* in Britain. Some authors have termed the fully-developed condition as *'chronic interstitial pneumonitis'* or *'usual interstitial pneumonitis'* and distinguished it from the early stage of the disease called *'desquamative interstitial pneumonitis'*.

Pathogenesis. The pathogenesis of idiopathic pulmonary fibrosis is unknown and the condition is diagnosed by excluding all known causes of interstitial fibrosis. However, a few evidences point toward immunologic mechanism. These are:

1. High levels of autoantibodies such as rheumatoid factor and antinuclear antibodies.

2. Elevated titres of circulating immune complexes.

3. Immunofluorescent demonstration of the deposits of immunoglobulins and complement on the alveolar walls in biopsy specimens.

Pathologic changes. The lung involvement in idiopathic pulmonary fibrosis is often bilateral and widespread.

Grossly, the lungs are firm, heavier with reduced volume. Honeycombing (i.e. enlarged, thick-walled air spaces) develops in parts of lung, particularly in the subpleural region.

Histologically, the changes vary according to the stage of the disease.

• *In early stage,* there is widening of the alveolar septa by oedema and cellular infiltrate by mononuclear inflammatory cells. The alveolar lining cells may show hyperplasia at places and are flattened at other places. There is often formation of hyaline membranes. The alveolar spaces contain exudate consisting of macrophages, lymphocytes and neutrophils. Many of the macrophages contain lamellar bodies derived from surfactant of the necrotic alveolar lining epithelial cells. Based on the observation of desquamative component in the cellular exudate, some authors label the early stage of idiopathic pulmonary fibrosis as *'desquamative interstitial pneumonitis'.*

• *In advanced stage,* there is organisation of the alveolar exudate and replacement fibrosis in the alveoli as well as in the interstitial septal wall with variable amount of inflammation. Eventually, there are small cystic areas (honeycomb lung) with alternating areas of fibrosis containing thick-walled and narrowed vessels. This stage is often referred to as *'chronic interstitial pneumonitis'* or *'usual interstitial pneumonitis'.*

TUMOURS OF LUNGS

A number of benign and malignant tumours occur in the lungs but the primary lung cancer, commonly termed bronchogenic carcinoma, is the most common (95% of all primary lung tumours). The lung is also the commonest site for metastasis from carcinomas and sarcomas.

BRONCHOGENIC CARCINOMA

Though the term bronchogenic carcinoma is commonly used for cancer of the lungs, it includes carcinomas having bronchial as well as bronchiolar origin.

Incidence. Bronchogenic carcinoma is the most common primary malignant tumour in men in industrialised nations and accounts for nearly one-third of all cancer deaths in both sexes. Currently, the incidence in females in the United States has already exceeded breast cancer as a cause of death in women. Cancer of the lung is a disease of middle and late life with peak incidence in 5th to 7th decades, after which there is gradual fall in its incidence.

Etiopathogenesis. The high incidence of lung cancer is associated with a number of etiologic factors, most important of which is *cigarette smoking.*

1. Smoking. The most important factor for rise in the incidence of bronchogenic carcinoma is tobacco smoking. About 80% of lung cancer occurs in active smokers. A number of evidences support the positive relationship of lung cancer with tobacco smoking:

i) Total dose: There is a direct statistical correlation between death rate from lung cancer and the total amount of cigarettes smoked e.g.

• An average regular smoker has 10 times greater risk of developing lung cancer than a non-smoker.

• The risk of smokers of more than 2 packs (40 cigarettes) per day for 20 years is 20 times greater.

• Cessation of smoking by a regular smoker results in gradual decline in the chances of developing lung cancer. After 10 years of abstinence from smoking, the risk is not greater than in a non-smoker.

• Pipe and cigar smokers, though have higher risk than non-smokers but are at lesser risk than cigarette smokers.

ii) Histologic alterations*:* The association of tobacco smoking is strongest for squamous cell carcinoma and small cell carcinoma of the lung. More than 90% of smokers have epithelial changes in the respiratory tract in the form of squamous metaplasia, dysplasia or carcinoma *in situ*.

iii) Mechanism*:* How tobacco smoking causes lung cancer is not quite clear.

• Analysis of the tar from cigarette smoke has revealed a number of known carcinogens (e.g. polycyclic aromatic hydrocarbons, nitrosamines) and tumour promoters (e.g. phenol derivatives).

• In experimental animal studies, it has been possible to induce cancer by skin painting experiments with smoke-tar. However, it has not been possible to reproduce pattern of human respiratory tract cancer, probably because of the difficulty in reproducing human smoking methods in animals.

2. Atmospheric pollution. There is increased risk of developing bronchogenic carcinoma in nonsmokers living in industrialised and smoky cities than in the less polluted rural areas. It is possible that specific industrial pollutants may be at fault as evidenced by high rates for lung cancer in people living in the neigh bour hood of petrochemical industries.

3. Occupational causes. There are number of well-established occupational causes of lung cancer. These include workers exposed to asbestos, radiation of all types, bisethers, nickel, beryllium, arsenic, metallic iron and iron-oxide. Some industrial carcinogens and cigarette smoking have cocarcinogenic effect, particularly in uranium mines and asbestos workers.

4. Dietary factors. Susceptibility to respiratory cancers is increased in vitamin A deficiency. Smokers with low vitamin A intake have a greater risk of lung cancer than those with vitamin A-rich diet. The incidence of lung cancer is inversely related to socioeconomic level reflecting their dietary pattern.

5. Genetic factors. The risk of developing lung cancer in the relatives of lung cancer patients is two and half times greater than that in the general population. A few studies have suggested that ability to metabolise carcino-

genic polycyclic aromatic hydrocarbons is under genetic control but the exact nature of genetic and familial influence is uncertain.

6. Chronic scarring. Peripheral adenocarcinomas occur more frequently in areas of chronic scarring caused by chronic inflammatory changes, old tuberculosis, asbestosis, chronic interstitial fibrosis, old infarcts and in scleroderma.

Pathologic changes. Bronchogenic carcinoma can occur anywhere in the lung but the most common location is *hilar*, followed in descending frequency by *peripheral* type.

Grossly, these 2 main types show variation in appearance:

1. Hilar type: Most commonly, the lung cancer arises in the main bronchus or one of its segmental branches in the hilar parts of the lung, more often on the right side. The tumour begins as a small roughened area on the bronchial mucosa at the bifurcation. As the tumour enlarges, it thickens the bronchial mucosa producing nodular or ulcerated surface. As the nodules coalesce, the carcinoma grows into a friable spherical mass, 1 to 5 cm in diameter, narrowing and occluding the lumen. The cut surface of the tumour is yellowish-white with foci of necrosis and haemorrhages which may produce cavitary lesions. It is common to find secondary changes in bronchogenic carcinoma of lung such as bronchopneumonia, abscess formation and bronchiectasis as a result of obstruction and intercurrent infections. The tumour soon spreads within the lungs by direct extension or by lymphatics, and to distant sites by lymphatic or haematogenous routes, as described later.

2. Peripheral type: A small proportion of lung cancers, chiefly adenocarcinomas including bronchioloalveolar carcinomas, originate from a small peripheral bronchiole but the exact site of origin may not be discernible. The tumour may be a single nodule or multiple nodules in the periphery of the lung producing pneumonia-like consolidation of a large part of the lung. The cut surface of the tumour is greyish and mucoid.

Histologically, as per the World Health Organisation recommendations, bronchogenic carcinoma is divided into 5 main histologic types: squamous cell or epidermoid carcinoma (35-50%), small cell carcinoma (20-25%), adenocarcinoma (15-35%), large cell carcinoma (10-15%), and combined squamous cell carcinoma and adenocarcinoma (adenosquamous carcinoma, 1-3%). For therapeutic purposes, bronchogenic carcinoma can be classified into 3 groups:

1. Small cell carcinoma (20-25%)

2. Non-small cell carcinomas (70-75%) (includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma)

3. Combined/mixed patterns (5-10%).

By light microscopy, precise histologic classification of bronchogenic carcinoma is possible which is important because of prognostic and therapeutic considerations.

1. Squamous cell (epidermoid) carcinoma: This is the most common type of bronchogenic carcinoma found more commonly in men, particularly with history of tobacco smoking. These tumours usually arise in a large bronchus and are prone to massive necrosis and cavitation. The tumour is diagnosed microscopically by identification of either intercellular bridges or keratinisation. The tumour may show varying histologic grades of differentiation such as well-differentiated, moderately-differentiated and poorly-differentiated. Occasionally, a variant of squamous cell carcinoma, *spindle cell carcinoma,* having biphasic pattern of growth due to the presence of a component of squamous cell carcinoma and the other sarcoma-like spindle cell component, is found. Usually the spread of squamous cell carcinoma is more rapid than the other histologic types. Frequently, the edge of the growth and the adjoining uninvolved bronchi show squamous metaplasia, epithelial dysplasia and carcinoma *in situ.*

2. Small cell carcinoma: Small cell carcinomas are frequently hilar or central in location, have strong relationship to cigarette smoking and are highly malignant tumours. They are most often associated with ectopic hormone production because of the presence of neurosecretory granules in majority of tumour cells which are similar to those found in argentaffin or Kulchitsky cells normally found in bronchial epithelium. Small cell carcinomas have 3 subtypes:

i) *Oat cell carcinoma* is composed of uniform, small cells, larger than lymphocytes with dense, round or oval nuclei having diffuse chromatin, inconspicuous nucleoli and very sparse cytoplasm *(oat* = a form of grain). These cells are organised into cords, aggregates and ribbons or around small blood vessels forming pseudorosettes.

ii) *Small cell carcinoma, intermediate cell type* is composed of cells slightly larger than those of oat cell carcinoma and have similar nuclear characteristics but have more abundant cytoplasm. These cells are organised into lobules,

iii) *Combined oat cell carcinoma* is a tumour in which there is a definite component of oat cell carcinoma with squamous cell and/or adenocarcinoma.

3. Adenocarcinoma: Adenocarcinoma, also called *peripheral carcinoma* due to its location and *scar carcinoma* due to its association with areas of chronic scarring, is the most common bronchogenic carcinoma in women and is slow-growing. Adenocarcinoma is further subclassified into 4 types:

i) *Acinar adenocarcinoma* which has predominance of glandular structure and often occurs in the larger bronchi.

ii) *Papillary adenocarcinoma* which has a pronounced papillary configuration and is frequently peripherally located in the lungs and is found in relation to pulmonary, scars (scar carcinoma),

iii) *Bronchiolo-alveolar carcinoma* is characterised by cuboidal to tall columnar and mucus-secreting epithelial cells growing along the existing alveoli and forming numerous papillary structures. Ultrastructurally, these tumour cells resemble Clara cells or less often type II pneumocytes.

iv) *Solid carcinoma* is a poorly-differentiated adenocarcinoma lacking acini, tubules or papillae but having mucus-containing vacuoles in many tumour cells.

4. Large cell carcinoma: These are undifferentiated carcinomas which lack the specific features by which they could be assigned into squamous cell carcinoma or adenocarcinoma. Large cell carcinomas are more common in men, have strong association with cigarette smoking and are highly malignant tumours. The tumour cells have large nuclei, prominent nucleoli, abundant cytoplasm and well-defined cell borders. Variants of large cell undifferentiated carcinomas include *giant cell carcinoma* with prominence of highly pleomorphic multinucleate cells and *clear cell carcinoma* composed of cells with clear or foamy cytoplasm without mucin.

5. Adenosquamous carcinoma: These are a small proportion of peripheral scar carcinomas having clear evidence of both keratinisation and glandular differentiation.

Spread. Bronchogenic carcinoma can invade the adjoining structures directly, or may spread by lymphatic and haematogenous routes.

1. Direct spread. The tumour extends directly by invading through the wall of the bronchus and destroys and replaces the peribronchial lung tissue. As it grows further, it spreads to the opposite bronchus and lung, into the pleural cavity, the pericardium and the myocardium and along the great vessels of the heart causing their constriction. Extension of the cancer located at the apex of the lung into the thoracic cage may involve brachial plexus and the sympathetic chain causing pain and sensory disturbances, so called *Pancoast's syndrome.*

2. Lymphatic spread. Initially, hilar lymph nodes are affected. Later, lymphatic metastases occur to the other groups leading to spread to mediastinal, cervical, supraclavicular and paraaortic lymph nodes. Invasion of the thoracic duct may produce chylous ascites.

3. Haematogenous spread. Distant metastases via blood stream are widespread and early. The sites affected, in descending order of involvement, are: the liver, adrenals, bones, pancreas, brain, opposite lung, kidneys and thyroid.

Staging and prognosis. The widely accepted clinical staging of lung cancer is according to the TNM classification, combining features of primary

Tumours, Nodal involvement and distant Metastases. TNM staging divides all lung cancers into the following 4 stages:

Occult: Malignant cells in the broncho-pulmonary secretions but no evidence of primary tumour or metastasis.

Stage I: Tumour less than 3 cm, with or without ipsilateral nodal involvement, no distant metastasis.

Stage II: Tumour larger than 3 cm, with ipsilateral hilar lymph node involvement, no distant metastasis.

Stage III: Tumour of any size, involving adjacent structures, involving contralateral lymph nodes or distant metastasis.

In general, tumour size larger than 5 cm has worse prognosis. Symptomatic patients, particularly with systemic symptoms, fare far badly than the non-symptomatic patients. The overall prognosis of bronchogenie carcinoma is dismal; 5-year survival rate with surgery combined with radiotherapy or chemotherapy is about 9%. Adenocarcinoma and squamous cell carcinoma which are localised, are resectable and have a slightly better prognosis. *Small cell carcinoma has the worst prognosis* since surgical treatment is ineffective though the rumour is sensitive to radiotherapy and chemotherapy.

BRONCHIAL CARCINOID

Bronchial carcinoids are tumours of low grade malignancy arising from neuroendocrine (Kulchitsky) cells of bronchial mucosa in common with cell of origin for small cell carcinomas described above. Formerly, they used to be classified as 'bronchial adenomas' but now it is known that these tumours are locally invasive and have the capacity to metastasise. Bronchial carcinoids tend to occur at a younger age than broncho-genie carcinoma, often appearing below the age of 40 years, and are not related to cigarette smoking.

Pathologic changes. *Grossly*, bronchial carcinoids most commonly arise from a major bronchus and project into the bronchial lumen as a spherical polypoid mass, 3-4 cm in diameter. Less commonly, the tumour may grow into the bronchial wall and produce collar-button like lesion. The overlying bronchial mucosa is usually intact. Cut surface of the tumour is yellow-tan in colour.

Histiologically, the tumour is composed of uniform cubodial cells forming aggregates, trabeculae or ribbons separated by fine fibrous septa. The tumour cells have abundant, finely granular cytoplasm and oval central nuclei with clumped nuclear chromatin. Mitoses are rare and necrosis is uncommon. The secretory granules of bronchial carcinoids resemble those of other foregut carcinoids and stain positively with argyrophilic stains in which exogenous reducing agent is added for the reaction.

HAMARTOMA

Hamartoma is a tumour-like lesion composed of an abnormal admixture of pulmonary tissue components and is discovered incidentally as a coin-lesion in the chest-X-ray. Pulmonary hamartomas are of 2 types: chondromatous and leiomyomatous.

• **Chondromatous hamartoma** is more common and usually asymptomatic. It forms a solitary, spherical mass, 2-5 cm in diameter, usually at the periphery of the lung. Typically, it shows nodules of cartilage associated with fibrous and adipose tissue admixed with bronchial epithelium.

• **Leiomyomatous hamartoma** has a prominent smooth muscle component and bronchiolar structures. They are frequently multiple, 1-2 mm in diameter and are more commonly located near the pleura.

METASTATIC LUNG TUMOURS

Secondary tumours of the lungs are more common than the primary pulmonary tumours. Metastases from carcinomas as well as sarcomas arising from anywhere in the body may spread to the lung by haematogenous or lymphatic routes, or by direct extension. Blood-borne metastases are the most common since emboli of tumour cells from any malignant tumour entering the systemic venous circulation are likely to be lodged in the lungs. Metastases are most common in the peripheral part of the lung forming single or multiple, discrete nodular lesions which appear radiologically as *'cannon-ball secondaries'*. Less frequently, the metastatic growth is confined to peribronchiolar and perivascular locations which is due to spread via lymphatics.

Most common sources of metastases in the lungs are: carcinomas of the bowel, breast, thyroid, kidney, pancreas, lung (ipsilateral or contralateral) and liver. Other tumours which frequently metastasise to the lungs are osteogenic sarcoma, neuroblastoma, Wilms' tumour, melanoma, lymphomas and leukaemias.

PLEURA

Normal structure. Visceral pleura covers the lungs and extends into the fissures while the parietal pleura limits the mediastinum and covers the dome of the diaphragm and inner aspect of the chest wall. The two layers between them enclose pleural cavity which contains less than 15 ml of clear serous fluid.

Microscopically, both the pleural layers are lined by a single layer of flattened mesothelial cells facing each other. Underneath the lining cells is a thin layer of connective tissue.

Diseases affecting the pleura are nearly always secondary to some other underlying disease. Broadly, they fall into inflammations, non-inflammatory pleural effusions, pneumothorax, and tumours.

INFLAMMATIONS

Inflammatory involvement of the pleura is commonly termed *pleuritis or pleurisy.* Depending upon the character of resultant exudate, it can be divided into serous, fibrinous and serofibrinous, suppurative or empyema, and haemorrhagic pleuritis.

1. Serous, fibrinous and serofibrinous pleuritis. Acute inflammation of the pleural sac (acute pleuritis) can result in serous, serofibrinous and fibrinous exudate. Most of the causes of such pleuritis are infective in origin, particularly within the lungs, such as tuberculosis, pneumonias, pulmonary infarcts, lung abscess and bronchiectasis. Other causes include a few collagen diseases (e.g. rheumatoid arthritis and disseminated lupus erythematosus), uraemia, metastatic involvement of the pleura, irradiation of lung tumours and diffuse systemic infections (e.g. typhoid fever, tularaemia, blastomycosis and coccidiodomycosis).

Pleurisy causes pain in the chest on breathing and a friction rub is audible on auscultation. In most patients, the exudate is minimal and is resorbed resulting in resolution. Repeated attacks of pleurisy may result in organisation leading to fibrous adhesions and obliteration of the pleural cavity.

2. Suppurative pleuritis (empyema thoracis). Bacterial or mycotic infection of the pleural cavity that converts a serofibrinous effusion into purulent exudate is termed suppurative pleuritis or empyema thoracis. The most common cause is direct spread of pyogenic infection from the lung. Other causes are direct extension from subdiaphragmatic abscess or liver abscess and penetrating injuries to the chest wall. Occasionally, the spread may occur by haematogenous or lymphatic routes.

In empyema, the exudate is yellow-green, creamy pus that accumulates in large volumes. Empyema is eventually replaced by granulation tissue and fibrous tissue. In time, tough fibrocollagenic adhesions develop which obliterate the cavity, and with passage of years, calcification may occur. The effect of these is serious respiratory difficulty due to inadequate pulmonary expansion.

3. Haemorrhagic pleuritis. Haemorrhagic pleuritis differs from haemothorax in having inflammatory cells or exfoliated tumour cells in the exudate. The causes of haemorrhagic pleuritis are metastatic involvement of the pleura, bleeding disorders and rickettsial diseases.

NON-INFLAMMATORY PLEURAL EFFUSIONS

These include fluid collections in the pleural cavity such as hydrothorax, haemothorax and chylothorax.

1. HYDROTHORAX. Hydrothorax is non-inflammatory accumulation of serous fluid within the pleural cavities. Hydrothorax may be unilateral or bilateral depending upon the underlying cause. Occasionally, an effusion is limited to part of a pleural cavity by preexisting pleural adhesions.

The most common cause of hydrothorax, often bilateral, is congestive heart failure. Other causes are renal failure, cirrhosis of liver. Meig's syndrome, pulmonary oedema and primary and secondary tumours of the lungs.

The non-inflammatory serous effusion in hydro-thorax is clear and straw-coloured and has the characteristics of transudate with a specific gravity of under 1.012, protein content below 1 gm/dl and little cellular content.

If the fluid collection in pleural cavity is less than 300 ml (normal is less than 15 ml), no signs or symptoms are produced and may be apparent in chest X-ray in standing posture as obliterated costodiaphragmatic angle. If the pleural cavity contains abundant fluid, it imparts a characteristic opaque radiographic appearance to the affected side with deviation of trachea to the opposite side. In such cases, symptoms such as respiratory embarrassment and dyspnoea are produced which are promptly relieved on withdrawal of fluid.

2. HAEMOTHORAX. Accumulation of pure blood in the pleural cavity is termed as haemothorax. The most common causes of haemothorax are trauma to the chest wall or to the thoracic viscera and rupture of aortic aneurysm. It is important to remove the blood from the pleural cavity as early as possible. Otherwise the blood will clot and organise, resulting in fibrous adhesions and obliteration of the pleural cavity.

3. CHYLOTHORAX. Chylothorax is an uncommon condition in which there is accumulation of milky fluid of lymphatic origin into the pleural cavity. Chylothorax results most commonly from rupture of the thoracic duct by trauma or obstruction of the thoracic duct such as by malignant tumours, most often malignant lymphomas. Chylothorax is more often confined to the left side. Chylous effusion is milky due to high content of finely emulsified fats in the chyle.

PNEUMOTHORAX

An accumulation of air in the pleural cavity is called pneumothorax. It may occur in one of the three circumstances: spontaneous, traumatic and therapeutic.

i) Spontaneous pneumothorax occurs due to spontaneous rupture of alveoli in any form of pulmonary disease. Most commonly, spontaneous pneumothorax occurs in association with emphysema, asthma and tuberculosis. Other causes include chronic bronchitis in an old patient, bronchiectasis, pulmonary infarction and bronchial cancer. In young patients, recurrent spontaneous rupture of peripheral subpleural blebs may occur without any cause resulting in disabling condition termed *spontaneous idiopathic pneumothorax.*

ii) Traumatic pneumothorax is caused by trauma to the chest wall or lungs, ruptured oesophagus or stomach, and surgical operations of the thorax.

iii) Therapeutic (artificial) pneumothorax used to be employed formerly in the treatment of chronic pulmonary tuberculosis in which air was introduced into the pleural sac so as to collapse the lung and limit its respiratory movements.

The effects of pneumothorax due to any cause depend upon the amount of air collected in the pleural cavity. If the quantity of air in the pleura is small, it is resorbed. Larger volume of air collection in the pleural cavity causes dyspnoea and pain in the chest. Pneumothorax causes lung collapse and pulls the mediastinum to the unaffected side. Occasionally, the defect in the lungs is such that it acts as flap-valve and allows entry of air during inspiration but does not permit its escape during expiration, creating *tension pneumothorax* which requires urgent relief of pressure so as to relieve severe dyspnoea and circulatory failure.

TUMOURS OF PLEURA

Pleural tumours may be primary or secondary. In line with pulmonary tumours, the secondary tumours in the pleura are more common. The only important primary tumour of pleura is mesothelioma.

MESOTHELIOMA

Mesothelioma is an uncommon tumour arising from mesothelial lining of serous cavities, most often in pleural cavity, and rarely in peritoneal cavity and pericardial sac. Mesotheliomas are of 2 types – *benign (solitary) and malignant (diffuse).* The biologic behaviour of pleural mesotheliomas is usually predicted by their gross appearance – those forming solitary, discrete masses are generally benign, whereas those which grow diffusely are usually malignant.

Benign (Solitary) Mesothelioma

Benign or solitary mesothelioma is also called as pleural fibroma. *Asbestos exposure plays no role in etiology of benign mesothelioma.*

Grossly, it consists of a solitary, circumscribed, small, firm mass, generally less than 3 cm in diameter. Cut surface shows whorls of dense fibrous tissue.

Microscopically, the tumour is predominantly composed of whorls of collagen fibres and reticulin with interspersed fibroblasts. Rarely, mesothelial-lined clefts are seen in the tumour.

Benign mesothelioma causes no symptoms and is detected as an incidental radiologic finding. Sometimes the tumour is associated with systemic syndrome of osteoarthropathy or hypoglycaemia. Removal of the tumour is generally curative.

Malignant (Diffuse) Mesothelioma

Malignant or diffuse mesothelioma is rare. It is a highly malignant tumour associated with high mortality. The tumour is significant in view of its *recognised association with occupational exposure to asbsestos* (particularly crocidolite) for a number of years, usually 20 to 40 years. About 90% of malignant mesotheliomas are asbestos-related. However, prolonged asbestos-exposure is considered more significant rather than heavy exposure as documented by occurrence of malignant mesothelioma in the family members of asbestos workers. There is no extra increased risk of developing mesothelioma in asbestos workers who smoke, while asbestos-related bronchogenic carcinoma has a much higher risk in smoker asbestos workers.

Grossly, the tumour is characteristically diffuse, forming a thick, white, fleshy coating over the parietal and visceral surfaces. *Microscopically*, malignant mesothelioma may have epithelial, sarcomatoid or biphasic patterns.

i) Epithelial pattern resembles an adenocarcinoma, consisting of tubular and tubulo-papillary formations. The tumour cells are usually well-differentiated, cuboidal, flattened or columnar cells.

ii) Sarcomatoid pattern consists of spindle cell sarcoma resembling fibrosarcoma. The tumour cells are arranged in a storiform pattern with abundant collagen between them.

iii) Biphasic pattern shows mixed growth having epithelial as well as sarcomatoid pattern. Usually, there are slit-like or gland-like spaces lined by neoplastic mesothelial cells separated by proliferating spindle-shaped tumour cells.

Asbestos bodies are found in the lungs of most patients with malignant mesothelioma of any histologic type.

Clinical manifestations include chest pain, dyspnoea, pleural effusion and infections. The tumour spreads rapidly by direct invasion into lung and by lymphatic spread into hilar lymph nodes and pericardium. Sometimes distant metastases, particularly to the liver, occur. The prognosis is poor; 50% of patients die within one year of diagnosis.

SECONDARY PLEURAL TUMORS

Metastatic malignancies in the pleura are more common than the primary tumours and appear as small nodules scattered over the lung surface. The most frequent primary malignant tumours metastasizing to the pleura are of the lung and breast through lymphatics, and ovarian cancers via haematogenous route.

PATHOLOGY OF DIGESTIVE SYSTEM

ORAL CAVITY

The oral cavity is the point of entry for digestive and respiratory tracts. The mucous membrane of the mouth consists of squamous epithelium covering vascularised connective tissue. The epithelium is keratinised over the hard palate, lips and gingiva, while elsewhere it is non-keratinised. Mucous glands (minor salivary glands) are scattered throughout the oral mucosa. Sebaceous glands are present in the region of the lips and the buccal mucosa only. Lymphoid tissue is present in the form of tonsils and adenoids.

The oral cavity is the site of numerous congenital and acquired diseases. Besides, many systemic diseases have oral manifestations. Some of the commonly occurring conditions are discussed here.

DEVELOPMENTAL ANOMALIES

1. *Facial clefts. Cleft upper lip (harelip) and cleft palate,* alone or in combination, are the commonest developmental anomalies of the face. These occur from the failure of fusion of facial processes.

2. *Fordyce's granules*. Fordyce's granules are symmetric, small, light yellow macular spots on the lips and buccal mucosa and represent collections of sebaceous glands. They remain undeveloped until puberty but occur quite commonly in adults.

3. *Leukoedema.* This is an asymptomatic condition occurring in children and is characterised by symmetric, gray white areas on the buccal mucosa. *Histologically,* there is pronounced intracellular oedema. There is no increased malignant potential compared to leukoplakia discussed below.

4. *Developmental defects of the tongue.*

These are as under:

i) Macroglossia is the enlargement of the tongue, usually due to lymphangioma or haemangioma, and sometimes due to amyloid tumour.

ii) Microglossia and aglossia are rare congenital anomalies representing small-sized and absence of tongue respectively.

iii) Fissured tongue (scrotal, furrowed or grooved tongue) is a genetically-determined condition characterised by numerous small furrows or grooves on the dorsum of the tongue. It is often associated with mild glossitis.

iv) Bifid tongue is a rare condition occurring due to failure of the two lateral halves of the tongue to fuse in the midline.

v) Tongue tie occurs when the lingual fraenum is quite short, or when the fraenum is attached near the tongue tip.

vi) Hairy tongue is not a true developmental defect, but is mentioned here along with other similar conditions. The fili form papillae are hypertrophied and elongated. These 'hairs' are stained black, brown or yellowish-white by food, tobacco, oxidising agents or by oral flora.

MUCOCUTANEOUS LESIONS

Lesions of the oral mucosa occur in many diseases of the skin. Some of these are as under:

1. *Lichen planus*. Characteristically, oral lichen planus appears as interlacing network of whitening or keratosis on the buccal mucosa.

2. *Vesicular lesions*. A number of vesicular or bullous diseases of the skin have oral lesions.

i) *Pemphigus vulgaris*. Vesicular oral lesions appear invariably in all cases at some time in the course of pemphigus vulgaris. In about half the cases oral lesions are the initial manifestations.

ii) *Pemphigoid*. Vesicles or bullae appear on oral mucosa as well as on conjunctiva in pemphigoid and are seen more often in older women.

iii) *Erythema multiforme*. Subepithelial vesicles may occur on the skin as well as mucosae.

iv) *Stevens-Johnson syndrome* is a rather fatal and severe form of erythema multiforme involving oral and other mucous membranes occurring following ingestion of sulfa drugs.

v) *Epidermolysis bullosa* is a hereditary condition having subepidermal bullae on the skin as well as has oral lesions.

INFLAMMATORY DISEASES

1. *Stomatitis*. Inflammation of the mucous membrane of the mouth is called stomatitis. It can occur in the course of many different diseases.

i) *Aphthous ulcers* (Canker sores) is the commonest form of oral ulceration. The etiology is unknown but may be precipitated by emotional factors, stress, allergy, hormonal imbalance, nutritional deficiencies, gastrointestinal disturbances, trauma etc. The condition is characterised by painful oral ulcers, 1 cm or more in size. Recurrent *aphthae* may form a part of Behcet's syndrome and inflammatory bowel disease.

ii) *Herpetic stomatitis* is an acute disease occurring in infants and young children. It is the most common manifestation of primary infection with herpes simplex virus. The lesions are in the form of vesicles around the lips. Similar lesions may appear on the genital skin. Recurrent attacks occur due to stress, emotional upsets and upper respiratory infections.

iii) *Necrotising stomatitis* (Noma or Cancrum oris) occurs more commonly in poorly-nourished children like in kwashiorkor; infectious diseases such as measles; immunodeficiencies and emotional stress. The lesions are characterised by necrosis of the marginal gingiva and may extend on to oral mucosa, causing cellulitis of the tissue of the cheek. The condition may progress to gangrene of the cheek.

iv) *Mycotic infections* commonly involving the oral mucosa are actinomycosis and candidiasis.

• *Cervicofacial actinomycosis* is the commonest form of the disease developing at the angle of the mandible.

• *Candidiasis (moniliasis or thrush)* is caused by *Candida albicans* which is a commensal in the mouth. It appears as an opportunistic infection in immunocompromised host. There are erythematous lesions on the palate and angular cheilitis.

2. *Glossitis*. Acute glossitis characterised by swollen papillae occurs in eruptions of measles and scarlet fever. In chronic glossitis, the tongue is raw and red without swollen papillae and is seen in malnutrition such as in pellagra, ariboflavinosis and niacin deficiency. In iron deficiency anaemia, pernicious anaemia and sprue, there is *chronic atrophic glossitis* characterised by atrophied papillae and smooth raw tongue.

3. *Syphilitic lesions*. Oral lesions may occur in primary, secondary, tertiary and congenital syphilis.

i) Extragenital chancre of *primary syphilis* occurs most commonly on the lips.

ii) Secondary syphilis shows maculopapular eruptions and mucous patches in the mouth.

iii) In the *tertiary syphilis*, gumrnas or diffuse fibrosis may be seen on the hard palate and tongue.

iv) Oral lesions of the *congenital syphilis* are fissures at the angles of mouth and characteristic peg-shaped notched Hutchinson's incisors.

4. *Tuberculous lesions*. Involvement of the mouth in tuberculosis is rare. The lesions are in the form of ulcers or elevated nodules.

5. *HIV infection*. HIV infection of low grade as well as full-blown acquired immunodeficiency syndrome (AIDS) are associated with oral manifestations such as opportunistic infections, malignancy, hairy leukoplakia and others. About half the cases of Kaposi's sarcoma have intraoral lesions as part of systemic involvement.

PIGMENTARY LESIONS

Oral and labial melanotic pigmentation may be observed in certain systemic and metabolic disorders such as Addison's disease, Albright syndrome, Peutz-Jeghers syndrome and haemochromatosis. All types of pigmented naevi as well as malignant melanoma can occur in oral cavity. Exogenous pigmentation such as due to deposition of lead sulfide can also occur.

TUMOURS AND TUMOUR-LIKE LESIONS

Benign and malignant tumours of various types and also a number of tumour-like lesions and premalignant lesions are encountered in the oral soft tissues.

A. TUMOUR-LIKE LESIONS

A number of proliferative lesions arising from the oral tissues are tumour-like masses which clinically may resemble neoplasms. Some of these are as under:

1. *Fibrous growths*. Fibrous growths of the oral soft tissues are very common. These are not true tumours (unlike intraoral fibroma and papilloma), but are instead inflammatory or irritative in origin. A few common varieties are as under:

i) Fibroepithelial polyps occur due to irritation or chronic trauma. These are composed of reparative fibrous tissue, covered by a thin layer of stratified squamous epithelium.

ii) Fibrous epulis is a lesion occurring on the gingiva and is localised hyperplasia of the connective tissue following trauma or inflammation in the area.

iii) Denture hyperplasia occurs in edentulous or partly edentulous patients. The lesion is an inflammatory hyperplasia in response to local irritation by ill-fitting denture or an elongated tooth.

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

3. *Mucocele.* Also called mucous cyst, it is a cystic dilatation of the mucous glands of the oral mucosa. The cyst often ruptures on distension and incites inflammatory reaction.

4. *Ranula.* It is a large mucocele located on the floor of the mouth. The cyst is lined by true epithelial lining.

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

B.BENIGN TUMOURS

Different parts of the mouth have a variety of mesodermal tissues and keratinising and non-keratinising epithelium. Therefore, the majority of neoplasms arising from the oral tissues are just like their counterparts in other parts of the body. Some of the common benign tumours of the mouth are as under:

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

Microscopically, each papilla is composed of valarised connective tissue covered by squa epithelium.

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

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

Microscopically, lymphangioma is characterised by large lymphatic spaces lined by endothelium and containing lymph.

4. *Fibroma*. The true fibroma of mouth is relatively uncommon benign tumour and is more often a tumour-like lesion (discussed above).

Microscopically, fibroma is composed of collagenic fibrous connective tissue covered by stratified squamous epithelium.

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

6. *Tumours of minor salivary glands*.

Minor salivary glands present in the oral cavity may sometimes be the site of origin of salivary tumours similar to those seen in the major salivary glands. Pleomorphic adenoma is a common example.

7. *Granular cell myoblastoma.* This is an unusual oral benign tumour, seen more often in the tongue.

Microscopically, the tumour is composed of large polyhedral cells with granular, acidophilic cytoplasm. The covering epithelium usually shows pronouncec pseudoepitheliomatous hyperplasia.

8. *Other rare benign tumours.* Some other rare benign tumours which can occur in the oral soft tissues are: neurilemmoma, neurofibroma, lipoma, giant cell granuloma, rhabdomyoma, leiomyoma, solitary plasmacytoma, osteoma, chondroma, naevi and vascular oral lesions seen in hereditary haemorrhagic telangiectasia (Osler-Rendu-Weber syndrome) and encephalofacial angiomatosis (Sturge-Weber syndrome).

C. PREMALIGNANT LESIONS

LEUKOPLAKIA (WHITE LESIONS)

Leukoplakia *(white plaque)* may be clinically defined as a white patch or plaque on the oral mucosa, exceeding 5 mm in diameter, which cannot be rubbed off nor can be classified into any other diagnosable disease. A number of other lesions are characterised by the formation of white patches. However, from the pathologist's point of view, the term 'leukoplakia' is reserved for epithelial thickening which may range from completely benign to atypical and to premalignant cellular changes.

Incidence. It occurs more frequently in males than females. The lesions may be of variable size and appearance. The sites of predilection, in descending order of frequency, are: cheek mucosa, angles of mouth, alveolar mucosa, tongue, lip, hard and soft palate, and floor of the mouth. In about 4-6% cases of leukoplakia, carcinomatous change is reported. However, it is difficult to decide which white lesions may undergo malignant transformation, but speckled or nodular form is more likely to progress to malignancy. Therefore, it is desirable that all oral white patches be biopsied to exclude malignancy.

Etiology. The etiological factors are similar to those suggested for carcinoma of the oral mucosa. It is most severe in heavy smokers, especially in pipe and cigar smokers, and improves when smoking is discontinued. The condition is also known by other names such as *smokers keratosis* and *stomatitis nicotina*. Other etiological factors implicated are chronic friction such as with ill-fitting dentures or jagged 'teeth, and local irritants like excessive consumption of alcohol and very hot and spicy foods and beverages. A special variety of leukoplakia called *'hairy leukoplakia'* has been described in patients of AIDS and has hairy or corrugated surface but is not related to development of oral cancer.

Pathologic changes. *Grossly*, the lesions of leukoplakia may appear white, whitish-yellow, or red-velvety of more than 5 mm diameter and variable in appearance. They are usually circumscribed, slightly elevated, smooth or wrinkled, speckled or nodular.

Histologicalty, leukoplakia is of 2 types:

1. Hyperkeratotic type. This is characterised by an orderly and regular hyperplasia of squamous epithelium with hyperkeratosis on the surface.

2. Dysplastic type. When the changes such as irregular stratification of the epithelium, focal areas of increased and abnormal mitotic figures, hyperchromatism, pleomorphism, loss of polarity and individual cell keratinisation are present, the lesion is considered as epithelial dysplasia. The subepithelial tissues usually show an inflammatory infiltrate composed of lymphocytes and plasma cells. The extent and degree of the epithelial changes indicate the degree of severity of the epithelial dysplasia. Usually, mild dysplasia may revert back to normal if the offending etiologic factor is removed, whereas severe dysplasia indicates that the case may progress to carcinoma. Erithroplasm is a form of dysplastic leukoplakia in which the epithelial atypia is more marked and thus has higher risk of developing malignancy. If the epithelial dysplasia is extensive so as to involve the entire thickness of the epithelium, the lesion is called carcinoma in situ which may progress to invasive carcinoma.

D. MALIGNANTTUMOURS

SQUAMOUS CELL (EPIDERMOID) CARCINOMA

Oral cancer is a disease with very poor prognosis because it is not recognised and treated when small and early.

Incidence. Squamous cell (epidermoid) carcinoma comprises 90% of all oral malignant tumours and 5% of all human malignancies. The peak incidence in the UK and the USA is from 55 to 75 years of age, whereas in India it is from 40 to 45 years of age. Oral cancer is a very frequent malignancy in India, Sri Lanka and some Eastern countries, probably related to habits of betel-nut chewing and reversed smoking. There is a definite male preponderance. It can occur anywhere in the mouth but certain sites are more commonly involved. These sites, in descending order of frequency, are: the lips (more commonly lower), tongue, anterior floor of mouth, buccal mucosa in the region of alveolar lingual sulcus, and palate.

Etiology. As with other forms of cancer, the etiology of squamous cell carcinoma is unknown. But a number of etiological factors have been implicated. These are:

i) Tobacco smoking and tobacco chewing, most important factor.

ii) Chronic alcohol consumption.

iii) Chronic irritation from ill-fitting denture or jagged teeth.

iv) Submucosal fibrosis as seen in Indians consuming excess of chillies.

v) Poor orodental hygiene.

vi) Nutritional deficiencies.

vii) Human papilloma virus infection, particularly HPV16, 18 and 11 types.

viii) Exposure to sunlight (in relation to lip cancer).

ix) Exposure to radiation.

x) Plummer-Vinson syndrome, characterised by atrophy of the upper alimentary tract.

Pathologic changes. Grossly, squamous cell carcinoma of oral cavity may have the following types:

i) Ulcerative type – is the most frequent type and is characterized by indurated ulcer and firm everted or rolled edges.

ii) Papillary or verrucous type is soft and wartlike growth.

iii) Nodular type appears as a firm, slow growing submucosal nodule.

iv) Seirrhous type is characterised by infiltration into deeper structures.

All these types may appear on a background of leukoplakia or erythroplasia of the oral mucosa. Enlarged cervical lymph nodes may sometimes be present.

Histologicalty squamous cell carcinoma ranges from well-differentiated keratinising carcinoma to highly-undifferentiated neoplasm. Changes of epithelial dysplasia are often present in the surrounding areas of

the lesion. Carcinoma of the lip and intraoral squamous carcinoma are usually always well-differentiated**.**

Carcinoma of the lip has a more favourable prognosis due to visible and easily accessible location and less frequent metastasis to the regional lymph nodes. However, intraoral squamous carcinomas have poor prognosis because they are detected late and metastasis to regional lymph nodes occur early, especially in the case of carcinoma of tongue and soft palate. *Verrucous carcinoma,* on the other hand, is composed of very well-differentiated squamous epithelium with minimal atypia and hence has very good prognosis.

OTHER MALIGNANT TUMOURS

Other less common malignant neoplasms which may be encountered in the oral cavity are: malignant melanoma, lymphoepithelial carcinoma, malignant lymphoma, malignant tumours of minor salivary glands, and various sarcomas like rhabdomyosarcoma, liposarcoma, alveolar soft part sarcoma, Kaposi's sarcoma and fibrosarcoma. Metastatic tumours can also occur in the soft tissues of the mouth.

TEETH AND PERIODONTAL TISSUES

Although care of the teeth belongs to the field of dental profession, the fully educated doctor should be familiar with certain principal diseases of teeth and periodontal tissues, especially about dental caries, periapical abscess and periodontitis, and common cysts and odontogenic tumours of the jaw. But first, a brief account of normal structure of these tissues.

NORMAL STRUCTURE

The teeth are normally composed of 3 calcified tissues, namely: enamel, dentine and cementum; and the pulp composed of connective tissue. The teeth are surrounded by the portion of oral mucosa called the gingiva or gum.

Enamel in the outer covering of teeth composed almost entirely of inorganic material (as in bone) which can be demonstrated in ground sections only as it is lost in decalcified section.

Dentine lies under the enamel and comprises most of the tooth substance. It is composed of organic material in the form of collagen fibrils as well as inorganic material in the form of calcium phosphates as in bone. Dentine is composed of odontoblasts or dentine cells which are counterparts of osteocytes in bone but differ from the latter in having odontoblast processes.

Cementum is the portion of tooth which covers the dentine at the root of tooth and is the site where periodontal ligament is attached. Cementum is similar to bone in morphology and composition.

Dental pulp is inner to dentine and occupies the pulp cavity and root canal. It consists of connective tissue, blood vessels and nerves.

DENTAL CARIES

Dental caries is the most common disease of dental tissues, causing destruction of the calcified tissues of the teeth.

Etiopathogenesis. Dental caries is essentially a disease of modern society, associated with diet containing high proportion of refined carbohydrates. It has been known for almost 100 years that mixture of sugar or bread with saliva in the presence of acidogenic bacteria of the mouth, especially streptococci, produces organic acids which can decalcify enamel and dentine. Enamel is largely composed of inorganic material which virtually disintegrates. Dentine contains organic material also which is left after decalcification. Bacteria present in the oral cavity cause proteolysis of the remaining organic material of dentine so that the process of destruction is complete. Diets rich in carbohydrates do not require much chewing and thus the soft and sticky food gets clung to the teeth rather than being cleared away, particularly in the areas of occlusal pits and fissures. 'Bacterial plaques' are formed in such stagnation areas. If these plaques are not removed by brushing or by vigorous chewing of fibrous foods, the process of tooth decay begins. There is evidence that consumption of water containing one part per million (ppm) fluoride is sufficient to reduce the rate of tooth decay in children.

Pathologic changes. Caries occurs chiefly in the areas of pits and fissures, mainly of the molars and premolars, where food retention occurs, and in the cervical part of the tooth.

Microscopically ,the earliest change is the appearance of a small, chalky-white spot on the enamel which subsequently enlarges and often becomes yellow or brown and breaks down to form carious cavity. Eventually/ the cavity becomes larger due to fractures of enamel. Once the lesion reaches enamel-dentine junction, destruction of dentine also begins.

Microscopically, inflammation (pulpitis) and necrosis of pulp take place. There is evidence of reaction of the tooth to the carious process in the formof *secondary dentine,* which is a layer of odontoblasts laid down under the original dentine.

Sequelae of caries. Carious destruction of dental hard tissues frequently produces pulpitis and other inflammatory lesions like apical granuloma and apical abscess. Other less common causes of these lesions are fracture of tooth and accidental exposure of pulp by the dentist.

1. Pulpitis. Pulpitis may be acute or chronic.

• *Acute pulpitis* is accompanied by severe pain which may be continuous, throbbing or dull, and is accentuated by heat or cold. It is often accompanied by mild fever and leucocytosis.

• *Chronic pulpitis* occurs when pulp is exposed widely. It is often not associated with pain. Chronically inflamed pulp tissue may protrude through the cavity forming polyp of the pulp. It may be partly covered by implanted squamous epithelium.

2. Apical granuloma. Pulpitis may lead to spread of infection through the apical foramen into the tissues surrounding the root of the tooth.

Histologically, there is chrome inflammatory reaction with formation of granulation tissue and inclusion of nests or strands of squamous epithelium derived from remnants of odontogenic epithelium normally present in the periodontal membrane. An apical granuloma may develop into a dental (radicular) cyst as discussed below.

3. Apical abscess. An apical granuloma or acute pulpitis may develop into apical abscess. Acute abscess is very painful, while pus in chronic abscess may escape through root canal and cause further complications like osteomyelitis, cellulitis, cerebral abscess, meningitis and cavernous sinus thrombosis.

PERIODONTAL DISEASE

Chronic inflammation and degeneration of the supporting tissues of teeth resulting in teeth loss is a common condition. Besides inflammation, two other diseases – leukaemia and scurvy, are associated with gingival swelling.

The inflammatory periodontal disease affects adults more commonly. Pregnancy, puberty and use of drugs like dilantin are also associated with periodontal disease more often. The disease begins as *chronic marginal gingivitis,* secondary to bacterial plaques around the teeth such as due to calculus (tartar) on the tooth surface, impacted food, uncontrolled diabetes, tooth-decay and ill-fitting dental appliances. The gingival sulcus acts as convenient site for lodgement of food debris and bacterial plaque leading to formation of periodontal pocket from which purulent discharge can be expressed by digital pressure.

Pathologically, chronic marginal gingivitis is characterised by heavy chronic inflammatory cell infiltrate, destruction of collagen, and epithelial hyperplasia so as to line the pocket. Untreated chronic marginal gingivitis slowly progresses to chronic periodontitis or pyorrhea in which there is inflammatory destruction of deeper tissues. At this stage, progressive resorption of alveolar bone occurs and the tooth ultimately gets detached.

EPITHELIAL CYSTS OF JAW

The epithelium-lined cysts of dental tissue can have inflammatory or developmental origin.

A. INFLAMMATORY CYSTS

Radicular Cyst

Radicular cyst, also called as apical, periodontal or simply dental cyst, is the most common cyst originating from the dental tissues. It arises consequent to inflammation following destruction of dental pulp such as in dental caries, pulpitis, and apical granuloma. The epithelial cells of Mallasez, which normally lie in the periodontal ligament, proliferate within apical granuloma

under the influence of inflammation, leading to the formation of an epithelium-lined cystic cavity. Most often, radicular cyst is observed at the apex of an erupted tooth and sometimes contains thick pultaceous material.

Hisiologically, the radicular cyst is lined by nonkeratinised squamous epithelium. Epithelial rete may penetrate the underlying connective ues. Radicular cyst of maxilla may be lined by respiratory epithelium. The cyst wall is fibrous and contains chronic inflammatory cells (lymphocytes, plasma cells with Russell bodies and macrophages) hyaline bodies and deposits of cholesterol crystals which may be associated with foreign body giant cells.

B. DEVELOPMENTAL CYSTS

1. Odontogenic Cysts

I) *Dentigerous (Follicular) Cyst.* Dentigerous cyst arises from enamel of an unerupted tooth. The mandibular third molars and the maxillary canines are most often involved. Dentigerous cysts are less common than radicular cysts and occur more commonly in children and young individuals. These cysts are more significant because of reported occurrence of ameloblastoma and carcinoma in them.

Histologically, dentigerous cyst is composed of a thin fibrous tissue wall lined by stratified squamous epithelium. Thus, the cyst may resemble radicular cyst, except that chronic inflammatory changes so characteristic of radicular cyst, are usually absent in dentigerous cyst.

II) *Eruption Cyst.* This is a cyst lying over the crown of an unerupted tooth and is lined by stratified squamous epithelium. It is thus a form of dentigerous cyst.

III) *Gingival Cyst.* It arises from the epithelial rests in the gingiva and is lined by keratinising squamous epithelium.

IV) *Primordial Cyst (Odontogenic Kera-Tocyst).* Primordial cyst, like dentigerous cyst, also arises from tooth-forming epithelium. The common location is mandibular third molar.

Histologically, the cyst wall is thin and is lined by regular layer of keratinising stratified squamous epithelium. Inflammatory changes are normally absent. Primordial cysts have a marked tendency to recur (50%). Multiple primordial cysts occur in association with naevoid basal cell carcinoma syndrome.

2. Non-Odontogenic and Fissural Cysts

I) Nasopalatine Duct (Incisive Canal, Median, Anterior Maxillary) Cyst. This is the most common non-odontogenic (fissural) cyst and arises from the epithelial remnants of the nasopalatine duct.

Histologically, the cyst is lined by stratified squamous epithelium, respiratory epithelium, or both.

II) Nasolabial (Nasoalveolar) Cyst. This cyst is situated in the soft tissues at the junction of median nasal, lateral nasal and maxillary processes, at the ala of the nose, and sometimes extending into the nostril.

*Histologicall*y, the cyst is lined by squamous or respiratory epithelium, or both.

III) Globulomaxillary Cyst. This is an intraosseous cyst and is rare.

IV) Dermoid Cyst. The dermoid cyst is common in the region of head or neck, especially in the floor of the mouth. The cyst arises from remains in the midline during closure of mandibular and branchial arches.

ODONTOGENIC TUMOURS

Odontogenic tumours are a group of uncommon lesions of jaw derived from the odontogenic apparatus. These tumours are usually benign but some have malignant counterparts.

A. BENIGN ODONTOGENIC TUMOURS

Ameloblastoma

Ameloblastoma is the most common benign but locally invasive epithelial odontogenic tumour. It is commonest in the 3rd to 5th decades of life. Preferential sites are the mandible in the molar-ramus area and the maxilla. The tumour originates from dental epithelium of the enamel itself or its epithelial residues. Sometimes, the tumour may arise from the epithelial lining of a dentigerous cyst or from basal layer of oral mucosa. Radiologically, typical picture is of a multilocular destruction of bone. Rare instances of an extraosseous example, presence of an embedded tooth, or unilocular ameloblastoma can occur. Tumour with histologic resemblance to ameloblastoma can occur occasionally in the long bone, like adamantinoma of the tibia.

Grossly, the tumour is greyish-white, usually solid, sometimes cystic, replacing and expanding the affected bone.

Histologicalty, ameloblastoma can show different patterns:

i) Follicular pattern is the most common. The tumour consists of follicles of variable size and shape and separated from each other by fibrous tissue. The structure of follicles is similar to that of enamel organ consisting of central area of stellate cells resembling stellate reticulum, and peripheral layer of cuboidal or columnar cells resembling epithelium. The central stellate areas may show cystic changes.

ii) Plexiform pattern is the next common pattern after foiiicular pattern. The tumour epithelium is seen to form irregular plexiform masses or network of strands. The stroma is usually scanty. Microcyst formation can occur in the stroma.

iii) Acanthomatous pattern is squamous metaplasia within the islands of tumour cells.

iv) Basal cell pattern of ameloblastoma is similar to basal cell carcinoma of the skin.

v) *Granular cell pattern* is characterised by appearance of acidophilic granularity in the cytoplasm of rumour cells.

Odontogenic Adenomatoid Tumour (Adeno-ameloblastoma)

This is a benign tumour seen more frequently in females in their 2nd decade of life. The tumour is commonly associated with an unerupted tooth and thus closely resembles dentigerous cyst radiologically. Unlike ameloblastoma, adenomatoid odontogenic tumour is not invasive nor does it recur after enucleation.

Histologically, the lesion has extensive cyst formations. The wall of cyst contains scanty fibrous connective tissue in which are present characteristic tubule-like structures composed of epithelial cells and hence the name 'adenomatoid' (gland-like).

Calcifying Epithelial Odontogenic Tumour

This is a rare lesion which is locally invasive and recurrent like ameloblastoma. It is seen commonly in 4th and 5th decades and occurs more commonly in the region of mandible.

Histologically, the tumour consists of closely packed polyhedral epithelial cells having features of nuclear pleomorphism, giant nuclei and rare mitotic figures. The stroma is often scanty and appears homogeneous and hyalinised in which small calcified deposits are seen which are a striking feature of this tumour.

Odontogenic Myxoma (Myxofibroma)

Odontogenic myxoma is a locally invasive and recurring rumour.

Microscopically, it is characterised by abundant mucoid stroma and loose stellate cells in which are seen a few strands of odontogenic epithelium.

Ameloblastic Fibroma

This is a benign tumour consisting of epithelial and connective tissues derived from odontogenic apparatus. It resembles ameloblastoma but can be distinguished from it because ameloblastic fibroma occurs in younger age group (below 20 years) and the clinical behaviour is always benign.

Histologically, it consists of epithelial follicles similar to those of ameloblastoma, set in a very cellular connective tissue stromc

Odontomas

Odontomas are hamartomas that contain both epithelial and mesodermal dental tissue components. There are 3 subtypes:

i) *Complex odontoma* is always benign and consists of enamel, dentine and cementum which are not differentiated, so that the structure of actual tooth is not identifiable.

ii) *Compound odontoma* is also benign and is comprised of differentiated dental tissue elements forming a number of denticles in fibrous tissue.

iii) *Ameloblastic fibro-odontoma* is a lesion that resembles ameloblastic fibroma with odontoma formation.

Cementomas

Cementomas are a variety of benign lesions which are characterised by the presence of cementum or cementum-like tissue. Five types of cementomas are described:

i) *Benign cementoblastoma* (true cementoma) is a solitary lesion of jaw, characterised by features comparable to those of osteoid osteoma and osteoblastoma.

ii) *Cementifying fibroma* consists of cellular fibrous tissue containing calcified masses of cementum-like tissue.

iii) *Periapical cemental dysplasia* (Periapical fibrous dysplasia) is most common and resembles cementifying fibroma except that it contains more fibrous tissue as well as cementum-like tissue.

iv) *Multiple apical cementomas* are found on the apical region of teeth and detected incidentally in post-menopausal women.

v) *Gigantiform cementoma* is a large lobulated mass of cementum-like tissue. Sometimes, there are multiple such masses in the jaw.

B. MALIGNANT ODONTOGENIC TUMOURS

Malignant odontogenic tumours are rare.

Odontogenic Carcinoma

i) *Malignant ameloblastoma* is the term used for the uncommon metastasising ameloblastoma.

ii) *Ameloblastic carcinoma* is the term employed for the ameloblastic tumour having cytologic features of malignancy in the primary tumour.

iii) *Primary intraosseous carcinoma* may develop within the jaw from the rests of odontogenic epithelium.

iv) Rarely, carcinomas may arise from the odontogenic epithelium lining the *odontogenic cysts.*

Odontogenic Sarcomas

The only example of odontogenic sarcoma is a rare ameloblastic fibrosarcoma. This tumour resembles ameloblastic fibroma but in this the mesodermal component is malignant (sarcomatous) whereas the ameloblastic epithelium remains differentiated and benign.

PATHOLOGY OF SALIVARY GLANDS

There are two main groups of salivary glands – major and minor. The major salivary glands are the three paired glands: parotid, submandibular and sublingual. The minor salivary glands are numerous and widely distributed in the mucosa of oral cavity. The main duct of the parotid gland drains into the oral cavity opposite the second maxillary molar, while the ducts of submandibular and sublingual glands empty in the floor of the

mouth. At times, heterotopic salivary gland tissue may be present in lymph nodes near or within the parotid gland.

Histologically, the salivary glands are tubuloalveolar glands and may contain mucous cells, serous cells, or both. The parotid gland is purely serous. The submandibular gland is mixed type but is predominantly serous, whereas the sublingual gland though also a mixed gland is predominantly mucous. Similarly, minor salivary glands may also be serous, mucous or mixed type.

The secretory acini of the major salivary glands are drained by ducts lined by: low cuboidal epithelium in the intercalated portion, by tall columnar epithelium in the intralobular ducts, and by simpler epithelium in the secretory ducts.

The product of major salivary glands is *saliva* which performs various functions such as lubrication for swallowing and speech, and has enzyme amylase and antibacterial properties too.

SALIVARY FLOW DISTURBANCES

Sialorrhoea (Ptyalism). Increased flow of saliva is termed sialorrhoea or ptyalism. It occurs commonly due to: stomatitis, teething, mentally retarded state, schizophrenia, neurological disturbances, increased gastric secretion and sialosis (i.e. uniform, symmetric, painless hypertrophy of salivary glands).

Xerostomia. Decreased salivary flow is termed xerostomia. It is associated with the following conditions: Sjogren's syndrome, sarcoidosis, mumps parotitis, Mikulicz's syndrome, megaloblastic anaemia, dehydration, drug intake (e.g. antihistamines, antihypertensives, antidepressants).

SIALADENITIS

Inflammation of salivary glands, sialadenitis, may be acute or chronic, the latter being more common.

Etiology. Sialadenitis can occur due to the following causes:

1. Viral infections. The most common inflammatory lesion of the salivary glands particularly of the parotid glands, is mumps occurring in children of school-age. It is characterised by triad of pathological involvement – *epidemic parotitis (mumps), orchitis-oophoritis, and pancreatitis*. Involvement of testis and pancreas may lead to their atrophy. Less commonly, cytomegalovirus infection may occur in parotid glands of infants and young children.

2. Bacterial and mycotic infections. Bacterial infections may cause acute sialadenitis more often. Sometimes there are recurrent attacks of acute parotitis when parotitis becomes chronic.

i) *Acute sialadenitis.* The causes are:

a) Acute infectious fevers,

b) Acute postoperative parotitis (ascent of microorganisms up the parotid duct from the mouth),

c) General debility,

d) Old age,

e) Dehydration.

ii) *Chronic sialadenitis.* This may result from the following causes:

a) Recurrent obstructive type. Recurrent obstruction due to calculi (sialolithiasis), stricture, surgery, injury etc may cause repeated attacks of acute sialadenitis by ascending infection and then chronicity.

b) Recurrent non-obstructive type. Recurrent mild ascending infection of the parotid gland may occur due to non-obstructive causes which reduce salivary secretion like due to intake of drugs causing hyposalivation (e.g. antihistamines, antihypertensives, antidepressants), effect of irradiation and congenital malformations of the duct system.

c) Chronic inflammatory diseases. Tuberculosis, actinomycosis and other mycoses may rarely occur in the salivary glands.

3. Autoimmune disease. Inflammatory changes are seen in salivary glands in 2 autoimmune diseases:

i) *Sjogren's syndrome* characterised by triad of dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia) and rheumatoid arthritis.

ii) *Mikulicz's syndrome* is the combination of inflammatory enlargement of salivary and lacrimal glands with xerostomia.

Pathologic changes. Irrespective of the underlying etiology of sialadenitis, there is swelling of the affected salivary gland, usually restricted by the fibrous capsule. Acute stage is generally associated with local redness, pain and tenderness with purulent ductal discharge. Late chronic cases may be replaced by firm fibrous swelling.

Microscopically, acute viral sialadenitis in mumps shows swelling and cytoplasmic vacuolation of the acinar epithelial cells and degenerative changes in the ductal epithelium. There is interstitial oedema, fibrinoid degeneration of the collagen and dense infiltration by mononuclear cells (lymphocytes, plasma cells and macrophages). *Chronic and recurrent sialadenitis* is characterised by increased lymphoid tissue in the interstitium, progressive loss of secretory tissue and replacement by fibrosis.

TUMOURS OF SALIVARY GLANDS

The major as well as minor salivary glands can give rise to a variety of benign and malignant tumours. The major glands, particularly the parotid glands (85%), are the most common sites. Majority of the parotid gland tumour (65-85%) are benign, while in the other major and minor salivary glands 35-50% of the tumours are malignant. Most of the salivary gland tumours originate from the ductal lining epithelium and the underlying myoepithelial cells; a few arise from acini. Recurrent tumours of the parotid glands, due to their location, are often associated with facial palsy and obvious scarring following surgical treatment.

A. BENIGN SALIVARY GLAND TUMOURS

ADENOMAS

The adenomas of the salivary glands are benign epithelial tumours. They are broadly classified into 2 major groups – pleomorphic and monomorphic adenomas.

Pleomorphic Adenoma (Mixed Salivary Tumour)

This is the most common tumour of major (60-75%) and minor (50%) salivary glands. Pleomorphic adenoma is the commonest tumour in the parotid gland and occurs less often in other major and minor salivary glands. The tumour is commoner in women and is seen more frequently in 3rd to 5th decades of life. The tumour is solitary, smooth-surfaced but sometimes nodular, painless and slow-growing. It is often located below and in front of the ear.

Pathologic changes. *Grossly,* pleomorphic adenoma is a circumscribed, pseudoencapsulated, rounded, at times multilobulated, firm mass, 2-5 cm in diameter, with bosselated surface. The cut surface is grey-white and bluish, variegated, semitranslucent, usually solid but occasionally may show small cystic spaces. The consistency is soft and mucoid.

Microscopically, the pleomorphic adenoma is characterised by pleomorphic or 'mixed' appearance in which there are epithelial elements present in a martix of mucoid, myxoid and chondroid tissue:

- The epithelial component may form various patterns like ducts, acini, tubules, sheets and strands of cells of ductal or myoepithelial origin. The ductal cells are cuboidal or columnar, and the underlying myoepithelial cells may be polygonal or spindle-shaped resembling smooth muscle cells. The material found in the lumina of duct-like structures is PAS-positive epithelial mucin. Focal areas of squamous metaplasia and keratinisation may be present. Immunohistochemically, the tumour cells are immunoreactive for epithelial (cytokeratin, EMA, CEA) as well as myoepithelial (actin, vimentin) antibodies.
- The mesencnymal elements are present as loose connective tissue and as myxoid, mucoid and chondroid matrix, which simulates cartilage *(pseudocartilage)* but is actually connective tissue mucin. More recently, the matrix of the tumour has been characterised as a product of myoepithelial cells. However, true cartilage and even bone is observed in a small proportion of these tumours.

The epithelial and mesenchymal elements are intermixed and either of the two components may be dominant in any tumour.

Prognosis. Pleomorphic adenoma is notorious for recurrences, sometimes after many years. The main factors responsible for the tendency to recur are incomplete surgical removal due to proximity to the facial nerve, multiple foci of tumour, pseudoencapsulation, and implantation in the surgical field. Although the tumour is entirely benign, under exceptionally rare circumstances, an ordi-

nary pleomorphic adenoma may metastasise to distant sites which too will have benign appearance as the original tumour. However, actual malignant transformation can also occur in a pleomorphic adenoma *(vide infra).*

Monomorphic Adenomas

These are benign epithelial tumours of salivary glands without any evidence of mesenchyme-like tissues. Their various forms are as under:

a) Warthin's Tumour (Papillary Cysta-Denoma Lymphomatosum, Adenolym-Phoma). It is a benign tumour of the parotid gland comprising about 8% of all parotid neoplasms, seen more commonly in men from 4th to 7th decades of life. Rarely, it may arise in the submandibular gland or in minor salivary glands. *Histogenesis* of the tumour has been much debated. Most accepted theory is that the tumour develops from parotid ductal epithelium present in lymph nodes adjacent to or within parotid gland.

Pathologic changes. *Grossly,* the tumour is encapsulated, round or oval with smooth surface. The cut surface shows characteristic slit-like or cystic spaces, containing milky fluid and having papillary projections.

Microscopically, the tumour shows 2 components: epithelial parenchyma and lymphoid stroma.

- The epithelial parenchyma is composed of glandular and cystic structures having papillary arrangement and lined by characteristic eosinophilic epithelium. Variants of epithelial patterns include presence of mucous goblet cells and sebaceous differentiation.
- The lymphoid stroma is present under the epithelium in the form of prominent lymphoid tissue, often with germinal centres.

b) Oxyphil Adenoma (Oncocytoma). It is a benign slow-growing tumour of the major salivary glands. The tumour consists of parallel sheets, acini or tubules of large cells with glandular eosinophilic cytoplasm (oncocytes) and hence the name.

c) Other Types Of Monomorphic Adenomas. There are some uncommon forms of monomorphic adenomas:

i) Myoepittielioma is an adenoma composed exclusively of myoepithelial cells which may be arranged in tubular, alveolar or trabecular pattern.

ii) Basal cell adenoma is characterised by the type and arrangement of cells resembling basal cell carcinoma of the skin.

iii) Clear cell adenoma has spindle-shaped or polyhedral cells with clear cytoplasm.

Miscellaneous Benign Tumours

A number of mesenchymal tumours can rarely occur in salivary glands. These include: fibroma, lipoma, neurilemmomas, neurofibroma, haemangioma and lymphangioma.

B. MALIGNANT SALIVARY GLAND TUMOURS

Mucoepidermoid Carcinoma. It`s status as an intermediate grade tumour in the previous classification has undergone upgradation to full-fledged mucoepidermoid carcinoma now having the following peculiar features:

• It is the most *common malignant* salivary gland tumour (both in the major and minor glands).

• The *parotid gland* amongst the major salivary glands and the minor salivary glands in the *palate* are the most common sites.

• The common age group affected is 30-60 years but it is also the most common malignant salivary gland tumour affecting *children and adolescents.*

• It is the most common example of *radiation-induced* malignant rumour, especially therapeutic radiation.

Pathologic changes. *Grossly,* the tumour is usually circumscribed but not encapsulated. It varies in size from 1 to 4 cm.

Microscopically, the tumour is classified into low, intermediate and high grade depending upon the degree of differentiation and tumour invasiveness. The tumour is composed of combination of epidermoid cells and mucus-secreting cells (as the name implies) as also cells with intermediate differentiation between these two cell types and clear cells.

Malignant Mixed Tumour comprises three distinct clinicopathologic entities:

- Carcinoma arising in benign mixed salivary gland tumour (carcinoma *ex* pleomorphic adenoma);
- Carcinosarcoma; and
- Metastasising mixed salivary tumour.

Carcinoma *ex* pleomorphic adenoma is more common while the other two are rare tumours. Approximately 2 to 5% of pleomorphic adenomas reveal areas of frank malignancy. The slow-growing adenoma may have been present for a number of years when suddenly it undergoes rapid increase in its size, becomes painful and the individual may develop facial palsy. Malignant transformation occurs in later age (6th decade) than the usual age for pleomorphic adenoma (4th to 6th decades). It may occur in primary tumour but more often occurs in its recurrences.

Pathologic changes. *Grossly,* the tumour is poorly-circumscribed with irregular infiltrating margin. Cut section may show haemorrhages, necrosis and cystic degeneration.

Microscopically, besides the typical appearance of pleomorphic adenoma, malignant areas show cytologic features of carcinoma such as anaplasia, nuclear hyperchromatism, large nucleolisation, mitoses and evidence of invasive growth.

Adenoid Cystic Carcinoma (Cylindroma) is a highly malignant tumour due to its typical infiltrative nature, especially along the nerve sheaths. Adenoid cystic carcinoma is histologically characterised by cribriform appearance i.e. the epithelial tumour cells of duct-lining and myoepithelial cells are arranged in duct-like structures or masses of cells, having typical fenestrations or cyst-like spaces and hence the name 'adenoid cystic'.

Acinic Cell Carcinoma is a rare tumour composed of acinic cells resembling serous cells of normal salivary gland. These cells are arranged in sheets or acini and have characteristic basophilic granular cytoplasm. The degree of arypia may vary from a benign cytologic appearance to cellular features of malignancy.

Adenocarcinoma of the salivary gland does not differ from adenocarcinoma elsewhere in the body. It may have some variants such as mucoid adenocarcinoma, clear-cell adenocarcinoma and papillary cystadenocarcinoma.

Epidermoid Carcinoma is rare tumour, has features of squamous cell carcinoma with keratin formation and has intercellular bridges. The tumour commonly infiltrates the skin and involves the facial nerve early.

Undifferentiated Carcinoma is highly malignant tumour, consists of anaplastic epithelial cells which are too poorly differentiated to be placed in any other known category.

Miscellaneous Malignant Tumours

Some rare malignant tumour of epithelial and mesenchymal origin are melanoma, sebaceous carcinoma, undifferentiated carcinoma, lymphoma, fibrosarcoma and leiomyosarcoma and are similar in morphology to such tumours elsewhere in the body. Besides, metastatic involvement of major salivary glands or the adjacent lymph nodes is common, especially from epidermoid carcinoma and malignant melanoma.

DISEASES OF ISTHMUS AND PHARYNX

TONSILLITIS

It is the more frequent infectious disease of tonsils. It may be acute and chronic.

Etiology. Tonsillitis develops due to action of pathogens on organism (e.g. streptococci, staphylococci and viruses). It can occur due to trauma and cold.

Forms of Acute tonsillitis:

1. *Catarrha*l – there is congestion and edema of tonsillary mucous membrane.

*2. Lacuna*r – there is accumulation of exudates in depth of tonsillary lacunas, then exudate appears on tonsillary surface as yellow spots. Tonsils ar*e infiltrated by leucocytes*.

3. *Follicular* – is charavterized by the damage of lymphoid follicles. Tonsils are enlarged and follicles contain purulent infiltrate and pus degradation.

4. *Fibrinous* – is charavterized by formation of fibrinous layers on tonsillar surface. This process is known as diphtheritic tonsillitis. Fibrinous exudate is tightly attached with tonsillar mucous membrane. Ulcer formation takes place if this fibrinous exudate is removed.

5. *Purulent* – is charavterized by formation of abscesses.

6. *Necrotic* – there is necrosis of tonsillary mucous membrane. It is usually secondary (in leucosis, scarlet fever).

In chronic tonsillitis there is sclerosis of tonsils, extension of lacunas and sometimes enlargement of tonsils.

DISEASES OF ESOPHAGUS

The oesophagus is a muscular tube extending from the pharynx to the stomach. In an adult, this distance measures 25 cm. However, from the clinical point of view, the distance from the incisor teeth to the gastro-oesophageal junction is about 40 cm. The region of proximal oesophagus at the level of cricopharyngeus muscle is called the *upper oesophageal sphincter,* while the portion adjacent to the anatomic gastro-oesophageal junction is referred to as *lower oesophageal sphincter.*

Histologically, the wall of the oesophagus consists of mucosa, submucosa, muscularis propria and adventitia/serosa.

The **mucosa** is composed of non-keratinising stratified squamous epithelium overlying lamina propria. The basal layer of the epithelium may contain some melanocytes, argyrophil cells and Langerhans' cells. At the lower end of the oesophagus, there is sudden change from stratified squamous epithelium to mucin-secreting columnar epithelium for a distance of 0.5 to 1.5 cm; this is called the *junctional mucosa.*

The **submucosa** consists of loose connective tissue with sprinkling of lymphocytes, plasma cells, and occasional eosinophil and mast cell. Mucus-producing glands are scattered throughout the submucosa.

The **muscularis propria** is composed of 2 layers of smooth muscle – an inner circular coat and an outer longitudinal coat. The proximal portion of oesophagus contains skeletal muscle fibres from cricopharyngeus muscle. The parasympathetic nerve supply by the vagus nerve is in the form of extrinsic and intrinsic plexuses.

The **adventitia/serosa** is the outer covering of oesophagus. Serosa is present in intra-abdominal part of oesophagus only, while elsewhere the perioesophageal adventitia covers it.

The **major functions** of oesophagus are swallowing by peristaltic activity and to prevent the reflux of gastric contents into the oesophagus.

CONGENITAL ANOMALIES

Congenital anomalies of the oesophagus are uncommon and are detected soon after birth. Some of these are as under:

Oesophageal atresia and tracheo- oesophageal fistula. In about 85% of cases, congenital atresia of the oesophagus is associated with tracheo-oesophageal fistula, usually at the level of tracheal bifurcation. For survival, the condition must be recognised and corrected surgically within 48 hours of birth of the newborn. Clinically, the condition is characterised by regurgitation of

every feed, hypersalivation, attacks of cough and cyanosis. Death usually results from asphyxia, aspiration pneumonia and fluid-electrolyte imbalance. Morphologically, the condition is recognised by cord-like non-canalised segment of oesophagus having blind pouch at both ends.

Certain uncommon congenital anomalies of oesophagus are as follows:

• **Agenesis.** Congenital absence of oesophagus is quite rare and is incompatible with life.

• **Duplication of oesophagus.** This is another rare congenital abnormality in which there is double oesophagus.

• **Stenosis.** Oesophageal stenosis may occur as developmental anomaly or may follow oesophagitis. There is fibrous thickening of the oesophageal wall and atrophy of the mucularis propria.

MUSCULAR DYSFUNCTIONS

These are disorders in which there is motor dysfunction of the oesophagus, manifested clinically by dysphagia.

These include achalasia, hiatus hernia, oesophageal diverticula, and webs and rings.

Achalasia (Cardiospasm)

Achalasia of the oesophagus is a neuromuscular dysfunction due to which the cardiac sphincter fails to relax during swallowing and results in progressive dysphagia and dilatation of the oesophagus *(mega-oesophagus).*

Etiology. The exact etiology is not known. It may be congenital. Emotional stress has been believed to contribute to the onset of the disease. Some investigators have demonstrated total absence of nerve fibres and ganglia of Auerbach's plexus in the terminal few centimetres of the oesophagus in achalasia. Chagas' disease, an epidemic parasitosis with *Trypansoma cruzi* has also been found to be associated with alterations of Auerbach's plexus.

Pathologic changes. There is dilatation above the short contracted terminal segment of the oesophagus. Muscularis propria of the wall may be of normal thickness, hypertrophied as a result of obstruction, or thinned out due to dilatation. Secondary oesophagitis may supervene and cause oesophageal ulceration and haematemesis.

Hiatus Hernia

Hiatus hernia is the herniation or protrusion of the stomach through the oesophageal hiatus of the diaphragm. Oesophageal hiatal hernia is the cause of diaphragmatic hernia in 98% of cases. The condition is diagnosed radiologically in about 5% of apparently normal asymptomatic individuals. In symptomatic cases, especially the elderly women, the clinical features are heartburn (retrosternal burning sensation) and regurgitation of gastric juice

into the mouth, both of which are worsened due to heavy work, lifting weights and excessive bending.

Etiology. The basic defect is the failure of the muscle fibres of the diaphragm that form the margin of the oesophageal hiatus. This occurs due to shortening of the oesophagus which may be congenital or acquired,

i) **Congenitally short oesophagus** may be the cause of hiatus hernia in a small proportion of cases,

ii) More commonly, it is **acquired** due to secondary factors which cause fibrous scarring of the oesophagus.

These factors are:

a) Degeneration of muscle due to aging.

b) Increased intra-abdominal pressure such as in pregnancy, abdominal tumours etc.

c) Recurrent oesophageal regurgitation and spasm causing inflammation and fibrosis.

d) Increase in fatty tissue in obese people causing decreased muscular elasticity of diaphragm.

Pathologic changes. There are 3 patterns in hiatus hernia:

i) Sliding or oesophago-gastric hernia is the most common, occurring in 85% of cases. The herniated part of the stomach appears as supradiaphragmatic bell due to sliding up on both sides of the oesophagus.

ii) Rolling or para-oesophageal hernia is **seen** in 10% of cases. This is a true hernia in which cardiac end of the stomach rolls up para-oesophageally, producing an intrathoracic sac.

iii) Mixed or transitional hernia constitutes the remaining 5% cases in which there is combination of sliding and rolling hiatus hernia.

Oesophageal Diverticula

Diverticula are the outpouchings of oesophageal wall at the point of weakness. They may be congenital or acquired.

Congenital diverticula occur either at the upper end of the oesophagus or at the bifurcation of trachea.

Acquired diverticula may be of 2 types:

a) Pulsion (Zenker's) type– is seen in the region of hypopharynx and occurs due to oesophageal obstruction such as due to chronic oesophagitis, carcinoma etc. The mucosa and submucosa herniate through the weakened area or through defect in the muscularis propria.

b) Traction type – occurs in the lower third of oesophagus from contraction of fibrous tissue such as from pleural adhesions, scar tissue of healed tuberculous lesions in the hilum, silicosis etc.

Complications of diverticula include obstruction, infection, perforation, haemorrhage and carcinoma.

Oesophageal Webs and Rings

Radiological shadows in the oesophagus resembling 'webs' and 'rings' are observed in some patients complaining of dysphagia.

Webs. Those located in the upper oesophagus, seen more commonly in adult women, and associated with dysphagia, iron deficiency anaemia and chronic atrophic glossitis (Plummer-Vinson syndrome) are called 'webs'.

Rings. Those located in the lower oesophagus, not associated with iron-deficiency anaemia, nor occurring in women alone, are referred to as 'Schatzki's rings'.

Pathologic changes. The rings and webs are transverse folds of mucosa and submucosa encircling the entire circumference, or are localised annular thickenings of the muscle. These give characteristic radiological shadows.

HAEMATEMESIS OF OESOPHAGEAL ORIGIN

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

1. Oesophageal Varices. Oesophageal varices are tortuous, dilated and engorged oesophageal veins, seen along the longitudinal axis of oesophagus. They occur as a result of elevated pressure in the portal venous system, most commonly in cirrhosis of the liver. Less common causes are: portal vein thrombosis, hepatic vein thrombosis (Budd-Chiari syndrome) and pylephlebitis. The lesions occur as a result of bypassing of portal venous blood from the liver to the oesophageal venous plexus. The increased venous pressure in the superficial veins of the oesophagus may result in ulceration and massive bleeding.

2. Mallory-Weiss Syndrome. In this condition, oesophageal lacerations and bleeding may occur following minor trauma such as reflex relaxation of the muscularis resulting in overstretching and subsequent tearing at the oesophago-gastric junction. The condition is common in chronic alcoholics who develop vomitings and haematemesis.

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

4. Other Causes. Oesophageal haematemesis may also occur in the following conditions:

i) Bursting of aortic aneurysm into the lumen of oesophagus,
ii) Vascular erosion by malignant growth in the vicinity,
iii) Hiatus hernia,
iv) Oesophageal cancer,
v) Purpuras,
vi) Haemophilia.

INFLAMMATORY LESIONS

Inflammation of the oesophagus, oesophagitis, occurs most commonly from reflux, although a number of other clinical conditions and infections may also cause oesophagitis as under:

REFLUX (PEPTIC) OESOPHAGITIS

Reflux of the gastric juice is the commonest cause of oesophagitis.

Pathogenesis. Gastro-oesophageal reflux, to an extent, may occur in normal healthy individuals after meals and in early pregnancy. However, in some clinical conditions, the gastro-oesophageal reflux is excessive, resulting in inflammation of the lower oesophagus. These conditions are:

i) Sliding hiatus hernia,
ii) Chronic gastric and duodenal ulcers,
iii) Nasogastric intubation,
iv) Persistent vomiting,
v) Surgical vagotomy,
vi) Neuropathy in alcoholics, diabetics,
vii) Oesophago-gastrostomy.

Pathologic changes. *Endoscopically,* the demarcation between normal squamous and columnar epithelium at the junctional mucosa is lost. The affected distal oesophageal mucosa is red, erythematous, friable and bleeds on touch. In advanced cases, there are features of chronic disease such as nodularity, strictures, ulcerations and erosions. *Microscopically,* the reflux changes in the distal oesophagus include basal cell hyperplasia and deep elongation of the papillae touching close to the surface epithelium. Inflammatory changes vary according to the stage of the disease. *In early stage,* mucosa and submucosa are infiltrated by some polymorphs and eosinophils; *in chronic stage,* there is lymphocytic infiltration and fibrosis of all the layers of the oesophageal wall.

BARRETT'S OESOPHAGUS

This is a condition in which, following reflux oesophagitis, the stratified squamous epithelium of the lower oesophagus is replaced by columnar epithelium. The condition is seen more commonly in later age and is caused by factors producing gastro-oesophageal reflux disease. Barrett's oesophagus is a premalignant condition in which changes of dysplasia and carcinoma have been reported.

Pathologic changes. *Endoscopically,* the affected area is red and velvety. Hiatus hernia and peptic ulcer at squamo-columnar junction (Barrett's ulcer) are frequently associated. *Microscopically,* the most common finding is the replacement of squamous epithelium by metaplastic columnar cells. Barrett's oesophagus may be composed of:

• Intestinal epithelium;
• Fundic gastric glands;
• Cardiac mucous glands.

Other cells present in the glands may be Paneth cells, goblet cells, chief cells, parietal cells, mucus-secreting cells and endocrine cells.

Inflammatory changes, acute or chronic, are commonly accompanied. Dysplastic changes of the columnar epithelium or glands may be present. Longstanding cases of Barrett's oesophagus have 5-8% risk of developing adenocarcinoma of the oesophagus.

INFECTIVE OESOPHAGITIS

A number of opportunistic infections in immuno- suppressed individuals can cause oesophagitis. Some of these agents are:

i) Candida (Monilial) oesophagitis,
ii) Herpes simplex (Herpetic oesophagitis),
iii)) Cytomegalovirus,
iv) Tuberculosis.

Other Causes of Oesophagitis

i) Intake of certain drugs (anticholinergic drugs, doxycycline, tetracycline),
ii) Ingestion of hot, irritating fluids,
iii)) Radiation,
iv) Crohn's disease,
v) Various vesiculobullous skin diseases.

TUMOURS OF OESOPHAGUS

BENIGN TUMOURS

Benign tumours of the oesophagus are uncommon and small in size (less than 3 cms). The epithelial benign tumours project as intraluminal masses arising from squamous epithelium (squamous cell papilloma), or from columnar epithelium (adenoma). The stromal or mesenchymal benign tumours are intramural masses such as leiomyoma and others like lipoma, fibroma, neurofibroma, rhabdomyoma, lymphangioma and haemangioma.

MALIGNANTTUMOURS

For all practical purposes, malignant tumours of the oesophagus are carcinomas because sarcomas such as leiomyo sarcoma and fibro sarcoma occur with extreme rarity.

Carcinoma of Oesophagus

Carcinoma of the oesophagus is diagnosed late, after symptomatic oesophageal obstruction (dysphagia) has developed and the tumour has trans-

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

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

1. Diet and personal habits:
   i) Heavy smoking,
   ii) Alcohol consumption,
   iii) Intake of foods contaminated with fungus,
   iv) Nutritional deficiency of vitamins and trace elements.
2. Oesophageal disorders:

i) Oesophagitis (especially Barrett's oesophagus in adenocarcinoma),
   ii) Achalasia,
   iii) Hiatus hernia,
   iv) Diverticula,
   v) Plummer-Vinson syndrome.

3. Other factors:

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

ii) *Family history* – association with tylosis (keratosis palmaris et plantaris).

iii) *Genetic factors* – predisposition with coeliac disease, epidermolysis bullosa, tylosis.

Pathologic changes. Carcinoma of the oesophagus is mainly of 2 types – squamous cell (epider-moid) and adenocarcinoma. The sites of predilection for each of these 2 forms.

Squamous Cell (Epidermoid) Carcinoma. Squamous cell or epidermoid carcinoma comprises 90% of primary oesophageal cancers. It is exceeded in incidence by carcinoma colon, rectum and stomach amongst all the gastrointestinal cancers. The disease occurs in 6th to 7th decades of life and is more common in men than women. The sites of predilection are the three areas of oesophageal constrictions. Half of the squamous cell carcinomas of oesophagus occur in the middle third, followed by lower third, and the upper third of oesophagus in that order of frequency. *Macroscopically*, 3 types are recognised:

i) *Polypoid fungating type* – is the most common form. It appears as a cauliflower-like friable mass protruding into the lumen.

ii) *Ulcerating type* – is the next common form. It looks grossly like a necrotic ulcer with everted edges.

iii) *Diffuse infiltrating type* – appears as an annular, stenosing narrowing of the lumen due to infiltration into the wall of oesophagus.

Microscopically, majority of the squamous cell carcinomas of the oesophagus are well-differentiated or moderately-differentiated. Prickle cells, keratin formation and epithelial pearls are commonly seen. However, non-keratinising and anaplastic growth patterns can also occur. An exophytic, slow-growing, extremely well-differentiated variant, *verrucous squamous cell carcinoma,* has also been reported in the oesophagus.

Adenocarcinoma. Adenocarcinoma of the oesophagus constitutes less than 10% of primary oesophageal cancer. It occurs predominantly in men in their 4th to 5th decades. The common locations are lower and middle third of the oesophagus. These tumours have a strong and definite association with Barrett's oesophagus in which there are foci of gastric or intestinal type of epithelium. *Macroscopically,* oesophageal adenocarcinoma appears as nodular, elevated mass in the lower oesophagus.

Microscopically, adenocarcinoma of the oesophagus can have 3 patterns:

i) *Intestinal type* – is the adenocarcinoma with a pattern similar to that seen in adenocarcinoma of intestine or stomach.

ii) *Adenosquamous type* – is the pattern in which there is an irregular admixture of adenocarcinoma and squamous cell carcinoma.

iii) *Adenoid cystic type* – is an uncommon variety and is akin to similar growth in salivary gland i.e. a cribriform appearance in an epithelial tumour.

The adenocarcinoma of the oesophagus must be distinguished from the adenocarcinoma of the gastric cardia. This is done by identifying normal oesophageal mucosa on distal as well as proximal margin of the tumour.

Other Carcinomas. Besides the two main histological types of oesophageal cancer, a few other varieties are occasionally encountered. These are as follow:

i) *Mucoepidermoid carcinoma* is a tumour having characteristics of squamous cell as well as mucus-secreting carcinomas.

ii) *Malignant melanoma* is derived from melanoblasts in the epithelium of the oesophagus,

iii) *Oat cell carcinoma* arises from argyrophil cells in the basal layer of the epithelium,

iv) *Undifferentiated carcinoma* is an anaplastic carcinoma which cannot be classified into any recognisable type of carcinoma.

v) *Carcinosarcoma* consists of malignant epithelial as well as sarcomatous components,

vi) *Secondary tumours* rarely occur in the oesophagus from carcinomas of the breast, kidney and adrenals.

Spread. The oesophageal cancer spreads locally as well as to distant sites.

i) Local spread. This is the most important mode of spread and is of great importance for surgical treatment. The local spread may occur in the transverse as well as longitudinal direction. The tumour may invade below into the stomach, above into the hypopharynx, into the trachea resulting in tracheo-oesophageal fistula, and may involve larynx causing hoarseness. The humour may invade the muscular wall of the oesophagus and involve the mediastinum, lungs, bronchi, pleura and aorta.

ii) Lymphatic spread. Submucosal lymphatic permeation may lead to multiple satellite nodules away from the main tumour. Besides, the lymphatic spread may result in metastases to the cervical, paraoesophageal, tracheo-bronchial and subdiaphragmatic lymph nodes.

iii) Haematogenous spread. Blood-borne metastases from the oesophageal cancer are rare, probably because the death occurs early due to invasion of important structures by other modes of spread. However, metastatic deposits by haematogenous route can occur in the lungs, liver and adrenals.

PATHOLOGY OF STOMACH

The stomach is 'gland with cavity', extending from its junction with lower end of the oesophagus (cardia) to its junction with the duodenum (pylorus). The *lesser curvature* is inner concavity on the right, while the *greater curvature* is the outer convexity on the left side of the stomach.

The stomach has 5 anatomical regions:

1. Cardia is the oesophago-gastric junction and lacks the sphincter.

2. Fundus is the portion above the horizontal line drawn across the oesophago-gastric junction.

3. Body is the middle portion of the stomach between the fundus and the pyloric antrum.

4. Pyloric antrum is the distal third of the stomach.

5. Pylorus is the junction of distal end of the stomach with the duodenum. It has powerful sphincter muscle.

The mucosal folds in the region of the body and the fundus are loose (rugae), while the antral mucosa is somewhat flattened. *Gastric canal* is the relatively fixed portion of the pyloric antrum and the adjoining lesser curvature; it is the site for numerous pathological changes such as gastritis, peptic ulcer and gastric carcinoma.

The stomach receives its blood supply from the left gastric artery and the branches of the hepatic and splenic arteries with widespread anastomoses. Numerous gastric lymphatics which communicate freely with each other are also present. The innervation of the stomach is by the vagi and branches of the sympathetic which are connected with ganglia in the muscular and submucous layers.

Histologically, the wall of the stomach consists of 4 layers – serosa, muscularis, submucosa and mucosa.

1. Serosa is derived from the peritoneum which is deficient in the region of lesser and greater curvatures.

2. Muscularis consists of 3 layers of smooth muscle fibres – the outer longitudinal, the middle circular and the inner oblique. Nerve plexuses and ganglion cells are present

between the longitudinal and circular layers of muscle. The pyloric sphincter is the thickened circular muscle layer at the gastroduodenal junction.

3. Submucosa is a layer of loose fibroconnective tissue binding the mucosa to the muscularis loosely and contains branches of blood vessels, lymphatics and nerve plexuses and ganglion cells.

4. Mucosa consists of 2 layers – superficial and deep. Between the two layers is the lamina propria composed of network of fibrocollagenic tissue with a few lymphocytes, plasma cells, macrophages and eosinophils. The mucosa is externally bounded by muscularis mucosae.

i) THE *SUPERFICIAL LAYER* consists of a single layer of surface epithelium composed of regular, mucin-secreting, tall columnar cells with basal nuclei. There is a very rapid turnover of these cells. These dip down at places to form crypts (or pits or foveolae).

• *Cardiac mucosa* is the transition zone between the oesophageal squamous mucosa and the oxyntic mucosa of the fundus and body with which it gradually merges.

• *Oxyntic mucosa* lines both gastric fundus and body.

• *Antral mucosa* lines the pyloric antrum.

ii) THE DEEP *LAYER* consists of glands that open into the bottom of the crypts. Depending upon the structure, these glands are of 3 types:

a) *Glands of the cardia* are simple tubular or compound tubulo-racemose, lined by mucin secreting cells. A few endocrine cells and occasional parietal and chief cells are also present.

b) *Glands of the body-fundus* are long, tubular and tightly packed which may be coiled or dilated. There are 4 types of cells present in the glands of body-fundic mucosa:

- *Parietal (Oxyntic) cells* – are the most numerous and line the superficial (upper) part of the glands. Parietal cells are triangular in shape, have dark-staining nuclei and epsinophilic cytoplasm. These cells are responsible for production of hydrochloric acid of the gastric juice and the blood group substances.
- *Chief (Peptic) cells* – are the dominant cells in the deeper (lower) parts of the glands. Their basal nuclei are large with prominent nucleoli and the cytoplasm is coarsely granular and basophilic. These cells secrete pepsin of the gastric juice.
- *Mucin-secreting neck cells* – are small and fewer. These cells are present in the region of the narrow neck of the gastric glands i.e. at the junction of the glands with the pits.
- *Endocrine (Kulchitsky or Enterochromaffin) cells* – are widely distributed in the mucosa of all parts of the alimentary tract and are described later.

c) *Glands of the pylorus* are much longer than the body- fundic glands. These are simple tubular glands which are often coiled. They are lined mainly by small, granular, mucin-secreting cells resembling neck cells and.occasional parietal cells but no chief cells. Gastrin- producing G-cells are present predominantly in the region of antropyloric mucosa, with a small number of these cells in the crypts and Brunner's glands of the proximal duodenum.

The secretory products of the gastric mucosa are the *gastric juice* and the *intrinsic factor,* required for absorption of vitamin B_{12}. Gastric juice consists of hydrochloric acid, pepsin, mucin and electrolytes like Na^+, K^+, HCO'_3 and Cl^-. Hydrochloric acid is produced by the parietal (oxyntic) cells by the interaction of Q' ions of the arterial blood with water and carbon dioxide in the presence of the enzyme, carbonic anhydrase. The degree of gastric activity is correlated with the 'total parietal cell mass'. Injection of histamine can stimulate the production of acid component of the gastric juice, while the pepsin-secreting chief cells do not respond to histamine. Physiologically, the gastric secretions are stimulated by the food itself.

CONGENITAL ANOMALIES

Pyloric Stenosis

Hypertrophy and narrowing of the pyloric lumen occurs predominantly in male children as a congenital defect *(infantile pyloric stenosis).* The *adult form* is rarely seen, either as a result of late manifestation of mild congenital anomaly or may be acquired type due to inflammatory fibrosis or invasion by tumours.

Etiology. The exact cause of *congenital (infantile)* pyloric stenosis is not known but it appears to have familial clustering and recessive genetic origin. The *acquired (adult)* pyloric stenosis is related to antral gastritis, and tumours in the region (gastric carcinoma, lymphoma, pancreatic carcinoma).

Pathologic changes. *Grossly and microscopically,* there is hypertrophy as well as hyperplasia of the circular layer of muscularis in the pyloric sphincter accompanied by mild degree of fibrosis.

Clinical features. The patient, usually a first born male infant 3 to 6 weeks old, presents with the following clinical features:

1. Vomiting, which may be projectile and occasionally contains bile or blood.
2. Visible peristalsis, usually noticed from left to right side of the upper abdomen.
3. Palpable lump, better felt after an episode of vomiting.
4. Constipation.
5. Loss of weight.

Other Congenital Anomalies

Some other rare congenital anomalies of the stomach are:

- Congenital diverticula
- Juxta-gastric cysts
- Misplacement of the stomach
- Heterotopic tissue.

MISCELLANEOUS ACQUIRED CONDITIONS

Bezoars. Bezoars are foreign bodies in the stomach, usually in patients with mental illness who chew these substances. Some of the common bezoars are:

- *Trichobezoars* composed of a ball of hair.
- *Phytobezoars* composed of vegetable fibres, seeds or fruit skin.
- *Trichophytobezoars* combining both hair and vegetable matter.

Acute Dilatation. Sudden and enormous dilatation of the stomach by gas or fluids due to paralysis of the gastric musculature may occur after abdominal operations, generalised peritonitis, and, in pyloric stenosis.

Gastric Rupture. The stomach may rupture rarely and prove fatal e.g. due to blunt trauma, external cardiac massage, ingestion of heavy meal or large quantity of liquid intake like beer.

INFLAMMATORY CONDITIONS

The two important inflammatory conditions of the stomach are *gastritis* and *peptic ulcer*. Rarely, stomach may be involved in tuberculosis, sarcoidosis and Crohn's disease.

GASTRITIS

The term 'gastritis' is commonly employed for any clinical condition with upper abdominal discomfort like indigestion or dyspepsia in which the specific clinical signs and radiological abnormalities are absent. The condition is of great importance due to its relationship with peptic ulcer and gastric cancer. Broadly speaking, gastritis may be of 2 types – acute and chronic. The chronic gastritis can further be of various types.

Acute Gastritis

Acute gastritis is a transient acute inflammatory involvement of the stomach, mainly mucosa.

Etiopathogenesis. A variety of etiologic agents have been implicated in the causation of acute gastritis. These are as follows:

1. Diet and personal habits:

- Highly spiced food
- Excessive alcohol consumption
- Malnutrition
- Heavy smoking

2. Infections:

- *Bacterial infections* e.g. Helicobacter pylori, diphtheria, salmonellosis, pneumonia, staphylococcal food poisoning.
- *Viral infections* e.g. viral hepatitis, influenza, infectious mononucleosis.

3. Drugs:

- Intake of drugs like aspirin, cortisone, phenylbuta-zone, indomethacin, preparations of iron, chemo-therapeutic agents.

4. Chemical and physical agents:

- Intake of corrosive chemicals such as caustic soda, phenol, lysol
- Gastric irradiation
- Freezing

5. Severe stress:

- Emotional factors like shock, anger, resentment etc.
- Extensive burns
- Trauma

• Surgery

The mucosal injury and subsequent acute inflammation in acute gastritis occurs by one of the following mechanisms:

1. *Reduced blood flow,* resulting in mucosal hypoperfusion due to ischaemia.

2. *Increased acid secretion* and its accumulation due to *H. pylori* infection resulting in damage to epithelial barrier.

3. *Decreased production of bicarbonate buffer.*

Pathologic changes. *Grossly,* the gastric mucosa is oedematous with abundant mucus and haemorrhagic spots. *Microscopically,* depending upon the stage (form), there is variable amount of oedema and infiltration by neutrophils in the lamina propria.

There are some forms of acute gastritis:

1. *Catarrhal* (edema and hyperemia of gastric mucosa, formation of mucous exudate, small hemorrhages and erosions (defect up to lamina propria of mucous membrane);

2. *Fibrou*s (on the gastric mucous membrane grey color fibrous layers are formed, superficial and deep necrosis develops at different depth of gastric mucosa,);

3. *Purulent* (whole gastric wall is infiltrated by neutrophilic granulocytes, and it can lead to peritonitis as complication).

4. *Necrotic* gastritis (superficial or deep damage of gastric mucosa develops after use of chemical substances (acids, bases). It leads to formation of erosions and ulcers.

In acute haemorrhagic and erosive gastritis, the mucosa is sloughed off and there are haemorrhages on the surface.

Chronic Gastritis

Chronic gastritis is the commonest histological change observed in biopsies from the stomach. The microscopic change is usually poorly correlated to the symptomatology, as the change is observed in about 35% of endoscopically normal mucosal biopsies. The condition occurs more frequently with advancing age; average age for symptomatic chronic gastritis being 45 years which corresponds well with the age incidence of gastric ulcer.

Etiopathogenesis. In the absence of clear etiology of chronic gastritis, a number of etiologic factors have been implicated. All the causative factors of acute gastritis described above may result in chronic gastritis too. Recurrent attacks of acute gastritis may result in chronic gastritis. Some other causes are as under:

1. *Reflux of duodenal contents into the stomach,* especially in cases who have undergone surgical intervention in the region of pylorus.

2. *Associated disease of stomach and duodenum,* such as gastric or duodenal ulcer, gastric carcinoma.

3. *Chronic hypochromic anaemia,* especially associated with atrophic gastritis.

4. *Immunological factors* such as autoantibodies to gastric parietal cells in atrophic gastritis and autoantibodies against intrinsic factor.

The mechanism of chronic gastric injury by any of the etiologic agents is by cytotoxic effect of the injurious agent on the gastric mucosal epithelium, thus breaking the barrier and then inciting the inflammatory response.

Classification. Based on the type of mucosa affected (i.e. cardiac, body, pyloric, antral or transitional), a clinicopathologic classification has been proposed.

1. Type A Gastritis (Autoimmune gastritis). Type A gastritis involves mainly the body-fundic mucosa. It is also called autoimmune gastritis due to the presence of circulating antibodies and is sometimes associated with other autoimmune diseases such as Hashimoto's thyroiditis and Addison's disease. As a result of the antibodies against parietal cells and intrinsic factor, there is depletion of parietal cells and impaired secretion of intrinsic factor. These changes may lead to significant gastric atrophy where intestinal metaplasia may occur, and a small proportion of these patients may develop pernicious anaemia. Due to depletion of gastric acid-producing mucosal area, there is hypo- or achlorhydria, and hyperplasia of gastrin-producing G cells in the antrum resulting in hypergastrinaemia.

2. Type B Gastritis (H. pylori-related). Type B gastritis mainly involves the region of antral mucosa and is more common. It is also called hypersecretory gastritis due to excessive secretion of acid, commonly due to infection with H. *pylori.* These patients may have associated duodenal or gastric ulcer. Unlike type A gastritis, this form of gastritis has no autoimmune basis nor has association with other autoimmune diseases.

3. Type AB Gastritis (Environmental gastritis, Chronic atrophic gastritis). Type AB gastritis affects the mucosal region of A as well as B types (body-fundic and antral mucosa). This is the most common type of gastritis in all age groups. It is also called environmental gastritis because a number of as yet unidentified environmental factors have been implicated in its etiopathogenesis. Chronic atrophic gastritis is also used synonymously with type AB gastritis because in advanced stage, there is progression from chronic superficial gastritis to chronic atrophic gastritis, characterised by mucosal atrophy and metaplasia of intestinal or pseudopyloric type.

Pathologic changes. *Macroscopically,* the features of all forms of gastritis are inconclusive. The gastric mucosa may be normal, atrophied, or oedematous. Chronic gastritis is essentially a histological diagnosis.

Histologically, based on:

i) the extent of inflammatory changes in the mucosa (i.e. superficial or deep),

ii) the activity of inflammation (i.e. quiscent or active; acute or chronic),

iii) the presence of and type of metaplasia (i.e. intestinal or pseudo-pyloric), the following simple classification has emerged:

1. Chronic superficial gastritis,
2. Chronic atrophic gastritis,
3. Gastric atrophy,
4. Chronic hypertrophic gastritis (Menetrier's disease),
5. Uncommon forms of chronic gastritis.

1. Chronic Superficial Gastritis. As the name suggests there is inflammatory infiltrate consisting of plasma cells and lymphocytes in the superficial layer of the gastric mucosa, but there are no histological changes in the deep layer of mucosa containing gastric glands. Chronic superficial gastritis may resolve completely or may progress to chronic atrophic gastritis.

H. pylori, a spiral-shaped bacteria, is found in almost all active cases of chronic superficial gastritis and about 65% of quiscent cases. The organism is identified on the epithelial layer on the luminal surface and does not invade the mucosa. It is not seen on areas with intestinal metaplasia. *H. Pylori* is easily identified with Giemsa, Steiner silver or Warthin-Starry stain. Chronic superficial gastritis due to H. *pylori* may lead to chronic atrophic gastritis, gastric atrophy, peptic ulcer and malignant transformation.

2. Chronic Atrophic Gastritis. In this stage, there is inflammatory cell infiltrate in the deeper layer of the mucosa and atrophy of the epithelial elements including destruction of the glands. Two types of metaplasia are commonly associated with atrophic gastritis:

i) *Intestinal metaplasia*. Intestinal metaplasia is more common and involves antral mucosa more frequently. Characteristic histologic feature is the presence of intestinal type mucus-goblet cells; Paneth cells and endocrine cells may also be present. Parietal cells are very few or absent. Intestinal metaplasia, focal or extensive, in atrophic gastritis is significant because its incidence is high in populations having high prevalence rate of gastric cancer like in Japan.

ii) *Pseudopyloric metaplasia*. It involves the body glands which are replaced by proliferated mucous neck cells, conforming in appearance to normal pyloric glands. Its significance is not known.

3. Gastric Atrophy. In this, there is thinning of the gastric mucosa with loss of glands but no inflammation though lymphoid aggregates may be present.

4. Chronic Hypertrophic Gastritis (Menetrier's Disease). This is an uncommon condition characterised pathologically by enormous thickening of gastric rugal folds resembling cerebral convolutions, affecting mainly the region of fundic-body mucosa and characteristically sparing antral mucosa. The patients present with dyspepsia, haematemesis, melaena or protein-losing enteropathy.

Histologically, the gastric pits are elongated and are tortuous. The mucosa is markedly thickened and parts of muscularis mucosae may extend into the thickened folds. Epithelium-lined cysts are commonly seen in the glandular layer. Inflammatory infiltrate is usually mild but lymphoid follicles may be present. The condition is considered significant in view of the risk of developing cancer.

5. Uncommon Forms Of Chronic Gastritis. A few other types of gastritis which do not fit into the description of the types of gastritis described above are listed below:

i) Gastric candidiasis. Infection with *Candida albicans* may occur as an opportunistic infection in immunosuppressed and debilitated individuals.

ii) Eosinophilic gastritis. This condition is characterised by diffuse thickening of the pyloric antrum due to oedema and extensive infiltration by eosinophils in all the layers of the wall of antrum. Eosinophilic gastritis probably has an allergic basis.

iii) Chronic follicular gastritis. This is a variant of chronic atrophic gastritis in which numerous lymphoid follicles are present in the mucosa and submucosa of the stomach.

iv) Haemorrhagic (Erosive) gastritis. In this condition, there are superficial erosions and mucosal haemorrhages, usually following severe haematemesis. The causes for such erosions and haemorrhages are duodenal-gastric reflux, administration of non-steroidal antiinflammatory drugs (NSAIDs), portal hypertension.

v) Granulomatous gastritis. Rarely, granulomas may be present in the gastric mucosa such as in tuberculosis, sarcoidosis, Crohn's disease, syphilis, various mycoses, and as a reaction to endogenous substance or foreign material.

PEPTIC ULCERS

Peptic ulcers are the areas of degeneration and necrosis of gastrointestinal mucosa exposed to acid-peptic secretions. Though they can occur at any level of the alimentary tract that is exposed to hydrochloric acid and pepsin, they occur most commonly (98-99%) in either the duodenum or the stomach in the ratio of 4:1. Each of the two main types may be acute or chronic. In the discussion below, a brief account of acute peptic ulcers (stress ulcers) is followed by detailed description of chronic peptic ulcers.

Acute Peptic (Stress) Ulcers

Acute peptic ulcers or stress ulcers are multiple, small mucosal erosions, seen most commonly in the stomach but occasionally involving the duodenum.

Etiology. These ulcers occur following severe stress. The causes are:

i) *Psychological stress*

ii) *Physiological stress* as in:

• Shock

• Severe trauma

• Septicaemia

• Extensive burns (Curling's ulcers in the posterior aspect of the first part of the duodenum).

• Intracranial lesions (Cushing's ulcers developing from hyperacidity following excessive vagal stimulation).

• Drug intake (e.g. aspirin, steroids, butazolidine, indomethacin).

• Local irritants (e.g. alcohol, smoking, coffee etc).

Pathogenesis. It is not clear how the mucosal erosions occur in stress ulcers because actual hypersecretion of gastric acid is demonstrable in only Cushing's ulcers occurring from intracranial conditions such as due to brain trauma, intracranial surgery and brain tumours. In all other etiologic factors, gastric acid secretion is normal or below normal. In these conditions, the possible hypotheses for genesis of stress ulcers are:

1. Ischaemic hypoxic injury to the mucosal cells.

2. Depletion of the gastric mucus 'barrier' rendering the mucosa susceptible to attack by acid-peptic secretions.

Pathologic changes. *Grossly,* acute stress ulcers are multiple (more than three ulcers in 75% of cases). They are more common anywhere in the stomach, followed in decreasing frequency by occurrence in the first part of duodenum. They may be oval or circular in shape, usually less than 1 cm in diameter.

Microscopically, the stress ulcers are shallow and do not invade the muscular layer. The margins and base may show some inflammatory reaction depending upon the duration of the ulcers. These ulcers commonly heal by complete re-epithelialisation without leaving any scars. Complications such as haemorrhage and perforation may occur.

Chronic Peptic Ulcers (Gastric and Duodenal Ulcers)

If not specified, chronic peptic ulcers would mean gastric and duodenal ulcers, the two major forms of 'peptic ulcer disease' of the upper GI tract in which the acid-pepsin secretions are implicated in their pathogenesis. Peptic

ulcers are common in the present-day life of the industrialised and civilised world.

Gastric and duodenal ulcers represent two distinct diseases as far as their etiology, pathogenesis and clinical features are concerned. However, pathological findings in both are similar and quite diagnostic. The contrasting features of both these conditions are described together below.

Incidence. Peptic ulcers are more frequent in middle-aged adults. The peak incidence for duodenal ulcer is 5th decade, while for gastric ulcer it is a decade later (6th decade). Duodenal as well as gastric ulcers are more common in males than in females. Duodenal ulcer is almost four times more common than gastric ulcer; the overall incidence of gastroduodenal ulcers being approximately 10% of the male population.

Etiology. The immediate cause of peptic ulcer disease is disturbance in normal protective mucosal 'barrier' by acid-pepsin, resulting in digestion of the mucosa. However, in contrast to duodenal ulcers, *the patients of gastric ulcer have low-to-normal gastric acid secretions, though true achlorhydria in response to stimulants never occurs in benign gastric ulcer.* Besides, 10-20% patients of gastric ulcer may have coexistent duodenal ulcer as well. Thus, the etiology of peptic ulcers possibly may not be explained on the basis of a single factor but is multifactorial. These factors are as under:

1. Psychological factors. Psychological stress, anxiety, fatigue and ulcer-type personality may exacerbate as well as predispose to peptic ulcer disease.

2. Acid-pepsin secretions. There is conclusive evidence that some level of acid-pepsin secretion is essential for the development of duodenal as well as gastric ulcer. Peptic ulcers never occur in association with pernicious anaemia in which there are no acid and pepsin-secreting parietal and chief cells respectively.

3. Mucus secretion. Any condition that decreases the quantity or quality of normal protective mucus 'barrier' predisposes to the development of peptic ulcer.

4. Gastritis. Some degree of gastritis is always present in the region of gastric ulcer, though it is not clear whether it is the cause or the effect of ulcer. Besides, the population distribution pattern of gastric ulcer is similar to that of chronic gastritis.

5. Local irritants. Pyloric antrum and lesser curvature of the stomach are the sites most exposed for longer periods to local irritants and thus are the common sites for occurrence of gastric ulcers. Some of the local irritating substances implicated in the etiology of peptic ulcers are heavily spiced foods, alcohol, cigarette smoking, unbuffered aspirin, non-steroidal anti-inflammatory drugs etc.

6. Dietary factors. Nutritional deficiencies have been regarded as etiologic factors in peptic ulcers e.g. occurrence of gastric ulcer in poor socioeconomic strata, higher incidence of duodenal ulcer in parts of South India. However, malnutrition does not appear to have any causative role in peptic ulceration in European countries and the U.S.

7. Helicobacter pylori gastritis. About 15-20% cases infected with *H. pylori* develop duodenal ulcer in their life time while gastric colonisation by *H. pylori* never develops ulceration and remain asymptomatic. However, there is evidence to suggest that increased density of *H. pylori* in the antrum is associated with greater likelihood of development of duodenal ulcer. H. *pylori* can be identified in mucosal samples by histologic examination, culture, increased activity, and serology (IgG and IgA antibodies to *H. pylori).*

8. Genetic factors. People with blood group O appear to be more prone to develop peptic ulcers than those with other blood groups. Genetic influences appear to have greater role in duodenal ulcers as evidenced by their occurrence in families, monozygotic twins and association with HLA-B5 antigen.

9. Hormonal factors. Secretion of certain hormones by tumours is associated with peptic ulceration e.g. elaboration of gastrin by islet cell tumour in Zollinger-Ellison syndrome, endocrine secretions in hyperplasia and adenomas of parathyroid glands, adrenal cortex and anterior pituitary.

10. Miscellaneous. Duodenal ulcers have been observed to occur in association with various other conditions such as alcoholic cirrhosis, chronic renal failure, hyperparathyroidism, chronic obstructive pulmonary disease, and chronic pancreatitis.

Pathogenesis. Although the role of various etiologic factors just described is well known in ulcerogenesis, two most important factors in peptic ulcer are:

• Exposure of mucosa to gastric acid and pepsin secretion; and

• Strong etiologic association with *H. pylori* infection. There are distinct differences in the pathogenetic

Mechanisms involved in duodenal and gastric ulcers as under:

Duodenal ulcer. There is conclusive evidence to support the role of high acid-pepsin secretions in the causation of duodenal ulcers. Besides this, a few other noteworthy features in the pathogenesis of duodenal ulcers are as follows:

1. There is generally *hypersecretion of gastric acid* into the fasting stomach at night which takes place under the influence of vagal stimulation. There is high basal as well as maximal acid output (BAO and MAO) in response to various stimuli.

2. Patients of duodenal ulcer have *rapid emptying* of the stomach so that the food which normally buffers and neutralises the gastric acid, passes

down into the small intestine, leaving the duodenal mucosa exposed to the aggressive action of gastric acid.

3. *Helicobacter* gastritis caused by H. *pylori* is seen in 95-100% cases of duodenal ulcers. The mucosal areas colonised by this organism are depleted of the protective mucus 'barrier', thus exposing the underlying epithelial cells to the injurious effects of acid-pepsin secretions.

Gastric ulcer. The pathogenesis of gastric ulcer is mainly explained on the basis of impaired gastric mucosal defenses against acid-pepsin secretions. Some other features in the pathogenesis of gastric ulcer are as follows:

1. Hyperacidity may occur in gastric ulcer due to *increased serum gastrin* levels in response to ingested food in an atonic stomach.

2 However, many a patients of gastric ulcer have low-to-normal gastric acid levels. Ulcerogenesis in such patients is explained on the basis of damaging influence of *other factors* such as gastritis, bile reflux, cigarette smoke etc.

3. The normally protective *gastric mucus 'barrier'* against acid-pepsin is deranged in gastric ulcer. There is depletion in the quantity as well as quality of gastric mucus. One of the mechanisms for its depletion is colonisation of the gastric mucosa by *H. pylori* seen in 75-80% patients of gastric ulcer.

Pathologic changes. *Gross* and microscopic changes in gastric and duodenal ulcers are similar and quite characteristic. *Gastric ulcers* are found predominantly along the lesser curvature in the region of pyloric antrum, more commonly on the posterior than the anterior wall. Most *duodenal ulcers* are found in the first part of the duodenum, usually immediate post-pyloric, more commonly on the anterior than the posterior wall. Uncommon locations include ulcer in the cardia, marginal ulcer and in the Meckel's diverticulum. *Grossly,* typical peptic ulcers are commonly solitary (80%), small (1-2.5 cm in diameter), round to oval and characteristically 'punched out'. Benign ulcers usually have flat margins in level with the surrounding mucosa. 'The mucosal folds converge towards the ulcer. The ulcers may vary in depth from being superficial (confined to mucosa) to deep ulcers (penetrating into the muscular layer). In about 10-20% of cases, gastric and duodenal ulcers are coexistent. Vast majority of the peptic ulcers are benign. *Chronic duodenal ulcer never turns malignant,* while chronic gastric ulcer may develop carcinoma in less than 1% of cases. Malignant gastric ulcers are larger, bowl-shaped with elevated and indurated mucosa at the margin.

Microscopically, chronic peptic ulcers have 4 histological zones. From within outside, these are as under;

1. *Necrotic zone* – lies in the floor of the ulcer and is composed of fibrinous exudate containing necrotic debris and a few leucocytes.

2. *Superficial exudative zone* – lies underneath the necrotic zone. The tissue elements here show coagulative necrosis giving eosinophilic, smudgy appearance with nuclear debris.

3. *Granulation tissue zone* – is seen merging into the necrotic zone. It is composed of nonspecific inflammatory infiltrate and proliferating capillaries.

4. *Zone of cicatrisation* – is seen merging into thick layer of granulation tissue. It is composed of dense fibrocollagenic scar tissue over which granulation tissue rests. Thrombosed or sclerotic arteries may cross the ulcer which on erosion haemorrhage.

Complications. Acute and subacute peptic ulcers usually heal without leaving any visible scar. However, healing of chronic, larger and deeper ulcers may result in complications. These are as follows:

1. Ulcerative- destructive:

Haemorrhage. Minor bleeding by erosion of small blood vessels in the base of an ulcer occurs in all the ulcers and can be detected by testing the stool for occult blood. Chronic blood loss may result in iron deficiency anaemia. Severe bleeding may cause 'coffee ground' vomitus or melaena. A penetrating chronic ulcer may erode a major artery (e.g. left gastric, gastroduodenal or splenic artery) and cause a massive and severe hematemesis and sometimes death.

Perforation. A perforated peptic ulcer is an acute abdominal emergency. Perforation occurs more commonly in chronic duodenal ulcers than chronic gastric ulcers. Following sequelae may result:

i) On perforation the contents escape into the lesser sac or into the peritoneal cavity, causing *acute peritonitis.*

ii) Air escapes from the stomach and lies between the liver and the diaphragm giving the characteristic radiological appearance of *air under the diaphragm.*

iii) *Subphrenic abscess* between the liver and the diaphragm may develop due to infection.

iv) Perforation may extend to involve the *adjacent organs* e.g. the liver and pancreas.

2. Ulcerative- obstructive. Development of fibrous scar at or near the pylorus results in pyloric stenosis. In the case of healed duodenal ulcer, it causes duodenal stenosis. Healed ulcers along the lesser curvatures may produce 'hour glass' deformity due to fibrosis and contraction.

3. Ulcerative-inflammatory (gastritis, perigastritis, duodenitis, periduodenitis)

4. Malignant transformation. The dictum *'cancers ulcerate but ulcers rarely cancerate'* holds true for most peptic ulcers. A chronic duodenal ulcer

never turns malignant, while less than 1% of chronic gastric ulcers may transform into carcinoma.

5. Combined.

HAEMATEMESIS AND MELAENA OF GASTRIC ORIGIN

In continuity with the discussion on peptic ulcers which are the commonest cause of haematemesis and melaena, it is worthwhile listing the various causes of haematemesis.

These are:

i) Chronic peptic ulcers (gastric as well as duodenal)
ii) Acute peptic ulcers (stress ulcers)
iii) Multiple gastric and duodenal erosions
iv) Carcinoma of the stomach
v) Peptic ulcer in Meckel's diverticulum
vi) Mallory-Weiss syndrome
vii) Anaemias
viii) rpuras
ix) Haemophilia.

TUMOURS AND TUMOUR-LIKE LESIONS

A. TUMOUR-LIKE LESIONS (POLYPS)

Tumour-like lesions are the polyps of the stomach which are of the following types:

Hyperplastic (Inflammatory) or inflammatory polyps are the regenerative, non-neoplastic lesions which are the most common type (90%). They may be single or multiple and are more often located in the pyloric antrum.

Grossly, the lesions may be sessile or pedunculated, 1 cm or larger in size, smooth and soft. The surface may be ulcerated or haemorrhagic. *Microscopically,* they are composed of irregular hyperplastic glands, which may show cystic change. The lining epithelium is mostly superficial gastric type but antral glands, chief cells and parietal cells may be present. These lesions do not have cellular atypia and do not have malignant potential.

Hamartomatous Polyps are not true neoplasms but are malformations. They are of various types such as gastric polyps of the Peutz-Jeghers syndrome, juvenile polyp, pancreatic heterotopia, heterotopia of Brunner's glands and inflammatory fibroid polyps (eosinophilic granulomatous polyps).

B.BENIGNTUMOURS

Benign tumours of the stomach are uncommon and usually incidental findings.

Adenomas (Adenomatous or Neoplastic Polyps)

Adenomas, also, referred to as adenomatous or neoplastic polyps, are true benign epithelial neoplasms and are much rarer in the stomach than in the large intestine. They are also found more often in the region of pyloric antrum. They are commonly associated with atrophic gastritis and pernicious anaemia.

Spindle Cell (Stromal) Tumours

These are a group of rare benign tumours of the stomach having spindle cell or stromal cell appearance. They are usually firm, circumscribed nodules, less than 4 cm in size and appear as submucosal nodules. The more common example is leiomyoma; others are neurofibromas, schwannomas etc. They resemble in gross and microscopic appearance with their counterparts in other parts of the body.

C. MALIGNANTTUMOURS

GASTRIC CARCINOMA

Incidence. Carcinoma of the stomach comprises more than 90% of all gastric malignancies and is the leading cause of cancer-related deaths in countries where its incidence is high. The highest incidence is between 4th to 6th decades of life and is twice more common in men than in women.

Etiology. A number of etiologic factors have been implicated in causation of gastric cancer. These are as under:

1. *H. pylori* infection. *H. pylori* infection of the stomach is an important risk factor for the development of gastric cancer. Epidemiologic studies throughout world have shown that a seropositivity with H. *pylori* is associated with 3 to 6 times higher risk of development of gastric cancer. It may be mentioned here that similar association of *H. pylori* infection exists with gastric lymphomas as well.

2. Dietary factors. Epidemiological studies suggest that dietary factors are most significant in the etiology of gastric cancer. The evidences in support of this are multifold:

i) Occurrence of gastric cancer in the region of gastric canal (i.e. along the lesser curvature and the pyloric antrum) where irritating foods exert their maximum effect.

ii) Populations consuming certain food stuffs have high risk of developing gastric cancer e.g. ingestion of smoked foods, high intake of salt, pickled raw vegetables, high intake of carcinogens as nitrates in foods and drinking water, nitrites as preservatives for certain meats etc. However, intake of green leafy vegetables, citrus fruits and animal fats has been reported to have protective role in gastric cancer.

iii) Tobacco smoke, tobacco juice and consumption of alcohol have all been shown to have carcinogenic effect on gastric mucosa.

3. Geographical factors. There are geographic variations in the incidence of gastric cancer. Japan, Chile, Finland and Iceland have highest recorded death rate from gastric cancer, while the incidence is considerably low in the US, UK and Canada. The higher incidence in certain geographic locales is likely to be the result of environmental influences as observed from the finding of incidence of gastric cancer in the next generation of Japanese immigrants to the US which is comparable to that of native Americans.

4. Racial factors. Within the country, different ethnic groups may have variations in incidence of gastric cancer e.g. incidence is higher in Blacks, American Indians, Chinese in Indonesia, North Wales than other parts of Wales.

5. Genetic factors. Generic influences have some role in the etiology of gastric cancer. Not more than 4% of patients of gastric cancer have a family history of this disease. Individuals with blood group A have higher tendency to develop gastric cancer (Recall that the peptic ulcer is more common in individuals with blood group O).

6. Pre-malignant changes in the gastric mucosa. There are some precancerous conditions of gastric mucosa implicated in the etiology of gastric cancer. These are:

i) Hypo- or achlorhydria in atrophic gastritis of gastric mucosa.

ii) Adenomatous (neoplastic) polyps of the stomach.

iii) Chronic gastric ulcer (ulcer-cancer), and its association with achlorhydria.

iv) Stump carcinoma in patients who have undergone partial gastrectomy.

Pathologic changes. Gastric carcinoma is most commonly located in the region of gastric canal (prepyloric region) formed by lesser curvature, pylorus and antrum. Other less common locations are the body, cardia and fundus.

Before turning to classification of carcinoma of the stomach, it must be stated here that current studies indicate a pathogenetic evolution for all gastric carcinomas from an initial stage of *in situ* carcinoma confined to mucosal layers called early gastric carcinoma (EGC). EGC eventually penetrates the muscularis or beyond, resulting in advanced gastric carcinoma.

Based on this pathogenetic sequence, gastric carcinomas are broadly classified into 2 main groups:

I. *Early gastric carcinoma (EGC).*

II. *Advanced gastric carcinoma,* which has 5 further major gross subtypes:

i) ulcerative carcinoma,

ii) fungating (polypoid) carcinoma,

iii) scirrhous carcinoma (Linitis plastica),

iv) colloid (mucoid) carcinoma,

v) ulcer-cancer.

In addition to the above classification, gastric carcinomas have been classified, *on the basis of extent of invasion,* into 2 groups:

I. *Expanding (formerly intestinal type) carcinomas* that grow laterally by an invasive margin. The tumour cells are in the form of cohesive clusters.

II. *Infiltrating (formerly diffuse type) carcinomas* have poorly-defined invasive border. The tumour cells are loose and invade singly or in small group.

I. Early Gastric Carcinoma (EGC). EGC is the term used to describe cancerlimited to the mucosa and submucosa. The diagnosis of this condition has been made possible by extensive work on histogenesis of gastric cancer by Japanese pathologists by the use of fibreoptic endoscope and gastrocarnera. In Japan, EGC comprises 35% of newly-diagnosed cases of gastric cancer.

Grossly, the lesion of EGC may have 3 patterns – polypoid (protruded), superficial and ulcerated:

Type I	Polypoid type
Type ILa	Superficial elevated
Type IIb	Superficial flat
Type IIc	Superficial depressed
Type III	Ulcerated type

Histologically, EGC is a typical glandular adenocarcinoma, usually well-differentiated type.

Prognosis of EGC after surgical resection is quite good; 5-year survival rate being 93-99%.

Early gastric carcinoma must be distinguished from certain related terms as under.

- *Epithelial dysplasia* is cellular atypia seen in intestinal metaplasia such as in atrophic gastritis and pernicious anaemia.
- *Carcinoma in situ* in the stomach is a state of severe cellular atypia or dysplasia, without invasion across the basement membrane of the glands.

II. Advanced Gastric Carcinoma. When the carcinoma crosses the basement membrane into the muscularis propria or beyond, it is referred to as advanced gastric carcinoma. Advanced gastric carcinoma has further 5 patterns:

i) Ulcerative carcinoma. This is the most common pattern. The tumour appears as a flat, infiltrating and ulcerative growth with irregular necrotic base and raised margin. It is seen more commonly in the region of gastric canal. *Histologically,* ulcerative carcinomas are poorly- differentiated adenocartinomas, which invade deeply into the stomach wall. Tubular and acinar patterns are seen more commonly.

ii) Fungating (polypoid) carcinoma. The second common pattern is a cauliflower growth projecting into the lumen, similar to what is commonly

seen in the large intestine. It is seen more often in the fundus. The tumour undergoes necrosis and infection commonly.

Histologically, fungating or polypoid carcinomas are well-differentiated adenocarcinomas, commonly papillary type.

iii) Scirrhous carcinoma (Linitis plastica). In this pattern, the stomach wall is thickened due to extensive desmoplasia giving the appearance as 'leather-bottle stomach' or 'linitis plastica'. The involvement may be localised to pyloric antrum, or diffuse affecting whole of the stomach from the cardia to pylorus. The lumen of the stomach is reduced. There are no ulcers but rugae are prominent.

Histologically, it may be an adenocarcinoma or signet-ring cell carcinoma, extensively infiltrating the stomach wall, but due to marked desmoplasia cancer cells may be difficult to find.

iv) Colloid (Mucoid) carcinoma- This pattern is usually seen in the fundus. The tumour grows like masses having gelatinous appearance due to secretion of large quantities of mucus. *Histologically,* mucoid carcinoma contains abundant pools of mucin in which are seen a small number of tumour cells, sometimes having signet-ring appearance.

v) Ulcer-cancer. Development of cancer in chronic gastric ulcer is a rare occurrence(less than 1%). Majority of ulcer-cancers are malignant lesions from the beginning. For confirmation of cancer in a pre-existing gastric ulcer, the characteristic microscopic appearance of peptic ulcer should be demonstrable with one portion of the base or the margin of the ulcer showing carcinomatous changes. *Histologically,* ulcer-cancers are adenocarcinomas without any specific features.

Spread. Carcinoma of the stomach may spread by the following routes:

1. Direct spread. Direct spread by local extension is the most common feature of gastric carcinoma. The spread occurs mainly from the loose submucosal layer but eventually muscularis and serosa are also invaded. After the peritoneal covering of the stomach is involved, transcoelomic dissemination may occur in any other part of the peritoneal cavity but ovarian masses (one side or both-sided) occur more commonly, referred to as *Krukenberg tumours*. Submucosal spread occurs more often upwards into the oesophagus due to continuity of the layers of stomach with those of oesophagus, while the spread downwards into the duodenum occurs less often due to the presence of pyloric sphincter and submucosal Brunner's glands. The tumour may directly involve other neighbouring structures and organs like lesser and greater omentum, pancreas, liver, common bile duct, diaphragm, spleen and transverse colon.

2. Lymphatic spread. Metastases to regional lymph nodes occur early, especially in the scirrhous carcinoma. The groups of lymph nodes involved are along the lesser and greater curvature around the cardia and suprapancreatic lymph nodes. Involvement of left supraclavicular lymph node, *Virchow* or *Troisier's sign,* is sometimes the presenting feature of gastric carcinoma.

3. Haematogenous spread. Blood spread of gastric carcinoma may occur to the liver, lungs, brain, bones, kidneys and adrenals. It occurs more commonly with the poorly-differentiated carcinoma.

The American joint Committee on Cancer has developed *TNM staging* system for gastric carcinoma based on tumour invasion (T)/ lymph node involvement (N) and distant metastasis (M) into earliest stage $T_{is}\ N_Q\ M_Q$ (intraepithelial tumour) to most advanced stage $T_{any}N_{any}M_1$.

Other Carcinomas

Besides the various morphologic patterns of adeno-carcinoma just described, other carcinomas that occur rarely in the stomach are: adenosquamous carcinoma, squamous cell carcinoma and undifferentiated carcinoma, all of which are morphologically similar to such tumours elsewhere.

Leiomyosarcoma, though rare, is the commonest soft tissue sarcoma, the stomach being the more common site in the gastrointestinal tract.

Grossly, the tumour may be of variable size but is usually quite large, pedunculated and lobulated mass into the lumen.

Microscopically, leiomyosarcoma is characterised by high cellularity and presence of mitotic figures. Tumour is usually well-differentiated.

Leiomyoblastoma (Epithelioid Leiomyoma) is a rare tumour, the behaviour of which is intermediate between clearly benign and malignant tumour.

Grossly, the tumour is large, circumscribed and projects into the lumen.

Microscopically, it is characterised by round to polygonal cells with clear perinuclear halos. The number of mitoses determines the biological behaviour of the tumour.

Carcinoid Tumours are rare in the stomach and are usually non-argentaffin type but argentaffinomas also occur. Their behaviour is usually malignant.

Lymphomas of Gut

Primary gastrointestinal lymphomas are defined as lymphomas arising in the gut without any evidence of systemic involvement at the time of presentation.

*Secondary gastrointestinal lymphomas***,** on the other hand, appear in the gut after dissemination from other primary site. Gastric lymphomas constitute over 50% of all bowel lymphomas; other sites being small and large bowel in decreasing order of frequency. Prognosis of primary gastric lymphoma is better

than for intestinal lymphomas. Primary lymphoma of stomach is the most common malignant gastric tumour (4%) next to carcinoma.

Clinical manifestations of gastric lymphomas may be similar to gastric carcinoma. Age incidence for lymphomas of the gastrointestinal tract is usually lower than that for carcinoma (30-40 years as compared to 40-60 years in gastric carcinoma) and may occur even in childhood. Relationship with long-standing chronic *H. pylori* gastritis with lymphoid hyperplasia has been strongly suggested.

Grossly, gastric lymphomas have 2 types of appearances:

1. *Diffusely infiltrating type,* producing thickening of the affected gut wall, obliteration of mucosal folds and ulcerations. Cut section shows lesions in the mucosa and submucosa but in late stage whole thickness of the gut wall may be affected.

2. *Polypoid type,* which produces large protruding mass into the lumen with ulcerated surface.

Lymph node involvement may occur in either of the two patterns.

Microscopically gastric lymphomas are most often non-Hodgkin's lymphomas of the following types:

• *High-grade* large cell immunoblastic lymphoma being the most common.

• *Low-grade* small lymphocytic well-differentiated B-cell lymphoma referred to as *MALToma* is the next in frequency (arising from Mucosa Associated Lymphoid Tissue). The term *pseudolymphoma* is sometimes used for non-invasive stage of MALToma.

PATHOLOGY OF SMALL INTESTINE

Anatomically, the small bowel includes the duodenum, jejunum and ileum and tends to become narrower throughout its course.

Histologically, the small bowel is identified by recognition of villi. The wall of the small intestine consists of 4 layers:

1. The serosa is the outer covering of the small bowel which is complete except over a part of the duodenum.

2. The muscularis propria is composed of 2 layers of smooth muscle tissue – outer thinner longitudinal and inner thicker circular layer. These muscles are functionally important for peristalsis. Between the two layers of muscle lie ganglionated plexus, myenteric plexus of Auerbach.

3. The submucosa is composed of loose fibrous tissue with blood vessels and lacteals in it. It contains a gangliated plexus, Meissner's plexus, having fewer and smaller cells than the Auerbach's plexus.

4. The mucosa consists of glandular epithelium overlying the lamina propria composed of loose connective tissue and contains phagocytic cells and abundance of lymphoid cells (Peyer's patches in the ileum) and plasma cells. It is supported externally by thin lay-

er of smooth muscle fibres, *muscularis mucosae.* The mucous membrane is thrown into folds or *plicae* which are more in the jejunum and less in the ileum, thus increasing the absorptive surface enormously. The absorptive surface is further increased by the intestinal villi. *Villi* are finger-like or leaf-like projections which contain 3 types of cells:

i) *simple columnar cells* which perform absorptive function due to the presence of brush border consisting of large number of microvilli.

ii) *goblet cells* which are mucus-secreting cells and are interspersed between the columnar cells.

iii) *endocrine cells.* These are scattered in the villi as well as are widely distributed throughout the gastrointestinal tract. These cells have various synonyms as under:

• *Kulchitsky cells,* after the name of its discoverer;

• *Enterochromaffin cells,* due to their resemblance to chromaffin cells of the adrenal medulla;

• *Argentaffin cells,* as the intracytoplasmic granules stain positively with silver salts by reduction reaction (argyrophil cells, on the other hand, require the addition of exogenous reducing substance for staining); and

• *Endocrine cells,* as these specialised cells are considered to be part of APUD cell system (having common properties as Amine content, amine Precursor Uptake and Decarboxylation). APUD cells are considered to be of endodermal origin, while previously they were thought to be neural crest derivative. Other endocrine cells belonging to the APUD cell system are C-cells of the thyroid, chromaffin cells of the adrenal medulla, certain cells of the carotid body, bronchi, hypothalamus, pituitary and sympathetic ganglia.

Endocrine cells are heavily populated in the proximal small bowel as this is the most active site for absorption and secretory activities. They are sparse in the colon which is less active site for such functions.

The duodenum contains distinctively branched *Brunner's glands* present in the submucosa and going up to muscularis mucosae. The deeper layer of the mucosa of the small intestine elsewhere contains intestinal glands or *crypts of Lieberkuhn.* They are lined by columnar cells, goblet cells, endocrine cells and Paneth cells. Paneth cells are normally exclusively found in the small intestine and occasionally in the caecum. These cells are characterised by the presence of supranuclear granules rich in lysozyme.

The blood supply of the whole of small intestine, except the first part of the duodenum, is by the superior mesenteric artery which supplies blood by mesenteric arterial arcades and the straight arteries.

The main function of the small intestine is digestion and absorption so that ultimately nutrients passing into the blood stream are utilised by the cells in metabolism. The mucosal layer of the small intestine has remarkable capacity for regeneration and new lining is laid every 3-4 days.

CONGENITAL ANOMALIES

INTESTINAL ATRESIA AND STENOSIS

• Intestinal atresia is congenital absence of lumen, most commonly affecting the ileum or duodenum. The proximal segment has a blind end which is separated from distal segment freely, or the two segments are joined by a fibrous cord. The condition must be recognised early and treated surgically, as otherwise it is incompatible with life.

• Intestinal stenosis is congenital narrowing of the lumen affecting a segment of the small intestine. Intestinal segment above the level of obstruction is dilated and that below it is collapsed.

MECKEL'S DIVERTICULUM

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, occurring in 2% of population. It is more common in males. The anomaly is commonly situated on the antimesenteric border of the ileum, about 1 meter above the ileocaecal valve. Like other true diverticula, Meckel's diverticulum is an outpouching containing all the layers of the intestinal wall in their normal orientation. It is almost always lined by small intestinal type of epithelium, though at times it may contain islands of gastric mucosa and ectopic pancreatic tissue. Embryologic origin of Meckel's diverticulum is from incomplete obliteration of vitellointestinal duct. (Other anomalies resulting from the remnants of vitellointestinal duct are vitelline sinus and vitelline cyst).

The common *complications* of Meckel's diverticulum are perforation, haemorrhage and diverticulitis.

In addition to congenital Meckel's diverticulum, *acquired diverticula* also occur in the small intestine.

These are commonly multiple (diverticulosis), frequently located on the mesenteric border, and are sometimes associated with malabsorption.

INTESTINAL MALROTATION

Malrotation is a developmental abnormality of the midgut (i.e. the portion of intestine between the duodeno-jejunal flexure and the middle of transverse colon). Due to failure of normal rotation of midgut, the following consequences can occur:

i) Exomphalos i.e. intestinal eventration at the umbilicus.

ii) Misplacement of the caecum, appendix and ascending colon,

iii) Mobile caecum.

COELIAC SPRUE (NON-TROPICAL SPRUE, GLUTEN-SENSITIVE ENTEROPATHY, IDIOPATHIC STEATORRHOEA)

This is the most important cause of primary malabsorption occurring in temperate climates. The condition is characterised by significant loss of villi in the small intestine and thence diminished absorptive surface area. The condition occurs in 2 forms:

Childhood form, seen in infants and children and is commonly referred to as coeliac disease.

Adult form, seen in adolescents and early adult life and used to be called idiopathic Steatorrhoea.

In either case, there is genetic abnormality resulting in sensitivity to gluten (a protein) and its derivative, gliadin, present in diets such as grains of wheat, barley and rye. The symptoms are usually relieved on elimination of gluten from the diet. The role of heredity is further supported by the observation of familial incidence and HLA association of the disease. Exact pathogenesis of the condition is not clear. However, following hypotheses are significant in causing mucosal cell damage:

1. Hypersensitivity reaction as evidenced by gluten-stimulated antibodies.
2. Toxic effect of gluten due to inherited enzyme deficiency in the mucosal cells.

Pathologic changes. There are no differences in the pathological findings in children and adults. Histologically, there is variable degree of flattening of the mucosa, particularly of the upper jejunum, and to some extent of the duodenum and ileum. The surface epithelial cells are cuboidal or low columnar type. There may be partial villous atrophy which is replacement of normal villous pattern by convolutions, or subtotal villous atrophy characterised by flat mucosal surface. Lamina propria shows increased number of plasma cells and lymphocytes.

The major sequela of long-term coeliac sprue is increased incidence of intestinal carcinoma in these cases.

COLLAGENOUS SPRUE

This entity is regarded as the end-result of coeliac sprue in which the villi are totally absent (total villous atrophy) and there are unique and diagnostic broad bands of collagen under the basal lamina of surface epithelium. The condition is refractory to any treatment and the course is generally fatal. Some workers consider collagenous sprue as a variant of coeliac sprue without classifying it separately.

TROPICAL SPRUE

This disease, as the name suggests, occurs in individuals living in or visiting tropical areas such as Caribbean countries, South India, Sri Lanka and Hong Kong. Pathogenesis of the condition is not clear but there is evidence to support enterotoxin production by some strains of E. coli which causes the intestinal injury. Severe cases are characterised by additional features such as macrocytic anaemia, glossitis and emaciation due to intestinal malabsorption of vitamin B^{12} and folate.

WHIPPLE'S DISEASE (INTESTINAL LIPODYSTROPHY)

This is an uncommon bacterial disease involving not only the intestines but also various other systems such as central nervous system, heart, blood vessels, skin, joints, lungs, liver, spleen and kidneys. The disease is more

common in males in 4th to 5th decades of life. Patients may present with features of malabsorption or may have atypical presentation in the form of migratory polyarthritis, neurological disturbances and focal hyperpigmentation of the skin.

Pathologic changes. Histologically, the affected tissues show presence of characteristic macrophages containing PAS-positive granules and rod-shaped microorganisms (Whipple's bacilli). These macrophages are predominantly present in the lamina propria of the small intestine and mesenteric lymph nodes.

Patients respond very well to oral antibiotic therapy.

PROTEIN-LOSING ENTEROPATHIES

A number of disorders of the gastrointestinal tract are accompanied by excessive protein loss without concomitant increase in protein synthesis, thus resulting in hypoproteinaemia. These diseases are listed below: i) Whipple's disease ii) Crohn's disease iii) Ulcerative colitis iv) Sprue v) Intestinal lymphangiectasia vi) Menetrier's disease (Hypertrophic gastritis).

SMALL INTESTINAL TUMOURS

For obscure reasons, benign as well as malignant tumours of the small bowel are surprisingly rare. Most common benign tumours, in descending order of frequency, are: leiomyomas, adenomas and vascular rumours (haemangioma, lymphangioma). Amongst the malignant tumours, the most frequently encountered, in descending frequency, are: carcinoid tumours, lympho-mas and adenocarcinoma. All these tumours are identical in morphology to those seen elsewhere in the alimentary tract. Carcinoid rumour, a peculiar neoplasm most common in the midgut, is described below.

CARCINOID TUMOUR (ARGENTAFFINOMA)

Carcinoid tumour or argentaffinoma is a generic term applied to tumours originating from endocrine cells (synonyms: argentaffin cells, Kulchitsky cells, enterochromaffin cells) belonging to APUD cell system and are therefore also called as apudomas. The endocrine cells are distributed throughout the mucosa of GI tract. These cells have secretory granules which stain positively with silver salts (argentaffin granules) or many stain after addition of exogenous reducing agent (non-argentaffin or argyrophil granules). Accordingly, carcinoid tumour may be argentaffin or argyrophil type. Depending upon the embryologic derivation of the tissues where the tumour is located, these are classified as foregut, midgut, and hindgut carcinoids.

• *Midgut carcinoids*, seen in terminal ileum and appendix are the most common (60-80%) and are more often argentaffin positive.

• *Hindgut carcinoids*, occurring in rectum and colon are more commonly argyrophil type, and comprise about 10-20% of carcinoids.

• *Foregut carcinoids*, located in the stomach, duodenum and oesophagus are also argyrophil type and are encountered as frequently as in the hindgut (10-20%).

Other uncommon locations are bronchus, trachea, gallbladder, and Meckel's diverticulum.

Appendix and terminal ileum, the two most common sites for carcinoids, depict variation in their age and sex incidence and biologic behaviour:

• Appendiceal carcinoids, occur more frequently in 3rd and 4th decades of life without any sex predilection, are often solitary and behave as locally malignant tumours.

• Ileal carcinoids, on the other hand, are seen more often in later age (7th decade) with female preponderance, are more commonly multiple and behave like metastasising carcinomas.

Pathologic changes. Macroscopically, all carcinoids are small, button-like submucosal elevations with intact or ulcerated overlying mucosa. They are usually small; those larger than 2 cm are more often metastasising. Ileal and gastric carcinoids are commonly multiple, whereas appendiceal carcinoids commonly involve the tip of the organ and are solitary. Cut section of all the carcinoids is bright yellow.

Histologically, the tumour cells may be arranged in a variety of patterns — solid nests, sheets, cords, trabeculae and clusters, all of which show characteristic palisading of the peripheral cells. Aeirtar arrangement and rosettes are rarely seen. The rumour cells are classically small, monotonous, having uniform nuclei and poorly-defined cell boundaries. The argentaffin carcinoids show eosinophilic granules in the cytoplasm which stain positively by the argentaffin reaction. Mitotic figures are rare. However, the cytologic features are a poor guide for distinguishing clinically benign from malignant behaviour of the tumour, but all carcinoids infiltrate the bowel wall.

CARCINOID SYNDROME

Carcinoid tumours that metastasise, especially to the liver, are sometimes associated with the carcinoid syndrome. The syndrome consists of the following features:

1. Intermittent attacks of flushing of the skin of face
2. Episodes of watery diarrhoea
3. Abdominal pain
4. Attacks of dyspnoea due to bronchospasm
5. Right-sided heart failure due to involvement of tricuspid and pulmonary valves and endocardium.

A number of secretory products in a functioning carcinoid tumour have been demonstrated. These are:

i) 5-Hydroxytryptamine (5-HT, serotonin)

ii) 5-Hydroxytryptophan

iii) 5-Hydroxyindole acetic acid (5-HIAA)

iv) Histamine

v) Kallikrein

vi) Bradykinin

However, 5-HT and its degradation product, 5-HIAA, are particularly significant in the production of carcinoid syndrome. 5-HT, a potent vasodilator and smooth muscle stimulant, is normally synthesised in the endocrine cells of the gut from dietary tryptophan. Tryptophan is first hydroxylated to 5-hydroxytryptophan, then decarboxylated to 5-HT and further oxidised to 5-HLAA by the monoamine oxidase in the liver cells. It is then excreted in the urine. This capacity to synthesise 5-HT and 5-HIAA is markedly elevated in primary and hepatic metastatic carcinoids. Midgut carcinoids have rich decarboxylating enzymes and are thus able to produce large quantities of 5-HT and 5-HIAA, accounting for high frequency of carcinoid syndrome in them. Foregut and hindgut carcinoids, on the other hand, lack decarboxylating enzymes and, therefore, are less often associated with carcinoid syndrome.

INFLAMMATORY BOWEL DISEASE

The term 'inflammatory bowel disease (IBD)' is commonly used to include 2 idiopathic bowel diseases having many similarities but the conditions usually have distinctive morphological appearance. These 2 conditions are Crohn's disease (regional enteritis) and ulcerative colitis:

1. **CROHN'S DISEASE OR REGIONAL ENTERITIS** is an idiopathic chronic ulcerative IBD, characterised by transmural, non-caseating granulomatous inflammation, affecting most commonly the segment of terminal ileum and/or colon, though any part of the gastrointestinal tract may be involved.

2. **ULCERATIVE COLITIS** is an idiopathic form of acute and chronic ulcero-inflammatory colitis affecting chiefly the mucosa and submucosa of the rectum and descending colon, though sometimes it may involve the entire length of large bowel.

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

Etiopathogenesis. The exact etiology of IBD remains unknown. A few hypotheses, however, have been postulated. These are as follows:

1. *Infectious mechanism.* Many microorganisms have been implicated as causative for IBD but none has been conclusively proved. These include: bacteria (e.g. mycobacteria, dysentery bacilli, chlamydia), viruses (e.g. rotaviruses, EB virus, intestinal cytopathic viruses), protozoa and fungi. There is, however, indirect evidence in support of their role in the etiology of IBD like production of pathologic changes in the bowel of experimental animals by injecting tissue homogenates of Crohn's disease or of ulcerative colitis.

2. *Immunologic mechanisms.* Immunologic factors, both humoral and cellular, as well as immunodeficiency, have been recently shown to play significant, but as yet unproven role, in the pathogenesis of IBD.

i) *Humoral factors* implicated in the pathogenesis of IBD are as under:

a) Demonstration of specific anti-colon antibodies to bacterial antigen such as Escherichia coli which may cause the lesions but there is no correlation between the levels of these antibodies and activity of the IBD.

b) Increased synthesis of IgG by the lymphoid cells of the diseased bowel may produce antibody-mediated damage but IBD has been observed to occur in patients with agammaglobulinaemia as well.

c) Circulating immune complexes may produce extra-intestinal lesions of IBD but their role in the intestinal lesions of IBD is not established.

d) IgE-mediated hypersensitivity reaction leading to excessive histamine release by mast cells in the bowel wall may cause oedema of the bowel wall in IBD but the evidence is not conclusive as administration of antihistaminics does not alter the course of the disease,

ii) *Cell-mediated immunologic factors* have attracted more attention. The evidences in support are:

a) Decreased number of peripheral T cells and cutaneous anergy.

b) Presence of T cells sensitised to various bowel antigens may be cytotoxic to mucosa.

c) Antibody-dependent cellular cytotoxicity (ADCC) may occur by interaction of K cells with humoral antibodies.

iii) I*mmunodeficiency of IgA* in Crohn's disease has been suggested more recently as possible immune mechanism for the lesions.

3. *Other mechanisms.* Many other etiologic factors have been implicated in the etiopathogenesis of IBD, all without definite proof of their involvement. These are as under:

i) Psychological factors such as individuals who are unduly sensitive, dependent on others and unable to express themselves suffer from irritable colon.

ii) Genetic factors have been implicated due to familial incidence of IBD. Recently, certain HLA antigens have also been found to be associated with IBD.

iii) Racial factors have been reported such as observation of high incidence of IBD in Jews and in Whites.

iv) Food allergies, particularly to milk, have been shown to provoke attacks of IBD.

v) Trauma has been thought to activate clinically latent disease.

CROHN'S DISEASE

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

Grossly, characteristic feature is the multiple, well-demarcated segmental bowel involvement with intervening uninvolved 'skip areas'. The wall of the affected bowel segment is thick and hard, resembling a 'hose pipe'. Serosa may be studded with minute granulomas. The lumen of the affected segment is markedly narrowed. The mucosa shows 'serpiginous ulcers', while intervening surviving mucosa is swollen giving 'cobblestone appearance'. There may be deep fissuring into the bowel wall. Histologically, the characteristic features are as follows:

1. Transmural inflamatory cell infiltrate consisting of chronic inflammatory cells (lymphocytes, plasma cells and macrophages) is the classical microscopic feature.

2. Non-caseating, sarcoid-like granulomas are present in all the layers of the affected bowel wall in 60% of cases and may even be seen in the regional lymph nodes.

3. There is patchy ulceration of the mucosa which may take the form of deep fissures, accompanied by inflammatory infiltrate of lymphocytes and plasma cells.

4. There is widening of the submucosa due to oedema and foci of lymphoid aggregates.

5. In more chronic cases, fibrosis becomes increasingly prominent in all the layers disrupting muscular layer.

Complications of Crohn's disease are:

1. Malabsorption due to impaired absorption of fat, vitamin B^{12}, proteins and electrolytes from the diseased small bowel.

2. Fistula formation may occur in long-standing cases. These may be internal fistulae between the loops of the intestine, or external fistulae such as enterocutaneous, rectal and anal fistulae.

3. Stricture formation may occur in chronic cases due to extensive fibrosis in the affected bowel wall.

4. Carcinoma may develop very rarely in the small intestine as a late complication of Crohn's disease.

ULCERATIVE COLITIS

Classically, ulcerative colitis begins in the rectum, and in continuity extends upwards into the sigmoid colon, descending colon, transverse colon, and sometimes may involve the entire colon. The colonic contents may rarely backflow into the terminal ileum in continuity, causing 'back-wash ileitis' in about 10% of cases.

Grossly, the characteristic feature is the continuous involvement of rectum and colon without any uninvolved skip areas as seen in Crohn's disease. The appearance of colon may vary depending upon the stage and intensity of the disease because of remissions and exacerbations. Mucosa shows linear and superficial ulcers, usually not penetrating the muscular layer. The intervening intact mucosa may form inflammatory 'pseudopolyps.' The muscle layer is thickened due to contraction, producing shortening and narrowing of the affected colon with loss of normal haustral folds giving 'garden-hose appearance'.

Histologicalty, ulcerative colitis because of remission and exacerbations, is characterised by alternating 'active disease process' and 'resolving colitis.' The changes in the 'active disease process' are as under:

1. Crypt distortion, cryptitis and focal accumulations of neutrophils forming crypt abscesses.
2. Marked congestion, dilatation and haemorrhages from mucosal capillaries.
3. Superficial mucosal ulcerations, usually not penetrating into the muscle coat, except in severe cases, and is accompanied by nonspecific inflammatory cell infiltrate of lymphocytes, plasma cells, neutrophils, some eosinophils and mast cells in the lamina propria.
4. Goblet cells are markedly diminished in cases of active disease.
5. Areas of mucosal regeneration and mucodepletion of lining cells.
6. In long-standing cases, epithelial cytologic atypia ranging from mild to marked dysplasia and sometimes developing into carcinoma-in-situ and frank carcinoma.

Complications of ulcerative colitis are as follows:

1. Toxic megacolon (Fulminant colitis) is the acute fulminating colitis in which the affected colon is thin-walled and dilated and is prone to perforation and faecal peritonitis. There is deep penetration of the inflammatory cell infiltrate into muscle layer which is disrupted.
2. Perianal fistula formation may occur rarely.

3. Carcinoma may develop in long-standing cases of ulcerative colitis of more than 10 years duration.

4. Stricture formation almost never occurs in ulcerative colitis.

OTHER INFLAMMATORY LESIONS OF THE BOWEL

Besides the IBD, a variety of other acute and chronic inflammatory conditions affect small bowel (enteritis), large bowel (colitis), or both (enterocolitis); the last named being more common. Hence, all these conditions involving small bowel and/or large bowel are described together here for better correlation of features.

The various other forms of inflammations of the bowel (besides IBD) can be categorised broadly into 'infective enterocolitis' and 'pseudomembranous enterocolitis.'

INFECTIVE ENTEROCOLITIS

These are a group of acute and chronic inflammatory lesions of small intestine and/or colon caused by microorganisms (bacteria, viruses, fungi, protozoa and helminths). All these are characterised by diarrhoeal syndromes. Pathogenetically speaking, these microorganisms can cause enterocolitis by 2 mechanisms— by enteroinvasive bacteria producing ulcerative lesions, and by enterotoxin-producing bacteria resulting in non-ulcerative lesions.

Some of the important forms are described below:

INTESTINAL TUBERCULOSIS

Intestinal tuberculosis can occur in 3 forms: primary, secondary and hyperplastic caecal tuberculosis.

1. Primary intestinal tuberculosis.

Though an uncommon disease in the Western world, primary tuberculosis of the ileocaecal region is quite common in India. It used to occur by ingestion of unpas-teurised cow's milk infected with Mycobacterium bovis. But nowadays due to control of tuberculosis in cattle and pasteurisation of milk, virtually all cases of intestinal tuberculosis are caused by M, tuberculosis. The predominant changes are in the mesenteric lymph nodes without any significant intestinal lesion.

Grossly, the affected lymph nodes are enlarged, matted and caseous (tabes mesenterica). Eventually, there is healing by fibrosis and calcification.

Microscopically, in the initial stage, there is primary complex or Ghon's focus in the intestinal mucosa. Subsequently, the mesenteric lymph nodes are affected which show typical tuberculous granulomatous inflammatory reaction with caseation necrosis. Tuberculous peritonitis may occur due to spread of the infection.

2. Secondary intestinal tuberculosis.

Swallowing of sputum in patients with active pulmonary tuberculosis may cause secondary intestinal tuberculosis, most commonly in the terminal ileum and rarely in the colon.

Grossly, the intestinal lesions are prominent than the lesions in regional lymph nodes as in secondary pulmonary tuberculosis. The lesions begin in the Peyer's patches or the lymphoid follicles with formation of small ulcers that spread through the lymphatics to form large ulcers which are transverse to the long axis of the bowel. These ulcers may be coated with caseous material. Serosa may be studded with visible tubercles. In advanced cases, transverse fibrous strictures and intestinal obstruction are seen.

Histologically, the tuberculous lesions in the intestine are similar to those observed elsewhere i.e. presence of tubercles. Mucosa and submucosa show ulceration and the muscularis may be replaced by variable degree of fibrosis. Tuberculous peritonitis may be observed.

3. Hyperplastic caecal tuberculosis. This is a variant of secondary tuberculosis secondary to pulmonary tuberculosis.

Grossly, the caecum and/or ascending colon are thick-walled with mucosal ulceration. Clinically, the lesion is palpable and may be mistaken for carcinoma.

Microscopically, the presence of caseating tubercles distinguishes the condition from Crohn's disease in which granulomas are non-caseating. Besides, bacteriological evidence by culture or animal inoculation and Mantoux test are helpful in differential diagnosis of the two conditions.

ENTERIC FEVER

The term enteric fever is used to describe acute infection caused by Salmonella typhi (typhoid fever) or Salmonella paratyphi (paratyphoid fever). Besides these 2 salmonellae, Salmonella typhimurium causes food poisoning.

Pathogenesis. The typhoid bacilli are ingested through contaminated food or water. During the initial asymptomatic incubation period of about 2 weeks, the bacilli invade the lymphoid follicles and Peyer's patches of the small intestine and proliferate. Following this, the bacilli invade the blood stream causing bacteraemia, and the characteristic clinical features of the disease like continuous rise in temperature and 'rose spots' on the skin are observed. Immunological reactions (Widal's test) begin after about 10 days and peak titres are seen by the end of the third week. Eventually, the bacilli are localised in the intestinal lymphoid tissue (producing typhoid intestinal lesions), in the mesenteric lymph nodes (leading to haemorrhagic lymphadenitis), in the liver (causing foci of parenchymal necrosis), in the gall bladder

(producing typhoid cholecystitis), and in the spleen (resulting in splenic reactive hyperplasia).

Pathologic changes. The lesions are observed in the intestines as well as in other organs.

1. *Intestinal lesions.* Macroscopically, terminal ileum is affected most often, but lesions may be seen in the jejunum and colon. The Peyer's patches show oval typhoid ulcers with their long axis along the length of the bowel. The base of the ulcers is black due to sloughed mucosa. The margins of the ulcers are slightly raised due to inflammatory oedema and cellular proliferation. There is never significant fibrosis and hence fibrous stenosis seldom occurs in healed typhoid lesions. The regional lymph nodes are invariably enlarged.

Microscopically, there is hyperaemia, oedema and cellular proliferation consisting of phagocytic histiocytes (showing characteristic erythrophagocytosis), lymphocytes and plasma cells. Though enteric fever is an example of acute inflammation, neutrophils are invariably absent from the cellular infiltrate and this is reflected in the leucopenia with neutropenia and relative lymphocytosis in the peripheral blood.

The main complications of the intestinal lesions of typhoid are perforation of the ulcers and haemorrhage.

2. *Other lesions.* Besides the intestinal involvement, various other organs and tissues showing pathological changes in enteric fever are:

i) Mesenteric lymph nodes—haemorrhagic lymphadenitis.
ii) Liver—foci of parenchymal necrosis,
iii) Gallbladder—typhoid cholecystitis,
iv) Spleen—splenomegaly with reactive hyperplasia.
v) Kidneys—nephritis.
vi) Abdominal muscles—Zenker's degeneration,
vii) Joints—arthritis,
viii) Bones—osteitis,
ix) Meninges—Meningitis.
x) Tesfz's—-Orchitis.

Persistence of organism in the gallbladder or urinary tract may result in passage of organisms in the faeces or urine creating a 'carrier state' which is a source of infection to others.

BACTERIAL FOOD POISONING

This is a form of acute bacterial illness that occurs following ingestion of food or water contaminated with bacteria other than those that cause specific acute intestinal infections like typhoid, paratyphoid, cholera or dysentery bacilli. The illness results from either bacterial invasion or bacterial toxi-

genic effect on the bowel. The commonest causes of bacterial food poisoning resulting in enteritis or enterocolitis are as under:

1. *Staphylococcal food poisoning.* Staphylococcus aureus infection acquired from contaminated food produces either mild food poisoning by enterotoxins, or may cause more severe form of the illness called pseudomembranous enterocolitis described below. Staphylococcal food poisoning occurs due to liberation of enterotoxins by the bacteria.

2. *Clostridial food poisoning.* Infection with anaerobic organisms Clostridium welchii, following consumption of contaminated meat results in acute food poisoning. The illness occurs both by bacterial invasion as well as by toxins.

3. *Botulism.* This is a severe form of paralysing illness caused by ingestion of organism, Clostridium botulinum, which produces neurotoxin.

4. *Salmonella food poisoning (Salmonellosis).* This is an infection (and not caused by toxins) occurring due to food contaminated by S. typhimurium or S. enteritidis. The condition manifests with fever, vomiting, and diarrhoea. Death may result from depletion of water and electrolytes.

DYSENTERIES

The term 'dysentery' is used to mean diarrhoea with abdominal cramps, tenesmus and passage of mucus in the stools, from any cause. There are 2 main forms of dysenteries — bacillary and amoebic.

1. Bacillary dysentery. Bacillary dysentery is the term used for infection by shigella species: S. dysenteriae, S. flexneri, S. boydii and S. sonnei. Infection occurs by foecooral route and is seen with poor personal hygiene, in densely populated areas, and with contaminated food and water. The common housefly plays a role in spread of infection.

Microscopically, the lesions are mainly found in the colon and occasionally in the ileum. Superficial trans-weise tikerations of mucosa of the bowel wall occur in the region of lymphoid follicles but perforation is seldom seen. The intervening intact mucosa is hyperaemic and oedematous. Following recovery from the acute attack, complete healing usually takes place. Microscopically, the mucosa overlying the lymphoid follicles is necrosed. The surrounding mucosa shows congestion, oedema and infiltration by neutrophils and lymphocytes. The mucosa may be covered by greyish-yellow 'pseudomembrane' composed of fibrino-suppurative exudate.

The complications of bacillary dysentery are haemorrhage, perforation, stenosis, polyarthritis and iridocyclitis.

2. Amoebic dysentery. This is due to infection by Entamoeba histolytica. It is more prevalent in the tropical countries and primarily affects the large intestine. Infection occurs from ingestion of cyst form of the parasite. The cyst wall is dissolved in the small intestine from where the liberated

amoebae pass into the large intestine. Here, they invade the epithelium of the mucosa, reach the submucosa and produce the characteristic flask-shaped ulcers.

Macroscopically, early intestinal lesions appear as small areas of elevation on the mucosal surface. In advanced cases, typical flask-shaped ulcers having narrow neck and broad base are seen. They are more conspicuous in the caecum, rectum and in the flexures.

Microscopically, the ulcerated area shows chronic inflammatory reaction consisting of lymphocytes, plasma cells, macrophages and eosinophils. The trophozoites of Entamoeba are seen in the inflammatory exudate and are concentrated at the advancing margin of the lesion. Intestinal amoebae characteristically have ingested red cells in their cytoplasm. Oedema and vascular congestion are present in the area surrounding the ulcers.

Complications of intestinal amoebic ulcers are: amoebic liver abscess or amoebic hepatitis, perforation, haemorrhage and formation of amoeboma which is a tumour-like mass.

PSEUDOMEMBRANOUS ENTEROCOLITIS (ANTIBIOTIC-ASSOCIATED DIARRHOEA)

Pseudomembranous enterocolitis is a form of acute inflammation of colon and/or small intestine characterised by formation of 'pseudomembrane' over the site of mucosal injury.

Etiology. Numerous studies have established the overgrowth of Clostridium difficile with production of its toxin in the etiology of antibiotic-associated diarrhoea culminating in pseudomembranous colitis. Oral antibiotics such as clindamycin, ampicillin and the cephalosporins are more often (20%) associated with antibiotic-associated diarrhoea, while development of pseudomembranous colitis may occur in 1-10% cases. Pseudomembrane formation may also occur in various other conditions such as in:

- Staphylococcal enterocolitis
- Bacillary (Shigella) dysentery
- Candida enterocolitis

Pathologic changes. Macroscopically, the lesions may be confined, to the large intestine or small intestine, or both may be involved. The mucosa of the bowel is covered by patchy, raised yellow-white plaques. Elsewhere, the mucosa is congested and may show small mucosal ulcerations. Microscopically, the 'pseudomembrane' is composed of network of fibrin and mucus, in which are entangled inflammatory cells and mucosal epithelial cells. There is focal necrosis of surface epithelial cells. The lamina propria contains inflammatory cell infiltrate, mainly neutrophils. The submucosa has congested capillaries and may show micrpthrombi. The inflammation spreads laterally rather than deeply.

INTESTINAL OBSTRUCTION

Conditions which interfere with the propulsion of contents in the intestine are considered under the heading of intestinal obstruction. The causes of intestinal obstruction can be classified under the following 3 broad groups:

1. Mechanical obstruction. It can occur as a result of the following causes:

i) *Internal obstruction* (in the wall or the lumen) such as due to:

- inflammatory strictures (e.g. crohn's disease),
- congenital stenosis, atresia, imperforate anus,
- tumours,
- meconium in mucoviscidosis,
- roundworms,
- gallstones, faecoliths, foreign bodies,
- ulceration induced by potassium chloride tablets prescribed to counter hypokalaemia.

ii) *External compression* such as from:

- peritoneal adhesions and bands,
- strangulated hernias,
- intussusception,
- volvulus,
- intra-abdominal tumour.

2. Neurogenic obstruction. It occurs due to paralytic ileus i.e. paralysis of muscularis of the intestine as a result of shock after abdominal operation or by acute peritonitis.

3. Vascular obstruction. Obstruction of the superior mesenteric artery or its branches may result in infarction causing paralysis. The causes are thrombosis, embolism, accidental ligation.

Out of the various causes listed above, conditions producing external compression on the bowel wall are the most common cause of intestinal obstruction (80%). Some of these are described below.

Peritoneal Adhesions and Bands

Adhesions and bands in the peritoneum composed of fibrous tissue result following healing in peritonitis. Rarely, such fibrous adhesions and bands may be without any preceding peritoneal inflammation and are of congenital origin. In either case, peritoneal bands and adhesions result in partial or complete intestinal obstruction by outside pressure on the bowel wall.

Hernias

Hernia is protrusion of portion of a viscus through an abnormal opening in the wall of its natural cavity.

- **External hernia** is the protrusion of the bowel through a defect or weakness in the peritoneum.

• **Internal hernia** is the term applied for herniation that does not present on the external surface.

Two major factors involved in the formation of a hernia are:

i) *Local weakness* which may be congenital e.g. at the umbilicus, inguinal and femoral canals, and in surgical scars called 'incisional hernia'.

ii) *Increased intra-abdominal pressure* that is produced by coughing, straining and exertion.

Inguinal hernias are more common, followed in decreasing frequency, by femoral and umbilical hernias. Inguinal hernias may be:

• **Direct** when hernia passes medial to the inferior epigastric artery and it appears through the external abdominal ring; and

• **Indirect** when it follows the inguinal canal lateral to the inferior epigastric artery.

When the contents of hernia such as loop of intestine can be returned to the abdominal cavity, it is called *reducible.* When it is not possible to reduce hernia due to large contents or due to adhesions in the hernial sac, it is referred to as *irreducible.*

When the blood flow in the hernial sac is obstructed, it results in *strangulated hernia.* Obstruction to the venous drainage and arterial supply may result in infarction or gangrene of the affected loop of intestine. The gross and microscopic appearance of strangulated intestine is the same as that of infarction of intestine.

Intussusception

Intussusception is the telescoping of a segment of intestine into the segment below due to peristalsis. The telescoped segment is called the *intussusceptum* and lower receiving segment is called the *intussuscipiens.* The condition occurs more commonly in infants and young children, more often in the ileocaecal region when the portion of ileum invaginates into the ascending colon without affecting the position of the ileocaecal valve. Less common forms are ileo-ileal and colo-colic intussusception.

In children, the cause is usually not known though enlargement of the lymphoid tissue in the terminal ileum has been suggested by some. In the case of adults, the usual causes are foreign bodies and tumours.

The main *complications* of intussusception are intestinal obstruction, infarction, gangrene, perforation and peritonitis.

Volvulus

Volvulus is the twisting of loop of intestine upon itself through 180° or more. This leads to obstruction of the intestine as well as cutting off of the blood supply to the affected loop. The usual causes are bands and adhesions (congenital or acquired) and long mesenteric attachment. The condition is more common in the sigmoid colon than the small bowel.

LIVER DISEASES

The liver is the largest organ in the body weighing 1400-1600 gm in the males and 1200-1400 gm in the females. There are 2 main anatomical lobes – right and left, the right being about six times the size of the left lobe. The right lobe has quadrate lobe on its inferior surface and a caudate lobe on the posterior surface. The right and left lobes are separated anteriorly by a fold of peritoneum called the *falciform ligament,* inferiorly by the fissure for the *ligamentum teres*, and posteriorly by the fissure for the *ligamentum venosum*.

The *port a hepatis* is the region on the inferior surface of the right lobe where blood vessels, lymphatics and common hepatic duct form the hilum of the liver. A firm smooth layer of connective tissue called *Glisson's capsule* encloses the liver and is continuous with the connective tissue of the porta hepatis forming a sheath around the structures in the porta hepatis. The liver has a double blood supply – the portal vein brings the venous blood from the intestines and spleen, and the hepatic artery coming from the coeliac axis supplies arterial blood to the liver. This dual blood supply provides sufficient protection against infarction in the liver.

The portal vein and hepatic artery divide into branches to the right and left lobes in the porta. The right and left hepatic ducts also join in the porta to form the common hepatic duct. The venous drainage from the liver is into the right and left hepatic veins which enter the inferior vena cava. Lymphatics and the nerve fibres accompany the hepatic artery into their branchings and terminate around the porta hepatis.

The hepatic parenchyma is composed of numerous hexagonal or pyramidal *classical lobules;* each with a diameter of 0.5 to 2 mm. Each classical lobule has a central tributary from the hepatic vein and at the periphery are 4 to 5 portal tracts or triads containing branches of bile duct, portal vein and hepatic artery. Cords of hepatocytes and blood-containing sinusoids radiate from the central vein to the peripheral portal triads. The *functioning lobule* or *liver acinus* as described by Rappaport has a portal triad in the centre and is surrounded at the periphery by portions of several classical lobules. However, in most descriptions on pathology of the liver, the term *lobule* is used in its classical form.

The blood supply to the liver parenchyma flows from the portal triads to the central veins. Accordingly, the hepatic parenchyma of liver lobule is divided into 3 zones:

- Zone 1 or the *periportal (peripheral) area* is closest to the arterial and portal blood supply and hence bears the brunt of all forms of toxic injury.
- Zone 3 or the *centrilobular area* surrounds the central vein and is most remote from the blood supply and thus suffers from the effects of hypoxic injury.
- Zone 2 is the intermediate *midzonal area.*

The hepatocytes are polygonal cells with a round single nucleus and a prominent nucleolus. The liver cells have a remarkable capability to undergo mitosis and regeneration. Thus it is not uncommon to find liver cells containing more than one nuclei and having polyploidy up to octoploidy. A hepatocyte has 3 surfaces: *one* facing the sinusoid and space of Disse, the *second* facing the canaliculus, and the *third* facing neighbouring hepatocytes.

The blood-containing *sinusoids* between cords of hepatocytes are lined by discontinuous endothelial cells and scattered flat Kupffer cells belonging to the reticuloendothelial system.

The *space of Disse* is the space between hepatocytes and sinusoidal lining endothelial cells. A few scattered fat storing *Ito cells* lie within the space of Disse.

The *portal triad or tract* besides containing portal vein radicle, the hepatic arteriole and bile duct, has a few mononuclear cells and a little connective tissue considered to be extension of Glisson's capsule. The portal triads are surrounded by a limiting plate of hepatocytes.

The *intrahepatic biliary system* begins with the bile canaliculi interposed between the adjacent hepatocytes.

The bile canaliculi are simply grooves between the contact surfaces of the liver cells and are covered by microvilli. These canaliculi join at the periphery of the lobule to drain eventually into terminal bile ducts or ductules (canal of Hering) which are lined by cuboidal epithelium.

JAUNDICE

Jaundice or icterus refers to the yellow pigmentation of the skin or sclerae by bilirubin. Bilirubin pigment has high affinity for elastic tissue and hence jaundice is particularly noticeable in tissues rich in elastin content. Jaundice is the result of elevated levels of bilirubin in the blood termed hyperbilirubinaemia. Normal serum bilirubin concentration ranges from 0.2-0.8 mg/ dl, about 80% of which is unconjugated. Jaundice becomes clinically evident when the total serum bilirubin exceeds 2 mg/dl. A rise of serum bilirubin between the normal and 2 mg/dl is generally not accompanied by visible jaundice and is called *latent jaundice.*

Before considering the features and types of jaundice, it is essential to review the normal bilirubin metabolism.

Classification and features of jaundice

Based on pathophysiology, jaundice may result from one or more of the following mechanisms:

1. Increased bilirubin production,
2. Decreased hepatic uptake,
3. Decreased hepatic conjugation,
4. Decreased excretion of bilirubin into bile Accordingly, a simple classification of jaundice is into 3 predominant types: *pre-hepatic (haemolytic), hepatic*, and *post-hepatic cholestatic*. Hyperbilirubinaemia due to first three mechanisms is *mainly unconjugated* while the last variety yields *mainly conjugated* hyperbilirubinaemia. A simple test to determine whether hyperbilirubinaemia is of unconjugated or conjugated variety is to determine whether bilirubin is present in urine or not; its absence in urine suggests unconjugated hyperbilirubinaemia since unconjugated bilirubin is not filtered by the glomerulus. The presence of bilirubin in the urine is evidence of conjugated hyperbilirubinaemia. Based on these mechanisms, the pathogenesis and main features of the two predominant forms of hyperbilirubinaemia are discussed below.

Predominantly Unconjugated Hyperbilirubinaemia

This form of jaundice can result from the following three sets of conditions:

1. Increased Bilirubin Production (Haemolytic, Acholuric Or Prehepatic Jaundice). This results from excessive red cell destruction as occurs in intra- and extravascular haemolysis or due to ineffective erythropoiesis. There is increased release of haemoglobin from excessive breakdown of red

cells that leads to overproduction of bilirubin. Hyperbilirubinaemia develops when the capacity of the liver to conjugate large amount of bilirubin is exceeded. In premature infants, the liver is deficient in enzyme necessary for conjugation while the rate of red cell destruction is high. This results in *icterus neonatorum* which is particularly severe in haemolytic disease of the newborn due to maternal isoantibodies. Since there is predominantly unconjugated hyperbilirubinaemia in such cases, there is danger of permanent brain damage in these infants when the serum level of unconjugated bilirubin exceeds 15 mg/dl.

Laboratory data in haemolytic jaundice, in addition to predominant unconjugated hyperbilirubinaemia, reveal normal serum levels of transaminases, alkaline phosphatase and proteins. Bile pigment being unconjugated type is absent from urine (acholuric jaundice). However, there is dark brown colour of stools due to excessive faecal excretion of bile pigment and increased urinary excretion of urobilinogen.

2. Decreased Hepatic Uptake. The uptake of bilirubin by the hepatocyte that involves dissociation of the pigment from albumin and its binding to cytoplasmic protein, ligandin, may be deranged in certain conditions e.g. due to drugs, prolonged starvation and sepsis.

3. Decreased Bilirubin Conjugation. This mechanism involves deranged hepatic conjugation due to defect or deficiency of the enzyme, glucuronosyl transferase. This can occur in certain inherited disorders of the enzyme (e.g. Gilbert's syndrome and Crigler-Najjar syndrome), or acquired defects in its activity (e.g. due to drugs, hepatitis, cirrhosis). However, hepatocellular damage causes deranged excretory capacity of the liver more than its conjugating capacity *(see below).* The physiologic neonatal jaundice is also partly due to relative deficiency of UDP-glucuronosyl transferase in the neonatal liver and is partly as a result of increased rate of red cell destruction in neonates.

II. Predominantly Conjugated Hyperbilirubinaemia (Cholestasis)

This form of hyperbilirubinaemia is defined as failure of normal amounts of bile to reach the duodenum. Morphologically, cholestasis means accumulation of bile in liver cells and biliary passages. The defect in excretion may be within the biliary canaliculi of the hepatocyte and in the microscopic bile ducts *(intrahepatic cholestasis or medical jaundice),* or there may be mechanical obstruction to the extrahepatic biliary excretory apparatus *(extrahepatic cholestasis or obstructive jaundice).* It is important to distinguish these two forms of cholestasis since extrahepatic cholestasis or obstructive jaundice is often treatable with surgery, whereas the intrahepatic cholestasis or medical jaundice cannot be benefitted by surgery but may in fact worsen by the operation. Prolonged cholestasis of either of the two types may progress to biliary cirrhosis.

1. Intrahepatic Cholestasis. Intrahepatic cholestasis is due to impaired hepatic excretion of bile and may occur from hereditary or acquired disorders.

i) Hereditary disorders producing intrahepatic obstruction to biliary excretion are characterised by *'pure cholestasis'* e.g. in Dubin-Johnson syndrome, Rotor syndrome, fibrocystic disease of pancreas, benign familial recurrent cholestasis, intrahepatic atresia and cholestatic jaundice of pregnancy.

ii) Acquired disorders with intrahepatic excretory defect of bilirubin are largely due to hepatocellular diseases and hence are termed *'hepatocellular cholestasis'* e.g. in viral hepatitis, alcoholic hepatitis, and drug-induced cholestasis such as from administration of chlorpromazine and oral contraceptives.

The features of intrahepatic cholestasis include: predominant conjugated hyperbilirubinaemia due to regurgitation of conjugated bilirubin into blood, bilirubinuria, elevated levels of serum bile acids and consequent pruritus, elevated serum alkaline phosphatase, hyperlipidaemia and hypoprothrombinaemia. 'Pure cholestasis' can be distinguished from 'hepatocellular cholestasis' by elevated serum levels of transaminases in the latter due to liver cell injury.

Liver biopsy in cases with intrahepatic cholestasis reveals milder degree of cholestasis than the extra-hepatic disorders. The biliary canaliculi of the hepatocytes are dilated and contain characteristic elongated green-brown *bile plugs.* The cytoplasm of the affected hepatocytes shows feathery degeneration. Canalicular bile stasis eventually causes proliferation of intralobular ductules followed by periportal fibrosis and produces a picture resembling biliary cirrhosis.

2. Extrahepatic Cholestasis. Extrahepatic cholestasis results from mechanical obstruction to large bile ducts outside the liver or within the porta hepatis. The common causes are gallstones, inflammatory strictures, carcinoma head of pancreas, tumours of bile duct, sclerosing cholangitis and congenital atresia of extrahepatic ducts. The obstruction may be complete and sudden with eventual progressive obstructive jaundice, or the obstruction may be partial and incomplete resulting in intermittent jaundice.

The features of extrahepatic cholestasis (obstructive jaundice), like in intrahepatic cholestasis, are predominant conjugated hyperbilirubinaemia, bilirubinuria, elevated serum bile acids causing intense pruritus, high serum alkaline phosphatase and hyperlipidaemia. However, there are certain features which help to distinguish extrahepatic from intrahepatic cholestasis. In obstructive jaundice, there is malabsorption of fat-soluble vitamins (A, D, E and K) and steatorrhoea resulting in vitamin K deficiency. Prolonged prothrombin time in such cases shows improvement following parenteral administration of vitamin K, whereas hypo-prothrombinemia due to hepatocellular disease shows no such improvement in prothrombin time with vitamin K administration. The stools of such patients are clay-coloured due to absence of bilirubin metabolite, stercobil-

in, in faeces and there is virtual disappearance of urobilinogen from the urine. These patients may have fever due to high incidence of ascending bacterial infections (ascending cholangitis).

Liver biopsy in cases with extrahepatic cholestasis shows more marked changes of cholestasis. Since the obstruction is in the extrahepatic bile ducts, there is progressive retrograde extension of bile stasis into intrahepatic duct system. This results in dilatation of bile ducts and rupture of canaliculi with extravasation of bile producing *bile lakes.* Since bile is toxic, the regions of bile lakes are surrounded by focal necrosis of hepatocytes. Stasis of bile predisposes to ascending bacterial infections with accumulation of polymorphs around the dilated ducts (ascending cholangitis). Eventually, there is proliferation of bile ducts and the appearance may mimic biliary cirrhosis.

NEONATAL JAUNDICE

Jaundice appears in neonates when the total serum bilirubin is more than 3 mg/dl. It may be the result of unconjugated or conjugated hyperbilirubinaemia; the former being more common. Important causes of neonatal jaundice. Some of these conditions are considered below, while others are discussed elsewhere in the relevant sections.

HEREDITARY NON-HAEMOLYTIC HYPERBILIRUBINAEMIAS

Hereditary non-haemolytic hyperbilirubinaemias are a small group of uncommon familial disorders of bilirubin metabolism when haemolytic causes have been excluded. The commonest is Gilbert's syndrome; others are Crigler-Najjar syndrome, Dubin-Johnson syndrome, Rotor's syndrome and benign familial recurrent cholestasis. The features common to all these conditions are presence of icterus but almost normal liver function tests and no well-defined morphologic changes except in Dubin-Johnson syndrome. Gilbert's syndrome and Crigler-Najjar syndrome are examples of *liereditary non-haemolytic unconjugated hyperbilirubinaemia,* whereas Dubin-Johnson syndrome, Rotor's syndrome and benign familial recurrent cholestasis are conditions with *hereditary conjugated hyperbilirubinaemia.*

Gilbert's Syndrome

This is the commonest of the familial, genetically-determined diseases of the liver affecting 2-5% of the population. Gilbert's syndrome is characterised by mild, benign, unconjugated hyperbilirubinaemia (serum bilirubin 1-5 mg/dl) which is not due to haemolysis. The condition is inherited as an autosomal dominant character. The defect in bilirubin metabolism is complex and appears to be reduced activity of UDP-glucuronosyl transferase with decreased conjugation, or an impaired hepatic uptake of bilirubin. The jaundice is usually mild and intermittent. There are no morphologic abnormalities in the liver except some increased lipofuscin pigment in centrilobular hepato-

cytes. The prognosis of patients with Gilbert's syndrome is excellent, though chronic jaundice persists throughout life.

Crigler-Najjar Syndrome

Crigler-Najjar syndrome is a rare form of familial non-haemolytic jaundice with very high *unconjugated hyperbilirubinaemia*. There are 2 forms of this condition: type I and type II.

Type I Crigler-Najjar syndrome. This is inherited as an autosomal recessive disorder. There is complete absence of conjugating enzyme UDP-glucuronosyl transferase in the hepatocytes and hence no conjugated bilirubin is formed. There is extreme elevation of unconjugated bilirubin (usually more than 20 mg/dl) with high risk of developing permanent CNS damage from kernicterus. The prognosis is generally fatal, with death coming from kernicterus usually in the first year of life. There are no significant morphologic changes except some canalicular stasis.

Type II Crigler-Najjar syndrome. This is inherited as an autosomal dominant disease. There is deficiency of enzyme UDP-glucuronosyl transferase but not complete absence. Thus, unconjugated hyperbilirubinaemia is generally mild to moderate (usually less than 20 mg/dl). Occurrence of kernicterus is exceptional and patients respond well to phenobarbital therapy. There are no morphologic changes in the liver.

Dubin-Johnson Syndrome

Dubin-Johnson syndrome is autosomal recessive disorder characterised by predominant *conjugated hyperbilirubinaemia* (usually less than 5 mg/dl) with genetic defect in canalicular excretion of conjugated bilirubin. The condition differs from other forms of hereditary hyperbilirubinaemias in producing grossly greenish-black pigmented liver. The hepatocytes show dark-brown, melanin-like pigment in the cytoplasm, the exact nature of which is obscure but it is neither iron nor bile. Unrelated viral hepatitis mobilises the hepatic pigment of Dubin-Johnson syndrome leading to its excretion in urine but the pigment reappears after recovery from viral hepatitis. A prolonged BSP dye excretion test is diagnostic of Dubin-Johnson syndrome. The disease runs a benign course and does not interfere with life.

Rotor's Syndrome

This is another form of familial *conjugated hyperbilirubinaemia* with mild chronic jaundice but differs from Dubin-Johnson syndrome in having no brown pigment in the liver cells. The disease is inherited as an autosomal recessive character. Rotor's syndrome has an excellent prognosis.

NEONATAL HEPATITIS

Neonatal hepatitis, also termed giant cell hepatitis or neonatal hepatocellular cholestasis, is a general term used for the constant morphologic

change seen in conjugated hyperbilirubinaemia as a result of known infectious and metabolic causes may have an idiopathic etiology. The 'idiopathic' neonatal hepatitis is more common and accounts for 75% of cases. Though all the cases with either known etiologies or idiopathic type are grouped together under neonatal hepatitis, all of them are not necessarily inflammatory conditions, thus belying their nomenclature as 'hepatitis'. The condition usually presents in the first week of birth with jaundice, bilirubinuria, pale stools and high serum alkaline phosphatase.

Pathologic changes. Irrespective of the etiology, there is morphologic similarity in all these cases. The histologic features are:

1. Loss of normal lobular architecture of the liver.
2. Presence of prominent multinucleate giant cells derived from hepatocytes.
3. Mononuclear inflammatory cell infiltrate in the portal tracts with some periportal fibrosis.
4. Haemosiderosis.
5. Cholestasis in small proliferated ductules in the portal tract and between necrotic liver cells.

BILIARY ATRESIAS

Biliary atresias, also called as *infantile cholangiopathies,* are a group of intrauterine developmental abnormalities of the biliary system. Though they are often classified as congenital, the abnormality of development in most instances is extraneous infection during the intrauterine development or shortly after birth that brings about inflammatory destruction of the bile ducts. The condition may, therefore, have various grades of destruction ranging from complete absence of bile ducts termed *atresia,* to reduction in their number called *paucity of bile ducts.*

Depending upon the portion of biliary system involved, biliary atresias may be extrahepatic or intrahepatic.

Extrahepatic Biliary Atresia

The extrahepatic bile ducts fail to develop normally so that in some cases the bile ducts are *absent* at birth, while in others the ducts may have been formed but start undergoing sclerosis in the perinatal period. It is common to have multiple defects and other congenital lesions. Extrahepatic biliary atresia is found in 1 per 10,000 livebirths. Cholestatic jaundice appears by the first week after birth. The baby has severe pruritus, pale stools, dark urine and elevated serum transa-minases. In some cases, the condition is correctable by surgery, while in vast majority the atresia is not correctable and in such cases hepatic portoenterostomy (Kasai procedure) or hepatic transplantation must be considered. Death is usually due to intercurrent infection, liver failure, and

bleeding due to vitamin K deficiency or oesophageal varices. Cirrhosis and ascites are late complications appearing within 2 years of age.

Pathologic changes. *Grossly,* the liver is enlarged and dark green. The atretic segments of biliary system are reduced to cord-like structures. *Histologically,* the condition must be distinguished from idiopathic neonatal hepatitis as surgical treatment is possible in extrahepatic biliary atresia but not in the latter. Besides, the α-l antitrypsin deficiency also produces similar appearance in liver biopsy. The main histologic features are:

1. Inflammation and fibrous obliteration of the extrahepatic ducts with absence of bile in them.
2. Ductular proliferation and periductular inflammation.
3. Cholestasis and bile thrombi in the portal area.
4. Periportal fibrosis and later secondary biliary cirrhosis (page 606).
5. Transformation of hepatic parenchyma to neonatal (giant cell) hepatitis in 15% of cases.

Intrahepatic Biliary Atresia

Intrahepatic biliary atresia is characterised by biliary hypoplasia so that there is *paucity of bile ducts* rather than their complete absence. The condition probably has its origin in viral infection acquired during intra-uterine period or in the neonatal period. Cholestatic jaundice usually appears within the first few days of birth and is characterised by high serum bile acids with associated pruritus, and hypercholesterolaemia with appearance of xanthomas by first year of life. Hepatic as well as urinary copper concentrations are elevated. In some cases, intrahepatic biliary atresia is related to α-1-antitrypsin deficiency.

Pathologic changes. The microscopic features are:

1. Paucity of intrahepatic bile ducts.
2. Cholestasis.
3. Increased hepatic copper.
4. Inflammation and fibrosis in the portal area, eventually leading to cirrhosis.

REYE'S SYNDROME

Reye's syndrome is defined as an acute postviral syndrome of encephalopathy and fatty change in the viscera. The syndrome may follow almost any known viral disease but is most common after influenza A or B and varicella. Viral infection may act singly, or more often its effect is modified by certain exogenous factors such as by administration of salicylates, aflatoxins and insecticides. These effects cause mitochondrial injury and decreased activity of mitochondrial enzymes in the liver. This eventually leads to rise in blood ammonia and accumulation of triglycerides within hepatocytes. The patients

are generally children between 6 months and 15 years of age. Within a week after a viral illness, the child develops intractable vomiting and progressive neurological deterioration due to encephalopathy, eventually leading to stupor, coma and death. Characteristic laboratory findings are elevated blood ammonia, serum transaminases, bilirubin and prolonged prothrombin time.

Pathologic changes. *Grossly,* the liver is enlarged and yellowish-orange. *Microscopically,* the hepatocytes show small droplets of neutral fat in their cytoplasm (microvesicular fat). Similar fatty change is seen in the renal tubular epithelium and in the cells of skeletal muscles and heart. The brain shows oedema and sometimes focal necrosis of neurons.

HEPATIC FAILURE

Though the liver has a marked regenerative capacity and a large functional reserve, hepatic failure may develop from severe acute and fulminant liver injury with massive necrosis of liver cells *(acute hepatic failure),* or from advanced chronic liver disease *(chronic hepatic failure).* Acute hepatic failure develops suddenly with severe impairment of liver functions whereas chronic liver failure comes insidiously. The prognosis is much worse in acute hepatic failure than that in chronic liver failure.

Etiology. The two types of hepatic failure result from different causes:

• **Acute (fulminant) hepatic failure** occurs most frequently in severe viral hepatitis. Other causes are hepatotoxic drug reactions (e.g. anaesthetic agents, nonsteroidal anti-inflammatory drugs, antidepressants), carbon tetrachloride poisoning, acute alcoholic hepatitis, mushroom poisoning and pregnancy complicated with eclampsia.

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

Manifestations. In view of the diverse functions performed by the liver, the syndrome of acute or chronic hepatic failure produces complex manifestations. The major manifestations are briefly discussed below.

1. Jaundice. Jaundice usually reflects the severity of liver cell damage since it occurs due to failure of liver cells to metabolise bilirubin. In acute failure such as in viral hepatitis, jaundice nearly parallels the extent of liver cell damage, while in chronic failure such as in cirrhosis jaundice appears late and is usually of mild degree.

2. Hepatic encephalopathy (Hepatic coma). Neuro-psychiatric syndrome may complicate liver disease of both acute and chronic types. The features include disturbed consciousness, personality changes, intellectual deterioration, low slurred speech, flapping tremors, and finally, coma and death. The genesis of CNS manifestations in liver disease is considered to be by

toxic products not metabolised by diseased liver. The toxic products may be ammonia and other nitrogenous substances from intestinal bacteria which reach the systemic circulation without detoxification in the damaged liver and thus damage the brain. Advanced cases of hepatic coma have poor prognosis but may respond favourably to hepatic transplantation.

3. Hyperkinetic circulation. All forms of hepatic failure are associated with a hyperkinetic circulation characterised by peripheral vasodilatation, increased splanchnic blood flow and increased cardiac output. There is increased splenic flow but reduced renal blood flow resulting in impaired renal cortical perfusion. These changes result in tachycardia, low blood pressure and reduced renal function.

4. Hepatorenal syndrome. The hepatorenal syndrome is a complication of both acute and chronic hepatic failure in which acute renal failure occurs in the absence of clinical, laboratory or morphologic evidence of other causes of renal dysfunction. The acute renal failure is usually associated with oliguria and uraemia but with good tubular function. The histology of kidney is virtually normal, suggesting functional defect for the renal failure. The pathogenesis of the syndrome is unclear but appears to be initiated by effective reduction of the renal blood flow (effective hypovolaemia) as a consequence of systemic vasodilatation and pooling of blood in portal circulation. The renal failure in the hepatorenal syndrome is reversible with improvement in hepatic function.

Diagnosis of hepatorenal syndrome should be made only after excluding other causes producing concomitant damage to both the organs, circulatory failure leading to acute tubular necrosis and other forms of reversible tubular damage.

5. Hepatopulmonary syndrome. The pulmonary changes in chronic hepatic failure such as in cirrhosis consist of pulmonary vasodilatation with intrapulmonary arteriovenous shunting. This results in ventilation-perfusion inequality that may lead to impaired pulmonary function, clubbing of fingers and sometimes cyanosis.

6. Coagulation defects. Impaired synthesis of a number of coagulation factors by the diseased liver may result in coagulation disorders. These include disseminated intravascular coagulation (consumption coagulopathy), thrombocytopenia and presence of fibrin degradation products in the blood.

7. Ascites and oedema. Chronic liver failure due to cirrhosis may result in portal hypertension and ascites. Decreased synthesis of albumin by the liver resulting in hypoproteinemia and consequent fall in plasma oncotic pressure, increased hydrostatic pressure due to portal hypertension and secondary hyperaldosteronism, contribute to the development of ascites and oedema in these patients.

8. Endocrine changes. Endocrine changes may be found in association with chronic hepatic failure. The changes are more common in alcoholic cirrhosis in active reproductive life. In the male, the changes are towards feminisation such as gynaecomastia and hypogonadism. In the female, the changes are less towards masculinisation but atrophy of gonads and breasts occurs. The underlying mechanism appears to be changed end-organ sensitiveness to sex hormones in cirrhosis.

9. Skin changes. In alcoholic cirrhosis *'arterial spiders'* having radiating small vessels from a central arteriole are frequent in the vascular region drained by superior vena cava such as in the neck, face, forearms and dorsum of hands. Less frequently, *palmar erythema,* especially in the hypothenar and thenar eminences and on the pulps of the fingers, is observed in chronic liver disease.

10. Foetor hepaticus. A sweetish pungent smell of the breath is found in severe cases of acute and chronic hepatocellular diseases. It appears to be of intestinal origin, possibly due to failure of the liver to detoxify sulfur-containing substances absorbed from the gut.

CIRCULATORY DISTURBANCES

Vascular disorders of general nature involving the liver such as chronic passive congestion and infarction have already been discussed elsewhere. Hepatic and portal venous obstruction and hepatic arterial obstruction are considered here.

1. Hepatic Venous Obstruction

The central veins of lobules of the liver are tributaries of the hepatic veins. In the normal liver, there are no anastomoses between hepatic vein and portal vein but in cirrhotic liver there are such anastomoses. Normal pressure in the free hepatic vein is about 6 mmHg.

Two uncommon diseases produced by obstruction of the hepatic veins are Budd-Chiari syndrome (hepatic vein thrombosis) and hepatic veno-occlusive disease.

Budd-Chiari Syndrome (Hepatic Vein Thrombosis)

Budd-Chiari syndrome in its pure form consists of slowly developing thrombosis of the hepatic veins and the adjacent inferior vena cava, while some workers include hepatic veno-occlusive disease in this syndrome.

Etiology. The etiology of hepatic venous thrombosis in about a third of cases is unknown (idiopathic), while in the remaining cases various causes associated with increased thrombotic tendencies are attributed such as due to polycythaemia vera, paroxysmal nocturnal haemoglobinuria, oral contraceptives, pregnancy, post-partum state, intra-abdominal cancers (e.g. hepatocellular carcinoma), chemotherapy, radiation and myeloproliferative diseases. Formation of membranous webs. probably congenital or as a consequence of

organised thrombosis, in the suprahepatic portion of inferior vena cava is another important cause.

Pathologic changes. *Grossly,* the liver is enlarged, swollen, red-purple and has a tense capsule.

Histologicallly, the changes in sudden hepatic vein occlusion are those of centrilobular congestion, necrosis and rupture of sinusoids into the space of Disse. In slowly developing thrombosis, the changes are more chronic and include fibrosing reaction in the centrilobular zone that may progress to cardiac cirrhosis.

Clinical features. Budd-Chiari syndrome is clinically characterised by either an acute form or chronic form depending upon the speed of occlusion.

• In the *acute form,* the features are abdominal pain, vomiting, enlarged liver, ascites and mild icterus.

• In the more usual *chronic form,* the patients present with pain over enlarged tender liver, ascites and other features of portal hypertension. The acute form of illness leads to acute hepatic failure and death, whereas in chronic form the patient may live for months to a few years.

Hepatic Veno-Occlusive Disease

Hepatic veno-occlusive disease consists of intimal thickening, stenosis and obliteration of the terminal central veins and medium-sized hepatic veins. The venous occlusion results in pathologic changes similar to those of Budd-Chiari syndrome and can be distinguished from the latter by demonstration of absence of thrombosis in the major hepatic veins.

The cause and stimulus for hepatic veno-occlusive disease are obscure. The condition is more widespread in countries such as Africa, India and certain other tropical countries where 'bush tea' (medicinal tea) is consumed that contains hepatotoxic alkaloids. More recently, the disease has been found in association with administration of antineoplastic drugs and immunosuppressive therapy.

II. Portal Venous Obstruction

Obstruction of the poral vein may occur within the intrahepatic course or in extrahepatic site.

• **Intrahepatic cause** of portal venous occlusion is hepatic cirrhosis as the commonest and most important, followed in decreasing frequency by tumour invasion, congenital hepatic fibrosis and schistosomiasis.

• **Extrahepatic causes** of portal vein obstruction are intra-abdominal cancers, intra-abdominal sepsis, direct invasion by tumour, myeloproliferative disorders and upper abdominal surgical procedure followed by thrombosis.

The effects of portal venous obstruction depend upon the site of obstruction. The most important effect, irrespective of the site of occlusion or cause, is portal hypertension and its manifestations. If the obstruction is in the

extrahepatic portal vein along with extension of occlusion into splenic vein, it may result in venous infarction of the bowel. Pylephlebitis may be followed by multiple pyaemic liver abscesses.

III. Hepatic Arterial Obstruction

Diseases from obstruction of the hepatic artery are uncommon. Rarely, accidental ligation of the main hepatic artery or its branch to right lobe may be followed by fatal infarction. Obstruction of the small intrahepatic arterial banches usually does not produce any effects because of good collateral circulation.

LIVER CELL NECROSIS

All forms of injury to the liver such as microbiologic, toxic, circulatory or traumatic, result in necrosis of liver cells. The extent of involvement of hepatic lobule in necrosis varies. Accordingly, liver cell necrosis is divided into 3 types: *diffuse* (submassive to massive), *zonal* and *focal*

1. Diffuse (Submassive To Massive) Necrosis. When there is extensive and diffuse necrosis of the liver involving all the cells in groups of lobules, it is termed diffuse, or submassive to massive necrosis. It is most commonly caused by viral hepatitis or drug toxicity.

2. Zonal Necrosis. Zonal necrosis is necrosis of hepatocytes in 3 different zones of the hepatic lobule. Accordingly, it is of 3 types; each type affecting respective zone is caused by different etiologic factors:

i) Centrilobular necrosis is the commonest type involving hepatocytes in zone 3 (i.e. located around the central vein). Centrilobular necrosis is characteristic feature of ischaemic injury such as in shock and CHF since zone 3 is farthest from the blood supply. Besides, it also occurs in poisoning with chloroform, carbon tetra-chloride and certain drugs.

ii) Midzonal necrosis is uncommon and involves zone 2 of the hepatic lobule. This pattern of necrosis is seen in yellow fever and viral hepatitis. In viral hepatitis, some of the necrosed hepatocytes of the mid-zone are transformed into acidophilic, rounded Councilman bodies.

iii) Periportal (peripheral) necrosis is seen in zone 1 involving the parenchyma closest to the arterial and portal blood supply. Since zone 1 is most well perfused, it is most vulnerable to the effects of circulating hepatotoxins e.g. in phosphorus poisoning and eclampsia.

3. Focal necrosis. This form of necrosis involves small groups of hepatocytes irregularly distributed in the hepatic lobule. Focal necrosis is most often caused by microbiologic infections. These include viral hepatitis, miliary tuberculosis, typhoid fever and various other forms of bacterial, viral and fungal infections. Focal necrosis may also occur in drug-induced hepatitis.

A group of liver diseases with dystrophy and necrosis of hepatocytes is termed **hepatosis**. It may be congenital and acquired (acute and chronic).

Acute hepatosis, or toxic dystrophy of liver is characterized by progressing massive liver necrosis and development of liver insufficiency.

Etiology:

1. Poisoning with food products (e.g. mushroom poisoning),
2. Poisons (e.g phosphor),
3. Auto intoxication (e.g. thyreotoxicosis),
4. Severe forms of viral hepatitis.

At 1st week in hepatocytes fat dystrophy develops. Then it leads to necrosis and autolysis of hepatocytes). Necrosis continues up to 2nd week of disease and effects all lobules of liver (*stage of yellow dystrophy*). In this stage fat – protein droplets are formed at the place of dead liver cells. On 3rd week the sizes of liver are more decreased and liver becomes red in color because the necrotic debris formed after death of hepatocytes are resolved and inflammatory reaction with hyperrhemia of blood vessels develops in the stroma (*stage of red dystrophy*).

These patients have:

a) Jaundice due to increased level of bilirubin in the blood.

b) Hemorrhagic syndrome due to deficiency of coagulation factors.

c) Acute renal deficiency due to necrosis of tubular epithelium.

d) *Dystrophic changes* in internal organs due to intoxication.

The death occurs due to liver insufficiency. If patient remain alive then post necrotic liver cirrhosis develops.

FAT HEPATOSIS, OR STEATOSIS, also called fatty change, is a chronic disease describing the abnormal retention of lipids within a hepatocytes or organ. When not further specified (such as cardiac steatosis), it is defined as affecting the liver. It reflects an impairment of the normal processes of synthesis and elimination of triglyceride fat.

Etiology.

1. Intoxication (alcohol, medicines).
2. Impairment of metabolism (Diabetes mellitus, Cushing`s desease, hypothyreosis and other).
3. Impaired diet (food conteinning more fats and carbohydrates).
4. Hypoxia (anemias, circulatory disordes).

Excess lipid accumulates in vesicles that displace the cytoplasm. Liver is increased in size with smooth surface and yellow or brown-red in color. Fat inclusions are determined in hepatocytes. These inclusions may be present in separate hepatocytes (disseminated obesity) or in group of hepatocytes (zonal obesity) or they may be present in whole parenchyma of liver (diffused obesity).

When the vesicles are large enough to distort the nucleus, the condition is known as macrovesicular steatosis; otherwise, the condition is known as microvesicular steatosis. While not particularly detrimental to the cell in mild cases, large accumulations can disrupt cell constituents, and in severe cases the cell may even burst.

Stages of fat hepatosis:

1. Simple obesity – there is accumulation of fat inclusions inside cells, but witout necrotic changes.
2. Obesity with necrobiosis of hepatocytes and inflammatory reaction.
3. Obesity with beginning of lobular structure damage.

Lipid inclusions may lead to death of hepatocytes and formation of fat droplets located outside the cells with inflammatory reaction surrounding them.

VIRAL HEPATITIS

The term viral hepatitis is used to describe infection of the liver caused by hepatotropic viruses. Currently there are *5* main varieties of these viruses and a sixth poorly-characterised virus, causing distinct types of viral hepatitis:

• *Hepatitis A virus (HAV),* causing a faecally-spread self-limiting disease;

• *Hepatitis B virus (HBV),* causing a parenterally transmitted disease that may become chronic;

• *Hepatitis C virus (HCV),* previously termed non-A, non-B (NANB) hepatitis virus involved chiefly in transfusion-related hepatitis;

• *Hepatitis delta virus (HDV)* which is sometimes associated as super-infection with hepatitis B infection;

• *Hepatitis E virus (HEV),* causing water-borne infection; and

• *Hepatitis G virus (HGV),* has recently been discovered.

All these human hepatitis viruses are RNA viruses except HBV which is a DNA virus.

Though a number of other viral diseases such as infection with Epstein-Barr virus (in infectious mononucleosis), arbovirus (in yellow fever), cytomegalovirus, herpes simplex and several others affect the liver but the changes produced by them are nonspecific and the term Viral hepatitis' is strictly applied to infection of the liver by the hepatitis viruses.

Etiologic classification. Based on the etiologic agent, viral hepatitis is currently classified into *6* etiologic types -hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E and hepatitis G.

HEPATITIS A

Infection with HAV causes hepatitis A (infectious hepatitis). Hepatitis A is responsible for 20-25% of clinical hepatitis in the developing countries of the world but the incidence is much lower in the developed countries. Hepatitis A is usually a benign, selk-limiting disease and has an incubation period of 15-45

days. The disease occurs in epidemic form as well as sporadically. It is usually spread by faeco-oral route. Parenteral transmission is extremely rare. The spread is related to close personal contact such as in overcrowding, poor hygiene and poor sanitation. Most frequently affected age is 5-14 years; adults are often infected by spread from children.

HEPATITIS A VIRUS (HAV). The etiologic agent for hepatitis A, HAV, is a small, 27 nm diameter, icosahedral non-enveloped, single-stranded RNA virus. Viral genome has been characterised but only a single serotype has been identified. HAV infection can be transmitted to primates and the virus can be cultivated in *vitro.* Inactivation of viral activity can be achieved by boiling for 1 minute, by ultraviolet radiation on by contact with formaldehyde and chlorine. The virus is present in the liver cells, bile, stool and blood during the incubation period and in pre-icteric phase but viral shedding diminishes after the onset of jaundice. Chronic carriers have not been identified for HAV infection.

Pathogenesis. The mechanism by which HAV infection causes hepatitis A is poorly understood. An immunologic basis is suspected but the evidence in support is indirect in the form of immunologic markers but not direct demonstration of the etiologic agent in the affected hepatocytes. These markers are:

1. *IgM anti-HAV antibody* appears in the serum at the onset of symptoms of acute hepatitis A.

2. *IgG anti-HAV antibody* is detected in the serum after IgM antibody and gives life-long protective immunity against reinfection with HAV.

HEPATITIS B

Hepatitis B (serum hepatitis) caused by HBV infection has a longer incubation period (30-180 days) and is transmitted parenterally such as in recipients of blood and blood products, intravenous drug addicts, patients treated by renal dialysis and hospital workers exposed to blood, and by intimate physical contact such as from mother to child and sexually. The disease may occur at any age. HBV infection causes more severe form of illness that includes: acute hepatitis B, chronic hepatitis, progression to cirrhosis, fulminant hepatitis and an asymptomatic carrier stage. HBV plays some role in the development of hepatocellular carcinoma.

HEPATITIS B VIRUS (HBV). The etiologic agent for hepatitis B, HBV, is a DNA virus which has been extensively studied. Electron microscopic studies on serum of patients infected with HBV show 3 types of viral particles: small 20 nm *spheres, tubules* 20 nm in diameter and 100 nm long, and large 42 nm *Dane particles.* Spherical and filamentous forms are most numerous

and represent excess of viral surface coat protein (HBsAg), while Dane particle is believed to represent the intact HBV.

Dane particle is spherical with a diameter of 42 nm, partially single-stranded and partially double-stranded. It has an outer *surface envelope* of protein, carbohydrate and lipid and an inner hexagonal *core* measuring 27 nm in diameter and containing double-stranded DNA which is associated with DNA polymerase. The surface envelope of Dane particle (as also the small spheres and tubules present in the serum of HBV-infected individual) contains hepatitis B surface antigen (HBsAg) and its subtypes, whereas the inner core has hepatitis core antigen (HBcAg), and another antigen subunit of the core protein called *'e'* (HBeAg).

Pathogenesis. The evidence linking immunopathogenetic mechanism with hepatocellular damage is much stronger in HBV infection than with HAV infection. In support of immune pathogenesis are several immunological markers, cellular immunity (delayed hypersensitivity) and immune-complex mediated tissue injury, discussed below.

I. *Immunological markers*. Various immunological markers indicative of presence of HBV infection can be demonstrated in the sera as well as in the hepatocytes of infected individuals. These are as under:

1. HBsAg. In 1965, Blumberg and colleagues in Philadelphia found a lipoprotein complex in the serum of a multiple-transfused haemophiliac of Australian aborigine which was subsequently shown by them to be associated with serum hepatitis. This antigen was termed Australia antigen by them (in 1977, Blumberg was awarded the Nobel prize for this discovery). Australia antigen is now used synonymous with hepatitis B surface antigen (HBsAg). HBsAg appears early in the blood after about 6 weeks of infection and its detection is an indicator of active HBV infection. It usually disappears in 3-6 months. Its persistence for more than 6 months implies a carrier state. HBsAg may also be demonstrated in the cell membrane of hepatocytes of carriers and chronic hepatitis patients by Orcein staining (orange positivity) but not in the hepatocytes during acute stage of illness.

2. Anti-HBs. Specific antibody to HBsAg in serum called anti-HBs appears late, about 3 months after the onset. Anti-HBs response may be both IgM and IgG type. The prevalence rate of anti-HBs ranges from 10-15%. In these individuals it persists for life providing protection against reinfection with HBV.

3. HBeAg. HBeAg derived from core protein is present transiently (3-6 weeks) during an acute attack. Its persistence beyond 10 weeks is indicative of development of chronic liver disease and carrier state.

4. Anti-HBe. Antibody to HBeAg called anti-HBe appears after disappearance of HBeAg. Seroconversion from HBeAg to anti-HBe during acute stage of illness is a prognostic sign for resolution of infection.

5. HBeAg. HBeAg derived from core protein cannot be detected in the blood. But HBeAg can be demonstrated in the nuclei of hepatocytes in carrier state and in chronic hepatitis patients by Orcein staining but not in the liver cells during acute stage.

6. Anti-HBe. Antibody to HBeAg called anti-HBe can, however, be detected in the serum of acute hepatitis B patients during pre-icteric stage. Anti-HBe may be IgM or IgG class antibody. IgM anti-HBe persists for 4-6 months and is followed later by IgG anti-HBe. Thus detection of high titre of IgM anti-HBe is indicative of recent acute HBV infection, while elevated level of IgG anti-HBe suggests HBV infection in the remote past.

7. HBV-DNA. Detection of HBV-DNA by molecular hybridisation using the Southern blot technique is the most sensitive index of hepatitis B infection. It is present in pre-symptomatic phase and transiently during early acute stage.

II. *Cellular Immunity (delayed hypersensitivity).* There is increasing evidence to suggest that hepatocellular damage results from cell-mediated immune mechanism rather than direct cytopathic effect by the virus. These evidences are:

1. Absence of hepatocellular damage in HBV-infected carrier state.
2. Demonstration, of specifically-sensitised cytotoxic T-lymphocytes at the sites of hepatocellular injury.
3. Patients with depressed cell-mediated immunity have high frequency of progression from acute to chronic hepatitis.

However, certain lacunae exist in the cell-mediated immune damage in HBV infection. These are explained by additional support from other influences such as genetic factors, increased T cell activity by antibody-dependent cellular cytotoxicity (ADCC), and possibly concomitant infection with another hepatotropic virus i.e. delta virus.

III. *Immune-complex mediated mechanism.* The formation of circulating immune complexes by combination of antigen (HBsAg) with antibody (anti-HBs) leads to activation of the complement system. This results in tissue damage which is the major pathogenetic mechanism for extrahepatic manifestations of HBV infection such as serum sickness-like syndrome, glomerulonephritis and polyarteritis nodosa.

HEPATITIS D

Infection with delta virus (HDV) in the hepatocyte nuclei of HBsAg-positive patients is termed hepatitis D. HDV is a defective virus for which

HBV is the helper. Thus, hepatitis D develops when there is concomitant hepatitis B infection. HDV infection and hepatitis B may be simultaneous *(co-infection),* or HDV may infect a chronic HBsAg carrier *(superinfection).*

• With co-infection, acute hepatitis D may range from mild to fulminant hepatitis but fulminant hepatitis is more likely in such simultaneous delta infection. Chronicity rarely develops in co-infection.

• With super-infection, (incubation period 30-35 days), chronic HBV infection gets worsened indicated by appearance of severe and fulminant acute attacks, progression of carrier stage to chronic delta hepatitis or acceleration towards cirrhosis. Hepatocellular carcinoma is, however, less common in HBsAg carriers with HDV infection.

HDV infection is worldwide in distribution though the incidence may vary in different countries. Endemic regions are Southern Europe, Middle-East, South India and parts of Africa. The high risk individuals for HDV infection are the same as for HBV infection i.e. intravenous drug abusers, homosexuals, transfusion recipients, and health care workers.

HEPATITIS DELTA VIRUS (HDV). The etiologic agent, HDV, is a small single-stranded RNA particle with a diameter of 36 nm. It is double-shelled – the outer shell consists of HBsAg and the inner shell consists of delta antigen provided by a circular RNA strand. It is highly infectious and can induce hepatitis in any HBsAg-positive host. HDV replication and proliferation takes place within the nuclei of liver cells. Markers for HDV infection include the following:

1. *HDV identification* in the blood and in the liver cell nuclei.
2. *HDAg* detectable in the blood and on fixed liver tissue specimens.
3. *Anti-HD antibody* in acute hepatitis which is initially IgM type and later replaced by IgG type anti-HD antibody which persists for life to confer immunity against reinfection.

Pathogenesis. HDV, unlike HBV, is thought to cause direct cytopathic effect on hepatocytes. However, there are examples of transmission of HDV infection from individuals who themselves have not suffered from any attack of hepatitis, suggesting that it may not be always cytopathic. Thus, the exact mechanism remains unresolved.

HEPATITIS C

The diagnosis of a third major category of hepatitis was earlier made after exclusion of infection with other known hepatitis viruses and was designated non-A, non-B (NANB) hepatitis. However, now this third type has been characterised and is called hepatitis C.

Hepatitis C infection is acquired by blood transfusions, blood products, haemodialysis, parenteral drug abuse and accidental cuts and needle-pricks in

health workers. About 90% of post-transfusion hepatitis is of hepatitis C type. About 1-2% of volunteer blood donors and up to 5% of professional blood donors are carriers of HCV. Hepatitis C has an incubation period of 20-90 days (mean 50 days). Clinically, acute HCV hepatitis is milder than HBV hepatitis but HCV has a higher rate of progression to chronic hepatitis than HBV. Persistence of infection and chronic hepatitis are the key features of HCV. Occurrence of cirrhosis after 5 to 10 years and progression to hepatocellular carcinoma are other consequences of HCV infection. Currently, HCV is considered more important cause of chronic liver disease worldwide than HBV.

HEPATITIS C VIRUS (HCV). HCV is a single-stranded, enveloped RNA virus, having a diameter of 30-60 nm. The serologic and virologic markers for HCV infection are as under:

1. *Anti-HCV antibodies.* Three generations of anti-HCV IgG assays are available:

i) Antibodies to C 100-3 region appear 1 to 3 months after infection, ii) Antibodies to C 33c region appear about one month earlier than the first generation, iii) Antibodies to NS-5 region are detected even earlier.

2. *HCV-RNA.* HCV infection is, however, confirmed by HCV-RNA employing PCR technique which can be detected within a few days after exposure to HCV infection, much before appearance of anti-HCV and persists for the duration of HCV infection.

Pathogenesis. How HCV causes liver cell injury is not yet clearly established. HCV virions have not been identified in hepatocytes. Possibly, immunologic mechanism and cell destructive replication are both involved. In patients with chronic hepatitis C, HCV-specific CD4 + T cells and HLA-restricted CDS + T cells have been identified.

HEPATITIS E

Hepatitis E is an enterically-transmitted virus, previously labelled as epidemic or enterically transmitted type of non-A non-B hepatitis. The infection occurs in young or middle-aged individuals, primarily in India, other Asian countries, Africa and central America.

The infection is generally acquired by contamination of water supplies such as after monsoon flooding. However, compared with HAV, secondary person-to-person infection does not occur with HEV. Thus HEV has some common epidemiologic features with HAV. HEV infection has a particularly high mortality in pregnant women but is otherwise a self-limited disease and has not been associated with chronic liver disease.

HEPATITIS E VIRUS (HEV). HEV is a single stranded 32-34 nm, icosahedral non-enveloped virus. The virus has been isolated from stools, bile and liver of infected persons. Serologic markers for HEV include the following:

1. Anti-HEV antibodies of both IgM and IgG class.
2. HEV-RNA.

However, testing for these markers for HEV is currently not available.

HEPATITIS G

A virus distinct from the foregoing hepatitis viruses has been designated separately by two groups of workers as hepatitis G (HGV) and hepatitis F (HFV) virus. Like HCV, HGV is a blood-borne infection and may cause acute and chronic viral hepatitis.

HEPATITIS G VIRUS (HGV). HGV is a single-stranded RNA virus. At present HGV infection has been found in blood donors and is transmitted by blood transfusion. The virus has been identified by PCR amplification technique but is yet to be fully characterised.

CLINICOPATHOLOGIC SPECTRUM

Of the various etiologic types of hepatitis, evidence linking HBV and HCV infection with the spectrum of clinicopathologic changes is stronger than with other hepatotropic viruses. The typical pathologic changes of hepatitis by all hepatotropic viruses are virtually similar. HAV and HEV, however, do not have a carrier stage or cause chronic hepatitis. The various clinical patterns and pathologic consequences of different hepatotropic viruses can be considered under the following headings:

i) Carrier state,
ii) Asymptomatic infection,
iii) Acute hepatitis,
iv) Chronic hepatitis,
v) Fulminant hepatitis (Submassive to massive necrosis).

In addition, progression to cirrhosis and association with hepatocellular carcinoma are known to occur in certain types of hepatitis which are discussed separately later.

1. Carrier State

An asymptomatic individual without manifest disease, harbouring infection with hepatotropic virus and capable of transmitting it is called carrier state. There can be 2 types of carriers:

1. An *'asymptomatic healthy carrier'* who does not suffer from ill-effects of the virus infection.

2. An *'asymptomatic carrier with chronic disease'* capable of transmitting the organisms.

As stated before, hepatitis A and E do not produce the carrier state. Hepatitis B is responsible for the largest number of carriers in the world, while concomitant infection with HDV more often causes progressive disease rather than an asymptomatic carrier state. An estimated 2-3% of the general

population are asymptomatic carriers of HCV. Data on HBV carrier state reveal role of 2 important factors rendering the individual more vulnerable to harbour the organisms—*early age at infection* and *impaired immunity.* Whereas approximately 10% of adults contracting hepatitis B infection develop carrier state, 90% of infected neonates fail to clear HBsAg from the serum within 6 months and become HBV carriers.

Clinical recognition of carrier state of HBV is more frequently done by detection of HBsAg in the serum and less often by other markers such as HBeAg, HBcAg and antibodies. Concomitant infection of HDV with HBV depends upon the demonstration of anti-HD.

Pathologic changes. Carriers of HBV may or may not show changes on liver biopsy.

• *Healthy HBV carriers* may show no changes or minor hepatic change such as presence of finely granular, ground-glass, eosinophilic cytoplasm as evidence of HBsAg.

• *Asymptomatic carriers with chronic disease* may show changes of chronic hepatitis and even cirrhosis.

II. Asymptomatic Infection

These are cases which are detected incidentally to have infection with one of the hepatitis viruses as revealed by their raised serum transaminases or by detection of the presence of antibodies but are otherwise asymptomatic.

III. Acute Hepatitis

The most common consequence of all hepatotropic viruses is acute inflammatory involvement of the entire liver. In general, type A, B, C, D and E run similar clinical course and show identical pathologic findings. Clinically, acute hepatitis is categorised into 4 phases: incubation period, pre-icteric phase, icteric phase and post-icteric phase.

1. Incubation period: It varies among different hepatotropic viruses: for hepatitis A it is about 4 weeks (15-45 days); for hepatitis B the average is 10 weeks (30-180 days); for hepatitis D about 6 weeks (30-50 days); for hepatitis C the mean incubation period is about 7 weeks (42-56 days), and for hepatitis E it is 2-8 weeks (15-60 days). The patient remains asymptomatic during incubation period but the infectivity is highest during the last days of incubation period.

2. Pre-icteric phase: This phase is marked by prodromal constitutional symptoms that include anorexia, nausea, vomiting, fatigue, malaise, distaste for smoking, arthralgia and headache. There may be low-grade fever preceding the onset of jaundice, especially in hepatitis A. The earliest laboratory evidence of hepatocellular injury in pre-icteric phase is the elevation of transaminases.

3. Icteric phase: The prodromal period is heralded by the onset of clinical jaundice and the constitutional symptoms diminish. Other features include dark-

coloured urine due to bilirubinuria, clay-coloured stools due to cholestasis, pruritus as a result of elevated serum bile acids, loss of weight and abdominal discomfort due to enlarged, tender liver. The diagnosis is based on deranged liver function tests (e.g. elevated levels of serum bilirubin, transaminases and alkaline phosphatase; prolonged prothrombin time and hyperglobulinaemia) and serologic detection of hepatitis antigens and antibodies.

4. Post-icteric phase: The icteric phase lasting for about 1 to 4 weeks is usually followed by clinical and biochemical recovery in 2 to 12 weeks. The recovery phase is more prolonged in hepatitis B and hepatitis C. Up to 1% cases of acute hepatitis may develop severe form of the disease (fulminant hepatitis); and 5-10% of cases progress on to chronic hepatitis. Evolution into the carrier state (except in HAV and HEV infection) has already been described above.

Pathologic changes. *Grossly,* the liver is slightly enlarged, soft and greenish. *Histologically,* the changes are as follows:

1. Hepatocellular injury: There may be variation in the degree of liver cell injury but it is most marked in zone 3 (centrilobular zone):

i) Mildly injured hepatocytes appear swollen with granular cytoplasm which tends to condense around the nucleus *(ballooning degeneration).*

ii) Others show acidophilic degeneration in which the cytoplasm becomes intensely eosinophilic, the nucleus becomes small and pyknotic and is eventually extruded from the cell, leaving behind necrotic, acidophilic mass called Councilman body or acidophil body by the process known as apoptosis.

iii) Another type of hepatocellular necrosis is *dropout necrosis* in which isolated or small clusters of hepatocytes undergo lysis.

iv) *Bridging necrosis* is a more severe form of hepatocellular injury in acute viral hepatitis and may progress to fulminant hepatitis or chronic hepatitis. Bridging necrosis is characterised by bands of necrosis linking portal tracts to central hepatic veins, one central hepatic vein to another, or a portal tract to another tract.

2. Inflammatory infiltrate: There is infiltration by mononuclear inflammatory cells, usually in the portal tracts, but may permeate into the lobules.

3. Kupffer cell hyperplasia: There is reactive hyperplasia of Kupffer cells many of which contain phagocytosed cellular debris, bile pigment and lipofuscip. granules.

4. Cholestasis: Biliary stasis is usually not severe in viral hepatitis and may be present as intracytoplasmic bile pigment granules.

5. Regeneration: As a result of necrosis of hepatocytes, there is lobular disarray. Surviving adjacent hepatocytes undergo regeneration and hyperplasia. If the necrosis causes collapse of reticulin framework of the lobule, healing by fibrosis follows, distorting the lobular architecture.

IV. Chronic Hepatitis

Chronic hepatitis is defined as continuing or relapsing hepatic disease for more than 6 months with symptoms alongwith biochemical, serologic and histopathologic evidence of inflammation and necrosis. Majority of cases of chronic hepatitis are the result of infection with hepatotropic viruses – hepatitis B, hepatitis C and combined hepatitis B and hepatitis D infection. However, some non-viral causes of chronic hepatitis include: Wilson's disease, α-1 antitrypsin deficiency, chronic alcoholism, drug-induced injury and autoimmune diseases. The last named gives rise to *autoimmune or lupoid hepatitis* which is characterised by positive serum autoantibodies (e.g. antinuclear, anti-smooth muscle and anti-mitochondrial) and a positive LE cell test but negative for serologic markers of viral hepatitis.

Until recent years, prediction of prognosis of chronic hepatitis used to be made on the basis of morphology which divided it into 2 types – *chronic persistent* and *chronic active (aggressive) hepatitis.* However, subsequent studies have revealed that morphologic subtypes do not necessarily correlate with the prognosis since the disease is not essentially static but may vary from mild form to severe and vice versa. Besides, two other factors which determine the vulnerability of a patient of viral hepatitis to develop chronic hepatitis are: *impaired immunity* and *extremes of age* at which the infection is first contracted.

Currently, chronic hepatitis is classified on the basis of etiology. The frequency and severity with which hepatotropic viruses cause chronic hepatitis varies with the organisms as under:

• *HCV* infection accounts for 40-60% cases of chronicity in adults. HCV infection is particularly associated with progressive form of chronic hepatitis that may evolve into cirrhosis.

• *HBV* causes chronic hepatitis in 90% of infected infants and in about 5% adult cases of hepatitis B.

• *HDV* superinfection on HBV carrier state may be responsible for chronic hepatitis in 10-40% cases.

• *HAV and HEV* do not produce chronic hepatitis.

Pathologic changes. The pathologic features are common to both HBV and HCV infection and include the following lesions.

1. Piecemeal necrosis. Piecemeal necrosis is defined as periportal destruction of hepatocytes at the limiting plate *(piecemeal* = piece by piece). Its features in chronic hepatitis are:

i) Necrosed hepatocytes at the limiting plate in periportal zone.

ii) Interface hepatitis due to expanded portal tract by infiltration of lymphocytes, plasma cells and macrophages.

iii) Expanded portal tracts are often associated with proliferating bile ductules as a response to liver cell injury.

2. Portal tract lesions. All forms of chronic hepatitis are characterised by variable degree of changes in the portal tract.

i) Inflammatory cell infiltration by lymphocytes, plasma cells and macrophages (triaditis).

ii) Proliferated bile ductules in the expanded portal tracts.

iii) Additionally, chronic hepatitis C may show lymphoid aggregates or follicles with reactive germinal centre and infiltration of inflammatory cells in the damaged bile duct epithelial cells.

3. Intralobular lesions. Generally, the architecture of lobule is retained in mild to moderate chronic hepatitis.

i) There are focal areas of necrosis and inflammation within the hepatic parenchyma.

ii) Scattered acidophilic bodies in the lobule.

iii) Kupffer cell hyperplasia.

iv) More severe form of injury shows bridging necrosis (i.e. bands of necrosed hepatocytes that may bridge portal tract-to-central vein, central vein-to-central vein, and portal tract-to-portal tract),

v) Regenerative changes in hepatocytes in cases of persistent hepatocellular necrosis,

vi) Cases of chronic hepatitis C show moderate fatty change.

vii) Cases of chronic hepatitis B show scattered ground-glass hepatocytes indicative of abundance of HBsAg in the cytoplasm.

4. Bridging fibrosis. The onset of fibrosis in chronic hepatitis from the area of interface hepatitis and bridging necrosis is a feature of irreversible damage,

i) At first, there is periportal fibrosis at the sites of interface hepatitis giving the portal tract stellate-shaped appearance.

ii) Progressive cases show bridging fibrosis connecting portal tract-to-portal tract or portal tract-to-central vein traversing the lobule,

iii) End stage of chronic hepatitis is characterised by dense collagenous septa destroying lobular architecture and forming nodules resulting in post-necrotic cirrhosis.

V. Fulminant Hepatitis (Submassive to Massive Necrosis)

Fulminant hepatitis is the most severe form of acute hepatitis in which there is rapidly progressive hepatocellular failure. Two patterns are recognized – *submassive necrosis* having a less rapid course extending up to 3 months; and *massive necrosis* in which the liver failure is rapid and fulminant occurring in 2-3 weeks.

Fulminant hepatitis of either of the two varieties can occur from viral and non-viral etiologies:

• *Acute viral hepatitis* accounts for about half the cases, most often from HBV and HCV; less frequently from combined HBV-HDV and rarely from HAV. However, HEV infection is a serious complication in pregnant women. In addition, herpesvirus can also cause serious viral hepatitis.

• *Non-viral causes* include acute hepatitis due to drug toxicity (e.g. acetaminophen, non-steroidal anti-inflammatory drugs, isoniazid, halothane and anti-depressants), poisonings, hypoxic injury and massive infiltration of malignant tumours into the liver.

The patients present with features of hepatic failure with hepatic encephalopathy. The mortality rate is high if hepatic transplantation is not undertaken.

Pathologic changes. *Grossly,* the liver is small and shrunken, often weighing 500-700 gm. The capsule is loose and wrinkled. The sectioned surface shows diffuse or random involvement of hepatic lobes. There are extensive areas of muddy-red and yellow necrosis (previously called *acute yellow atrophy)* and patches of green bile staining. *Histologically*, two forms of fulminant necrosis are distinguished submassive and massive necrosis,

i) In submassive necrosis, large groups of hepatocytes in zone 3 (centrilobular area) and zone 2 (mid zone) are wiped out leading to a collapsed reticulin framework. Regeneration in submassive necrosis is more orderly and may result in restoration of normal architecture.

ii) In massive necrosis, the entire liver lobules are necrotic. As a result of loss of hepatic parenchyma, all that is left is the collapsed and condensed reticulin framework and portal tracts with proliferated bile ductules plugged with bile. Inflammatory infiltrate is scanty. Regeneration, if it takes place, is disorderly forming irregular masses of hepatocytes. Fibrosis is generally not a feature of fulminant hepatitis.

OTHER INFECTIONS AND INFESTATIONS

Apart from viral hepatitis, the liver is affected by infections with bacteria, spirochaetes and fungi and is involved in some parasitic infestations. Some common examples of such conditions are described below.

CHOLANGITIS

Cholangitis is the term used to describe inflammation of the extrahepatic or intrahepatic bile ducts, or both. There are two main types of cholangitis – pyogenic and primary sclerosing. While primary sclerosing cholangitis is discussed later with biliary cirrhosis, pyogenic cholangitis is described below.

PYOGENIC CHOLANGITIS

Cholangitis occurring secondary to obstruction of a major extrahepatic duct causes pyogenic cholangitis. Most commonly, the obstruction is from impacted gallstone; other causes are carcinoma arising in the extrahepatic ducts,

carcinoma head of pancreas, acute pancreatitis and inflammatory strictures in the bile duct. Bacteria gain entry to the obstructed duct and proliferate in the bile. Infection spreads along the branches of obstructed duct and reaches the liver, termed *ascending cholangitis.* The common infecting bacteria are enteric organisms such as *E.coli, Klebsiella* and *Enterobacter.*

Pathologic changes. The affected ducts show serial beaded abscesses accompanied by bile stasis along their course and larger abscesses within the liver. The abscesses are composed of acute inflammatory cells which in time are replaced by chronic inflammatory cells and enclosed by fibrous capsule.

PYOGENIC LIVER ABSCESS

Most liver abscesses are of bacterial (pyogenic) origin; less often they are amoebic, hydatid and rarely actinomycotic. Pyogenic liver abscesses are becoming uncommon due to improved diagnostic facilities and the early use of antibiotics. However, their incidence is higher in old age and in immunosuppressed patients such as in AIDS, transplant recipients and those on intensive chemotherapy.

Pyogenic liver abscesses are classified on the basis of the mode of entry. These are:

1. *Ascending cholangitis* through ascending infection in the biliary tract due to obstruction e.g. gallstones, cancer, sclerosing cholangitis and biliary strictures.

2. *Portal pyaemia* by means of spread of pelvic or gastrointestinal infection resulting in portal pylephlebitis or septic emboli e.g. from appendicitis, empyema of gallbladder, diverticulitis, regional enteritis, pancreatitis, infected haemorrhoids and neonatal umbilical vein sepsis.

3. *Septicaemia* through spread by hepatic artery.

4. *Direct infection* resulting in solitary liver abscess e.g. from adjacent perinephric abscess, secondary infection in amoebic liver abscess, metastasis and formation of haematoma following trauma.

5. *Jatrogenic causes* include liver biopsy, percutaneous biliary drainage and accidental surgical trauma.

6. *Cryptogenic* from unknown causes, especially in the elderly.

The commonest infecting organisms are gram-negative bacteria chiefly *E. coli;* others are *Pseudomonas, Klebsiella, Enterobacter* and a number of anaerobic organisms, bacteroides and actinomyces.

Liver abscesses are clinically characterised by pain in the right upper quadrant, fever, tender hepatomegaly and sometimes jaundice. Laboratory examination reveals leucocytosis, elevated serum alkaline phosphatase, hypoalbuminaemia and a positive blood culture.

Pathologic changes. *Grossly* depending upon the cause for pyogenic liver abscess, they occur as single or multiple yellow abscesses, 1 cm or more

in diameter, in an enlarged liver. A single abscess generally has a thick fibrous capsule. The abscesses are particularly common in right lobe of the liver.

Microscopically, typical features of abscess are seen. There are multiple small neutrophilic abscesses with areas of extensive necrosis of the affected liver parenchyma. The adjacent viable area shows pus and blood clots in the portal vein, inflammation, congestion and proliferating fibroblasts. Direct extension from the liver may lead to subphrenic or pleuropulmonary suppuration or peritonitis. There may be small pyaemic abscesses elsewhere such as in the lungs, kidneys, brain and spleen.

AMOEBIC LIVER ABSCESS

Amoebic liver abscesses are less common than pyogenic liver abscesses and have many similar features. They are caused by the spread of *Entamoeba histolytica* from intestinal lesions. The trophozoite form of amoebae in the colon invade the colonic mucosa forming flask-shaped ulcers from where they are carried to the liver in the portal venous system. Amoebae multiply and block small intrahepatic portal radicles resulting in infarction necrosis of the adjacent liver parenchyma.

The patients, generally from tropical and subtropical countries, may give history of amoebic dysentery in the past. Cysts of E. *histolytica* in stools are present in only 15% of patients of hepatic amoebiasis. Intermittent low-grade fever, pain and tenderness in the liver area are common presenting features. A positive haemagglutination test is quite sensitive and useful for diagnosis of amoebic liver abscess.

Pathologic changes. *Grossly,* amoebic liver abscesses are usually solitary and more often located in the right lobe in the posterosuperior portion. Amoebic liver abscess may vary greatly in size but is generally of the size of an orange. The centre of the abscess contains large necrotic area having reddish-brown, thick pus resembling anchovy or chocolate sauce. The abscess wall consists of irregular shreds of necrotic liver tissue. *Histologically,* the necrotic area consists of degenerated liver cells, leucocytes, red blood cells, strands of connective tissue and debris. Amoebae are most easily found in the liver tissue at the margin of abscess. PAS-staining is employed to confirm the trophozoites of *E. histolytica.*

HEPATIC TUBERCULOSIS

Tuberculosis of the liver occurs as a result of miliary dissemination from primary complex or from chronic adult pulmonary tuberculosis. The diagnosis is possible by liver biopsy. The patients may have unexplained fever, jaundice, hepatomegaly or hepatosplenomegaly. There may be elevated serum alkaline phosphatase levels and hyperglobulinaemia.

Pathologic *changes*. The basic lesion is the epithelioid cell granuloma characterised by central caseation necrosis with destruction of the reticulin framework and peripheral cuff of lymphocytes. Ziehl-Neelsen staining for AFB or culture of the organism from the biopsy tissue is confirmatory. Rare lesions consist of tuberculous cholangitis and tuberculous pylephlebitis.

HYDATID DISEASE (ECHINOCOCCOSIS)

Hydatid disease occurs as a result of infection by the larval cyst stage of the tapeworm, *Echinococcus granulosus.* The dog is the common definite host, while man, sheep and cattle are the intermediate hosts. The dog is infected by eating the viscera of sheep containing hydatid cysts. The infected faeces of the dog contaminate grass and farmland from where the ova are ingested by sheep, pigs and man. Thus, man can acquire infection by handling dogs as well as by eating contaminated vegetables. The ova ingested by man are liberated from the chitinous wall by gastric juice and pass through the intestinal mucosa from where they are carried to the liver by portal venous system. These are trapped in the hepatic sinusoids where they eventually develop into hydatid cyst. About 70% of hydatid cysts develop in the liver which acts as the first filter for ova. However, ova which pass through the liver enter the right side of the heart and are caught in the pulmonary capillary bed and form pulmonary hydatid cysts. Some ova which enter the systemic circulation give rise to hydatid cysts in the brain, spleen, bone and muscles.

The disease is common in sheep-raising countries such as Australia, New Zealand and South America. The *uncomplicated hydatid cyst* of the liver may be silent or may produce dull ache in the liver area and some abdominal distension.

Complications of hydatid cyst include its rupture (e.g. into the peritoneal cavity, bile ducts and lungs), secondary infection and hydatid allergy due to sensitisation of the host with cyst fluid. The diagnosis is made by peripheral blood eosinophilia, radiologic examination and serologic tests such as indirect haemagglutination test and Casoni skin test.

Pathologic changes. Hydatid cyst grows slowly and may eventually attain a size over 10 cm in diameter in about 5 years. £. *granulosus* generally causes unilocular hydatid cyst while E. *multilocularis* results in multilocular or alveolar hydatid disease in the liver.

The cyst wall is composed of 3 distinguishable zones outer *pericyst,* intermediate characteristic *ectocyst* and inner *endocyst*:

1. Pericyst is the outer host inflammatory reaction consisting of fibroblastic proliferation, mononuclear cells, eosinophils and giant cells, eventually developing into dense fibrous capsule which may even calcify.

2. Ectocyst is the intermediate layer composed of characteristic acellular, chitinous, laminated hyaline material.

3. Endocyst is the inner germinal layer bearing daughter cysts (brood-capsules) and scolices projecting into the lumen.

Hydatid sand is the grain-like material composed of numerous scolices present in the hydatid fluid. Hydatid fluid, in addition, contains antigenic proteins so that its liberation into circulation gives rise to pronounced eosinophilia or may cause anaphylaxis.

ALCOHOLIC HEPATITIS

It is an acute or chronic liver disease caused by alcohol. Alcohol in large doses causes liver cell necrosis. It there is prolonged alcohol in take it may lead to chronic persistent hepatitis liver. In acute alcohol hepatitis liver becomes dense. Necrosis of hepatocytes is determined. There is leukocyte infiltration and alcoholic hyaline appears (Mallory`s body). It alcohol in take is stopped in early stages there may be complete recovery.

CIRRHOSIS

Cirrhosis of the liver is a diffuse disease having the following 4 features:

1. It involves the entire liver.
2. The normal lobular architecture of hepatic parenchyma is disorganised.
3. There is formation of nodules separated from one another by irregular bands of fibrosis.
4. It occurs following hepatocellular necrosis of varying etiology so that there are alternate areas of necrosis and regenerative nodules.

However, regenerative nodules are not essential for diagnosis of cirrhosis since biliary cirrhosis and haemochromatosis have little regeneration. The fibrosis once developed is irreversible.

In the Western world, cirrhosis of the liver is one of the ten leading causes of death.

Pathogenesis. Irrespective of the etiology, cirrhosis in general is initiated by hepatocellular necrosis. Continued destruction of hepatocytes causes collapse of normal lobular hepatic parenchyma followed *by fibrosis* around necrotic liver cells and proliferated ductules and there is formation of compensatory *regenerative nodules.*

Fibrogenesis. The mechanism of fibrosis that may be portal-central, portal-portal, or both, is by increased synthesis of all types of collagen and increase in the number of collagen-producing cells. Development of fibrosis leads to proliferation of fat-storing Ito cells underlying the sinusoidal epithelium which become transformed into myofibroblasts and fibrocytes. Besides collagen, two glycoproteins, fibronectin and laminin, are deposited in exces-

sive amounts in area of liver cell damage. The nature of factors acting as stimulants for fibrosis is not clearly known, but possible candidate mediators are lymphokines and monokines.

Regenerative nodule. The cause of compensatory proliferation of hepatocytes to form regenerative nodules is obscure. Possibly, growth factors, chalones and hormonal imbalance, play a role in regeneration.

CLASSIFICATION. Cirrhosis can be classified on the basis of morphology and etiology.

A. Morphologic Classification. There are 3 morphologic types of cirrhosis – micronodular, macronodular and mixed. Each of these forms may have an active and inactive form.

• An *active form* is characterised by continuing hepatocellular necrosis and inflammatory reaction, a process that closely resembles chronic hepatitis.

• An *inactive form,* on the other hand, has no evidence of continuing hepatocellular necrosis and has sharply-defined nodules of surviving hepatic parenchyma without any significant inflammation.

1. Micronodular cirrhosis. In micronodular cirrhosis, the nodules are usually regular and small, *less than 3 mm* in diameter. There is diffuse involvement of all the hepatic lobules forming nodules by thick fibrous septa which may be portal-portal, portal-central, or both. The micronodular cirrhosis includes etiologic types of alcoholic cirrhosis, nutritional cirrhosis and Laennec's cirrhosis and represents impaired capacity for regrowth as seen in alcoholism, malnutrition, severe anaemia and old age.

2. Macronodular cirrhosis. In this type, the nodules are of variable size and are generally *larger than 3 mm* in diameter. The pattern of involvement is more irregular than in micronodular cirrhosis, sparing some portal tracts and central veins, and more marked evidence of regeneration. Macronodular cirrhosis corresponds to post-necrotic or post-hepatitic cirrhosis of the etiologic classification.

3. Mixed cirrhosis. In mixed type, some parts of the liver show micronodular appearance while other parts show macronodular pattern. All the portal tracts and central veins are not involved by fibrosis but instead some of them are spared. Mixed pattern is a kind of incomplete expression of micronodular cirrhosis.

B. Etiologic Classification.

SPECIFIC TYPES OF CIRRHOSIS

ALCOHOLIC LIVER DISEASE AND CIRRHOSIS

Alcoholic liver disease is the term used to describe the spectrum of liver injury associated with acute and chronic alcoholism. There are three stages in alcoholic liver disease: *alcoholic steatosis (fatty liver), alcoholic hepatitis* and *alcoholic cirrhosis.* Though the relationship of these three patterns of liv-

er injury is controversial, available evidence suggests that an alcoholic who continues to drink, progresses from fatty liver to alcoholic hepatitis, and eventually to alcoholic cirrhosis in more than 10 years. On the other hand, there is experimental evidence that fatty change by itself does not lead to the development of cirrhosis, but alcoholic hepatitis in some cases appears to be the forerunner of alcoholic cirrhosis.

Ethanol Metabolism. One gram of alcohol gives 7 calories. But alcohol cannot be stored and must undergo obligatory oxidation, chiefly in the liver. Thus, these empty calories make no contribution to nutrition other than to give energy.

Ethanol after ingestion and absorption from the small bowel circulates through the liver where about 90% of it is oxidised to acetate by a *two-step enzymatic process* involving two enzymes: *alcohol dehydrogenase (ADH)* present in the cytosol, and *acetaldehyde dehydrogenase (ALDH)* in the mitochondria of hepatocytes. The remaining 10% of ethanol is oxidised elsewhere in the body.

First step: Ethanol is catabolised to acetaldehyde in the liver by the following three pathways, one major and two minor:

i) *In the cytosol,* by the major rate-limiting pathway of alcohol dehydrogenase (ADH).

ii) *In the smooth endoplasmic reticulum,* via microsomal P-450 oxidases (also called microsomal ethanol oxidising system, MEOS), where only part of ethanol is metabolised.

iii) *In the peroxisomes,* minor pathway via catalase such as H_2O_2.

Acetaldehyde is toxic and may cause membrane damage and cell necrosis. Simultaneously, the cofactor nicotinamide-adenine dinucleotide (NAD) which is a hydrogen acceptor, is reduced to NADH.

Second step: The second step occurs in the mitochondria where acetaldehyde is converted to acetate with ALDH acting as a co-enzyme. Most of the acetate on leaving the liver is finally oxidised to carbon dioxide and water, or converted by the citric acid cycle to other compounds including fatty acids. Simultaneously, the same cofactor, NAD, is reduced to NADH resulting in *increased NADH: NAD redox ratio* which is the basic biochemical alteration occurring during ethanol metabolism. A close estimate of NADH:NAD ratio is measured by the ratio of its oxidised and reduced metabolites.

Etiology. All those who indulge in alcohol abuse do not develop liver damage. The incidence of cirrhosis among alcoholics at autopsy is about 10-15%. Why some individuals are predisposed to alcoholic cirrhosis is not clearly known, but a few factors have been implicated. These are as under:

1. Drinking patterns. Most epidemiologic studies have attributed alcoholic cirrhosis to chronic alcoholism. The quantity and duration of drinking necessary to cause cirrhosis is largely unknown but it is generally agreed that continued daily imbibing of more than 80 gm of any type of alcoholic beverage for at least 10 years is likely to result in alcoholic cirrhosis. Liver injury is related to the alcoholic content only and not to the type of alcoholic beverage consumed. Intermittent drinking for long duration is less harmful since the liver is given chance to recover.

2. Malnutrition. Absolute or relative malnutrition of proteins and vitamins is regarded as a contributory factor in the evolution of cirrhosis. The combination of chronic alcohol ingestion and impaired nutrition leads to al-

coholic liver disease and not malnutrition *per se.* It appears that calories derived from alcohol displace other nutrients leading to malnutrition and deficiency of vitamins in alcoholics. Additional factors contributing to malnutrition in alcoholics are chronic gastritis and pancreatitis. The evidence in favour of synergistic effect of malnutrition in chronic alcoholism comes from clinical and morphologic improvement in cases of alcoholic cirrhosis on treatment with protein-rich diets.

3. Infections. Intercurrent bacterial infections are common in cirrhotic patients and may accelerate the course of the disease. Lesions similar to alcoholic cirrhosis may develop in non-alcoholic patients who have had viral infections in the past.

4. Genetic factors. The rate of ethanol metabolism is under genetic control. It is chiefly related to altered rates of elimination of ethanol due to genetic polymorphism for the two main enzyme systems, MEOS (microsomal P-450 oxidases) and alcohol dehydrogenase (ADH). Various HLA histocompatibility types have been associated with susceptibility of different populations to alcoholic liver damage but no single genotype has been identified yet.

Pathogenesis. The liver injury due to alcohol consumption culminating in morphologic lesions of alcoholic steatosis (fatty liver), alcoholic hepatitis and alcoholic cirrhosis is explained on the basis of the following mechanisms:

1. Hepatotoxicity by ethanol. There is some evidence to suggest that ethanol ingestion for a period of 8-10 days regularly may cause direct hepatotoxic effect on the liver and produce fatty change. Ethanol is directly toxic to microtubules, mitochondria and membrane of hepatocytes.

2. Hepatotoxicity by ethanol metabolites. The major hepatotoxic effects of ethanol are exerted by its metabolites, chiefly acetaldehyde. Acetaldehyde levels in blood are elevated in chronic alcoholics. Acetaldehyde is extremely toxic and can cause cytoskeletal and membrane damage and bring about hepatocellular necrosis.

3. Free radicals. Oxidation of ethanol by the cytochrome-450 oxidases (MEOS) leads to generation of free radicals which attack the membrane and proteins.

4. Increased redox ratio. Marked increase in the NADH:NAD redox ratio in the hepatocytes results in increased redox ratio of lactate-pyruvate, leading to lactic acidosis. This altered redox potential has been implicated in a number of metabolic consequences such as in fatty liver, collagen formation, occurrence of gout, impaired gluconeogenesis and altered steroid metabolism.

5. Retention of liver cell water and proteins. Alcohol is inhibitory to secretion of newly-synthesised proteins by the liver leading to their retention

in the hepatocytes. Water is simultaneously retained in the cell in proportion to the protein and results in swelling of hepatocytes resulting in hepatomegaly in alcoholics.

6. Hypoxia. Chronic ingestion of alcohol results in increased oxygen demand by the liver resulting in a hypoxic state which causes hepatocellular necrosis in centrilobular zone (zone 3). Redox changes are also more marked in zone 3.

7. Increased liver fat. In chronic alcoholism, there is rise in the amount of fat available to the liver which could be from exogenous (dietary) sources, excess mobilisation from adipose tissue or increased lipid synthesis by the liver itself. This may account for lipid accumulation in the hepatocytes.

8. Immunological mechanism. Cell-mediated immunity is impaired in alcoholic liver disease. Ethanol causes direct immunologic attack on hepatocytes. In a proportion of cases, alcohol-related liver cell injury continues unabated despite cessation of alcohol consumption which is attributed to immunologic mechanisms. Immunological mechanism may also explain the genesis of Mallory's alcoholic hyalin though more favoured hypothesis for its origin is the aggregation of intermediate filaments of prekeratin type due to alcohol-induced disorganisation of cytoskeleton.

9. Fibrogenesis and inflammation. The mechanisms of fibrosis and inflammatory response in alcoholic liver disease are uncertain but the possible mediators are lymphokines and monokines. The major stimulus for fibrogenesis is cell necrosis. All forms of collagen are increased and there is increased transformation of fat-storing Ito cells into myofibroblasts and fibrocytes. Leukotrienes which are important mediators of inflammation are produced by alcohol-damaged hepatocytes resulting in inflammatory reaction in the affected areas.

Pathologic changes. Three types of me logic lesions are described in alcoholic liver disease – alcoholic steatosis (fatty liver), alcoholic hepatitis and alcoholic cirrhosis.

1. Alcoholic Steatosis (Fatty Liver).

Grossly, the liver is enlarged, yellow, greasy and firm with a smooth and glistening capsule. *Microscopically,* the features consist of initial *microvesicular* droplets of fat in the hepatocyte cytoplasm followed by more common and pronounced feature of *macrovesicular* large droplets of fat displacing the nucleus to the periphery. *Fat cysts* may develop due to coalescence and rupture of fat-containing hepatocytes. Less often, *lipogranulomas* consisting of collection of lymphocytes, macrophages and some multinucleate giant cells may be found.

2. Alcoholic Hepatitis. Alcoholic hepatitis develops acutely, usually following a bout of heavy drinking. Repeated episodes of alcoholic hepatitis superimposed on pre-existing fatty liver are almost certainly a forerunner of alcoholic cirrhosis. *Histologically,* the features of alcoholic hepatitis are as follows.

i) *Hepatocellular necrosis*: Single or small clusters of hepatocytes, especially in the centrilobular area (zone 3), undergo ballooning degeneration and necrosis.

ii) *Mallory bodies or alcoholic hyalin*: These are eosinophilic, intracytoplasmic inclusions seen in perinuclear location within swollen and ballooned hepatocytes. They represent aggregates of cytoskeletal intermediate filaments (prekeratin). They can be best visualised with connective tissue stains like Masson's trichrome and chromophobe aniline blue, or by the use of immunoperoxidase methods. Mallory bodies are highly suggestive of, but not specific for, alcoholic hepatitis since Mallory bodies are also found in certain other conditions such as: primary biliary cirrhosis, Indian childhood cirrhosis, cholestatic syndromes, Wilson's disease, intestinal bypass surgery, focal nodular hyperplasia and hepatocellular carcinoma.

iii) *Inflammatory response:* The areas of hepatocellular necrosis and regions of Mallory bodies are associated with an inflammatory infiltrate, chiefly consisting of polymorphs and some scattered rnononuclear cells. In more extensive necrosis, the inflammatory infiltrate is more widespread and may involve the entire lobule.

iv) *Fibrosis:* Most cases of alcoholic hepatitis are accompanied by pericellular and perivenular fibrosis, producing a web-like or chickenwire-like appearance. This is also termed as *creeping collagenosis.*

3. Alcoholic Cirrhosis. Alcoholic cirrhosis is the most common form of lesion, constituting 60-70% of all cases of cirrhosis. A multitude of terms have been used for this type of cirrhosis such as *Laennec's cirrhosis, portal cirrhosis, hobnail cirrhosis, nutritional cirrhosis, diffuse cirrhosis* and *micronodular cirrhosis. Macroscopically,* alcoholic cirrhosis classically begins as micronodular cirrhosis (nodules less than 3 mm diameter), the liver being large, fatty and weighing usually above 2 kg. Eventually over a span of years, the liver shrinks to less than 1 kg in weight, becomes nonfatty, having macronodular cirrhosis (nodules larger than 3 mm in diameter), resembling postnecrotic cirrhosis. The nodules of the liver due to their fat content are tawny-yellow, on the basis of which Laennec in 1818 introduced the term *cirrhosis* first of all (from Greek *kirrhos*-tawny). The surface of liver in alcoholic cirrhosis is studded with diffuse nodules which vary little in size, producing hobnail liver (because of the resemblance of the surface with the sole of an old-fashioned shoe having short nails with heavy heads). On cut section, spheroidal or angular nodules of fibrous septa are seen.

Microscopically, alcoholic cirrhosis is a progressive alcoholic liver disease. Its features include the following:

i) Lobular architecture: No normal lobular architecture can be identified and central veins are hard to find.

ii) Fibrous septa: The fibrous septa that divide the hepatic parenchyma into nodules are initially delicate and extend from central vein to portal regions, or portal tract to portal tract, or both. As the fibrous scarring increases with time, the fibrous septa become jdense and more confluent.

iii) Hepatic parenchyma: The hepatocytes in the islands of surviving parenchyma undergo slow proliferation forming regenerative nodules having disorganised masses of hepatocytes. The hepatic parenchyma within the nodules shows extensive fatty change early in the disease. But as the fibrous septa become more thick, the amount of fat in hepatocytes is reduced. Thus, there is an inverse relationship between the amount of fat and the amount of fibrous scarring in the nodules.

iv) Necrosis, inflammation and bile duct proliferation: The etiologic clue to diagnosis in the form of Mallory bodies is hard to find in a fully-developed alcoholic cirrhosis. The fibrous septa usually contain sparse infiltrate of mononuclear cells with some bile duct proliferation. Bile stasis and increased cytoplasmic haemosiderin deposits due to enhanced iron absorption in alcoholic cirrhosis are some other noticeable findings.

Laboratory diagnosis. The laboratory findings in the course of alcoholic liver disease may be quite variable and liver biopsy is necessary in doubtful cases. Progressive form of the disease, however, generally presents the following biochemical and haematological alterations:

1. Elevated transaminases: increase in SCOT (AST) is more than that of SGPT (ALT).
2. Rise in serum γ-gluramyl transpeptidase (γ-GT).
3. Marked elevation in serum alkaline phosphatase.
4. Hyperbilirubinaemia.
5. Hypoproteinaemia with reversal of albumin-globulin ratio.
6. Prolonged prothrombin time and partial thromboplastin time.
7. Anaemia.

POST-NECROTIC CIRRHOSIS

Post-necrotic cirrhosis, also termed *post-hepatitic cirrhosis, macronodular cirrhosis and coarsely nodular cirrhosis,* is characterised by large and irregular nodules with broad bands of connective tissue and occurring most commonly after previous viral hepatitis.

Etiology. Based on epidemiologic and serologic studies, the following factors have been implicated in the etiology of post-necrotic cirrhosis.

1. *Viral hepatitis.* About 25% of patients give history of recent or remote attacks of acute viral hepatitis followed by chronic hepatitis. Most common association is with hepatitis C and B but hepatitis A is not known to evolve into cirrhosis.

2. *Drugs and chemical hepatotoxins.* A small percentage of cases may have origin from toxicity due to chemicals and drugs such as phosphorus, carbon tetrachloride, mushroom poisoning, acetaminophen and α-methyldopa.

3. *Others.* Certain infections (e.g. brucellosis), parasitic infestations (e.g. clonorchiasis), metabolic diseases (e.g. Wilson's disease or hepatolenticular degeneration) and advanced alcoholic liver disease may produce a picture of post-necrotic cirrhosis.

4. *Idiopathic.* After all these causes have been excluded, a group of cases remain in which the etiology is unknown.

Pathologic changes. Typically, post-necrotic cirrhosis is macronodular type. *Grossly,* the liver is usually small, weighing less than 1 kg, having distorted shape with irregular and coarse scars and nodules of varying size. Sectioned surface shows scars and nodules varying in diameter from 3 mm to a few centimeters. *Microscopically, the features are* as follows:

1. *Lobular architecture:* The normal lobular architecture of hepatic parenchyma is not completely lost. Instead, uninvolved portal tracts and central veins in the hepatic lobules can still be seen in some parts of surviving parenchyma.

2. *Fibrous septa:* The fibrous septa dividing the variable-sized nodules are generally thick.

3. *Necrosis, inflammation and bile duct proliferation:* Active liver cell necrosis is usually inconspicuous. Fibrous septa contain prominent mononuclear inflammatory cell infiltrate which may even form follicles. Often there is extensive proliferation of bile ductules derived from collapsed liver lobules.

4. *Hepatic parenchyma:* Liver cells vary considerably in size and multiple large nuclei are common in regenerative nodules. Fatty change may or may not be present in the hepatocytes.

BILIARY CIRRHOSIS

Biliary cirrhosis is defined as a chronic disorder characterised by clinical, biochemical and morphological features of long-continued cholestasis of intrahepatic or extrahepatic origin. Accordingly, biliary cirrhosis is of 2 main types:

• *Primary biliary cirrhosis* in which the destructive process of unknown etiology affects intrahepatic bile ducts.

• *Secondary biliary cirrhosis* resulting from prolonged mechanical obstruction of the extrahepatic biliary passages.

• In addition, a third cause for biliary cirrhosis is *primary sclerosing cholangitis* discussed at the end of this discussion.

Etiology. The etiology of the two forms of biliary cirrhosis is distinctive:

A. Primary biliary cirrhosis. The etiology of this type remains unknown. However, a few observations have been made to unfold its possible etiology:

1. The condition is predominant in middle-aged women (male: female ratio = 1:9) and has led to the suggestion of a possible *endocrine origin.*

2. *Familial incidence* has been observed suggesting the role of some genetic influence and certain HLA types.

3. There is *elevated cholesterol* level with appearance of xanthoma and xanthelasma. Hepatomegaly and chronic liver disease are late features of the disease.

4. However, presently the most widely accepted hypothesis is *autoimmune origin* of the disease. In support are the following observations:

- increased incidence of associated autoimmune diseases (e.g. scleroderma, Sjogren's syndrome, CREST syndrome, and autoimmune thyroiditis),
- circulating anti-mitochondrial antibody;
- elevated levels of immunoglobulins, particularly of IgM;
- increased levels of circulating immune complexes;
- decreased number of circulating T-cells; and
- accumulation of T cells around bile ducts.

B. Secondary biliary cirrhosis. Most cases of secondary biliary cirrhosis result from prolonged obstruction of extrahepatic biliary passages. These causes include:

1. Extrahepatic cholelithiasis, most common
2. Biliary atresia
3. Cancer of biliary tree and of head of pancreas
4. Postoperative strictures with superimposed ascending cholangitis.

Pathologic changes. *Grossly,* in both primary and secondary biliary cirrhosis, the liver is initially enlarged and greenish-yellow in appearance, but later becomes smaller, firmer and coarsely micronodular.

The salient features of the two forms of biliary cirrhosis are as under:

A. Primary biliary cirrhosis: The diagnostic histologic feature is a chronic, non-suppurative, destructive cholangitis involving intrahepatic bile ducts. The disease evolves through the following 4 histologic states:

Stage I: There are *florid bile duct lesions* confined to portal tracts. The changes in the affected area consist of destruction of bile ducts, presence of bile plugs, infiltration with acute and chronic inflammatory cells and sometimes formation of granulomas and lymphoid follicles.

Stage II: There is *ductular proliferation.* The ductal involvement is quite widespread with very few normal bile ducts. The inflammatory infiltrate too extends beyond the portal tracts into surrounding hepatic parenchyma. Periportal Mallory bodies may be present.

Stage III: This stage is characterised *by fibrous scarring* interconnecting the portal areas. There is diminished inflammatory infiltrate and reduced number of bile ducts.

Stage IV: Well-formed *micronodular pattern* of cirrhosis develops in a period of a few years.

B. Secondary biliary cirrhosis: Prolonged obstruction of extrahepatic bile ducts may produce the following histologic changes:

1. *Bile stasis*, degeneration and focal areas of centrilobular necrosis of hepatocytes.

2. Proliferation, dilatation and rupture of bile ductules in the portal area with formation of *bile lakes.*

3. *Cholangitis,* sterile or pyogenic, with accumulation of polymorphs around the bile ducts.

4. *Progressive expansion* of the portal tract by fibr and evolution into micronodular cirrhosis.

PRIMARY SCLEROSING CHOLANGITIS. Primary or idiopathic sclerosing cholangitis is characterised by progressive, inflammatory, sclerosing and obliterative process affecting mainly extra-hepatic, and sometimes intrahepatic ducts as well. The disease occurs in 3rd to 5th decade of life with two fold preponderance in males.

Etiology. Though idiopathic, the condition coexists with the following:

1. Inflammatory bowel disease, particularly idiopathic.
2. Multifocal fibrosclerosis syndromes
3. AIDS.

Pathologic changes. The liver shows varying grades of changes that include fatty change, acute and chronic active hepatitis, submassive liver necrosis and macronodular cirrhosis. Mallory bodies are present in some cases. Copper is usually deposited in the periportal hepatocytes in the form of reddish granules in the cytoplasm or as reddish cytoplasmic coloration, stainable by rubeanic acid or rhodamine stains for copper.

Involvement of basal ganglia in brain is in the form of toxic injury to neurons, in the cornea as greenish-brown deposits of copper in Descemet's membrane, and in the kidney as fatty and hydropic change.

CIRRHOSIS IN A1-ANTITRYPSIN DEFICIENCY

Alpha-1-antitrypsin deficiency is an autosomal codominant condition in which the homozygous state produces liver disease (cirrhosis), pulmonary disease (emphysema), or both. α1-antitrypsin is a glycoprotein normally synthesised in the rough endoplasmic reticulum of the hepatocytes and is the most potent protease inhibitor (Pi). A single autosomal dominant gene coding for oclan-

titrypsin is located on long arm of chromosome 14 that codes for immunoglobulin light chains too. Out of 24 different alleles labelled alphabetically, PiMM is the most common normal phenotype, while the most frequent abnormal phenotype in α1-antitrypsin deficiency leading to liver and/or lung disease is PiZZ in homozygote form. Other phenotypes in which liver disease occurs are PiSS and Pi-null in which serum α1-antitrypsin value is nearly totally deficient. Intermediate phenotypes, PiMZ and PiSZ persons are predisposed to develop hepatocellular carcinoma.

The patients may present with respiratory disease due to the development of emphysema, or may develop liver dysfunction, or both. At birth or in neonates, the features of cholestatic jaundice of varying severity may appear. In adolescence, the condition may evolve into hepatitis or cirrhosis which is usually well compensated.

Pathologic changes. Pulmonary changes in α1-antitrypsin deficiency in the form of emphysema. The hepatic changes vary according to the age at which the deficiency becomes apparent. At birth or in neonates, the histologic features consist of neonatal hepatitis that may be acute or 'pure cholestasis'. Micronodular or macronodular cirrhosis may appear in childhood or in adolescence in which the diagnostic feature is the presence of intracellular, acidophilic, PAS-positive globules in the periportal hepatocytes. Ultrastructurally, these globules consist of dilated rough endoplasmic reticulum.

CARDIAC CIRRHOSIS

Cardiac cirrhosis is an uncommon complication of severe right-sided congestive heart failure of longstanding duration. The common causes culminating in cardiac cirrhosis are cor pulmonale, tricuspid insufficiency or constrictive pericarditis. The pressure in the right ventricle is elevated which is transmitted to the liver via the inferior vena cava and hepatic veins. The patients generally have enlarged and tender liver with mild liver dysfunction. Splenomegaly occurs due to simple passive congestion.

Pathologic changes. *Grossly*, the liver is enlarged and firm with stretched Glisson's capsule. *Histologically*, in acute stage, the hepatic sinusoids are dilated and congested with haemorrhagic necrosis of centrilobular hepatocytes *(central haemorrhagic necrosis).* Severe and more prolonged heart failure results in delicate fibrous strands radiating from the central veins. These fibrous strands may form interconnections leading to cardiac cirrhosis and regenerative nodules.

INDIAN CHILDHOOD CIRRHOSIS

Indian childhood cirrhosis (ICC) is an unusual form of cirrhosis seen in children between the age of 6 months and 3 years in rural, middle class, Hin-

dus in India and in parts of South-East Asia and the Middle-East. The disease has some familial incidence suggesting a possible genetic or common environmental origin. Death occurs due to hepatic failure within a year of diagnosis.

Pathologic changes. Five histologic types ICC have been distinguished of which type II is the most common. This form is characterised by ballooning degeneration of hepatocytes, with some liver cells showing Mallory bodies and surrounded by neutrophilic exudate. Eventually, a fine micronodular cirrhosis results. Thus, the picture resembles acute alcoholic hepatitis but without the fatty change and with greatly impaired regeneration. There is marked increase in hepatic copper since the milk consumed by such infants is often boiled and stored in copper vessels in India. The condition should, therefore, be distinguished from Wilson's disease.

MISCELLANEOUS FORMS OF CIRRHOSIS

In addition to the various types of cirrhosis just described, a few other uncommon types are sometimes distinguished. These include the following:

1. Metabolic disorders e.g. in galactosaemia, hereditary fructose intolerance, glycogen storage diseases.

2. Infectious diseases e.g. in brucellosis, schistosomiasis, syphilis (hepar lobatum) and toxoplasma infection.

3. Gastrointestinal disorders e.g. in inflammatory bowel disease, cystic fibrosis of the pancreas and intestinal bypass surgery for obesity.

4. Infiltrative diseases e.g. in sarcoidosis.

CRYPTOGENIC CIRRHOSIS

Finally, when all the known etiologic types of cirrhosis have been excluded, there remain patients with cirrhosis in whom the cause is unknown. These cases are grouped under a waste-basket diagnosis of cryptogenic cirrhosis *(crypto* = concealed).

NON-CIRRHOTIC PORTAL FIBROSIS

Non-cirrhotic portal fibrosis (NCPF) is a group of congenital and acquired diseases in which there is localised or generalized hepatic fibrosis without nodular regenerative activity and there is absence of clinical and functional evidence of cirrhosis. One of the types associated with increased portal fibrosis without definite cirrhosis is seen in *idiopathic portal hypertension with splenomegaly,* reported from India and Japan. Another variant is *congenital hepatic fibrosis* seen in polycystic disease of the liver. The type common in India, particularly in young males, is related to *chronic arsenic ingestion* in drinking water and intake of orthodox medicines. NCPF is notable for its common association with portal hypertension in the absence of cirrhosis.

CLINICAL MANIFESTATIONS AND COMPLICATIONS OF CIRRHOSIS

The range of clinical features in cirrhosis varies widely, from an asymptomatic state to progressive liver failure and death. The onset of disease is insidious. In general, the features of cirrhosis are more marked in the alcoholic form than in other varieties. These include weakness, fatiguability, weight loss, anorexia, muscle wasting, and low grade fever due to hepatocellular necrosis or some latent infection. Advanced cases develop a number of complications which are as follows:

1. *Portal hypertension* and its major effects such as ascites, splenomegaly and development of collaterals (e.g. oesophageal varices, spider naevi etc) as discussed below.

2. *Progressive hepatic failure* and its manifestations as described already.

3. Development of *hepatocellular carcinoma,* more often in postnecrotic cirrhosis (HBV and HCV more often) than following alcoholic cirrhosis.

4. *Chronic relapsing pancreatitis,* especially in alcoholic liver disease.

5. *Steatorrhoea* due to reduced hepatic bile secretion.

6. *Gallstones* usually of pigment type, are seen twice more frequently in patients with cirrhosis than in general population.

7. *Infections* are more frequent in patients with cirrhosis due to impaired phagocytic activity of reticuloendothelial system.

8. *Haematologic derangements* such as bleeding disorders and anaemia due to impaired hepatic synthesis of coagulation factors and hypoalbuminaemia are present.

9. *Cardiovascular complications* such as atherosclerosis of coronaries and aorta and myocardial infarction are more frequent in cirrhotic patients.

10. *Musculoskeletal abnormalities* like digital clubbing, hypertrophic osteoarthropathy and Dupuytren's contracture are more common in cirrhotic patients.

11. *Endocrine disorders.* In males these consist of feminisation such as gynaecomastia, changes in pubic hair pattern, testicular atrophy and impotence, whereas in cirrhotic women amenorrhoea is a frequent abnormality.

12. *Hepatorenal syndrome* leading to renal failure may occur in late stages of cirrhosis.

The ultimate *causes of death* are hepatic coma, massive gastrointestinal haemorrhage from oesophageal varices (complication of portal hypertension), intercurrent infections, hepatorenal syndrome and development of hepatocellular carcinoma.

PORTAL HYPERTENSION

Increase in pressure in the portal system usually follows obstruction to the portal blood flow anywhere along its course. Portal veins have no valves

and thus obstruction anywhere in the portal system raises pressure in all the veins proximal to the obstruction. However, unless proved otherwise, portal hypertension means obstruction to the portal blood flow by cirrhosis of the liver. The normal portal venous pressure is quite low (10-15 mm saline). Portal hypertension occurs when the portal pressure is above 30 mm saline. Measurement of *intra-splenic pressure* reflects pressure in the splenic vein; the *percutaneous trans-hepatic pressure* provides a measure of pressure in the main portal vein; and wedged hepatic *venous pressure* represents sinusoidal pressure. Measurement of these pressures helps in localising the site of obstruction and classifying the portal hypertension.

Classification. Based on the site of obstruction to portal venous blood flow, portal hypertension is categorised into 3 main types – *intrahepatic, posthepatic* and *prehepatic*. Rare cases of idiopathic portal hypertension showing non-cirrhotic portal fibrosis are encountered as discussed above.

1. *Intrahepatic portal hypertension.* Cirrhosis is by far the commonest cause of portal hypertension. Other less frequent intrahepatic causes are metastatic tumours, non-cirrhotic nodular regenerative conditions, hepatic venous obstruction (Budd-Chiari syndrome), veno-occlusive disease, schistosomiasis, diffuse granulomatous diseases and extensive fatty change. In cirrhosis and other conditions, there is obstruction to the portal venous flow by fibrosis, thrombosis and pressure by regenerative nodules. About 30-60% patients of cirrhosis develop significant portal hypertension.

2. *Posthepatic portal hypertension.* This is uncommon and results from obstruction to the blood flow through hepatic vein into inferior vena cava. The causes are neoplastic occlusion and thrombosis of the hepatic vein or of the inferior vena cava (including Budd-Chiari syndrome). Prolonged congestive heart failure and constrictive pericarditis may also cause portal hypertension by transmitting the elevated pressure through the hepatic vessels into the portal vein.

3. *Prehepatic portal hypertension*. Blockage of portal flow before portal blood reaches the hepatic sinusoids results in prehepatic portal hypertension. Such conditions are thrombosis and neoplastic obstruction of the portal vein before it ramifies in the liver, myelofibrosis, and congenital absence of portal vein.

Major sequelae of portal hypertension.

Irrespective of the mechanisms involved in the pathogenesis of portal hypertension, there are 4 major clinical consequences – *ascites, varices* (collateral channels or portosystemic shunts), *splenomegaly* and *hepatic encephalopathy*.

1. ASCITES. Ascites is the accumulation of excessive volume of fluid within the peritoneal cavity. It frequently accompanies cirrhosis and other diffuse liver diseases. The development of ascites is associated with hae-

modilution, oedema and decreased urinary output. Ascitic fluid is generally transudate with specific gravity of 1.010, protein content below 3 gm/dl and electrolyte concentrations like those of other extracellular fluids. It may contain a few mesothelial cells and mononuclear cells. But presence of neutrophils is suggestive of secondary infection and red blood cells in ascitic fluid points to disseminated intra-abdominal cancer.

Pathogenesis. The ascites becomes clinically detectable when more than 500 ml of fluid has accumulated in the peritoneal cavity. Briefly, the systemic and local factors favouring ascites formation are as under:

A. Systemic factors:

i) *Decreased plasma colloid oncotic pressure.* There is hypoalbuminaemia from impaired hepatic synthesis of plasma proteins including albumin, as well as from loss of albumin from the blood plasma into the peritoneal cavity. Hypoalbuminaemia, in turn, causes reduced plasma oncotic pressure and leads to loss of water into extravascular space.

ii) *Hyperaldosteronism.* In cirrhosis, there is increased aldosterone secretion by the adrenal gland, probably due to reduced renal blood flow, and impaired hepatic metabolism and excretion of aldosterone.

iii) *Impaired renal excretion.* Reduced renal blood flow and excessive release of antidiuretic hormone results in renal retention of sodium and water and impaired renal excretion.

B. Local factors:

i) *Portal hypertension.* Portal venous pressure is not directly related to ascites formation but portal hypertension in combination with other factors contributes to the formation and localisation of the fluid retention in the peritoneal cavity.

ii) *Increased hepatic lymph formation.* Obstruction of hepatic vein such as in Budd-Chiari syndrome and increased intrasinusoidal pressure found in cirrhotic patients stimulates hepatic lymph formation that oozes through the surface of the liver.

2. VARICES (Collateral channels or Porto-systemic shunts). As a result of rise in portal venous pressure and obstruction in the portal Circulation within or outside the liver, the blood tends to bypass the liver and return to the heart by development of porto-systemic collateral channels (or shunts or varices). These varices develop at sites where the systemic and portal circulations have common capillary beds. The principal sites are as under:

i) Oesophageal varices: The development of oesophago-gastric varices which is frequently manifested by massive haematemesis is the most important consequence of portal hypertension.

ii) Haemorrhoids: Development of collaterals between the superior, middle and inferior haemorrhoidal veins resulting in haemorrhoids is another

common accompaniment. Bleeding from haemorrhoids is usually not as serious a complication as haematemesis from oesophageal varices.

iii) Caput medusae: Anastomoses between the portal and systemic veins may develop between the hilum of the liver and the umbilicus along the paraumbilical plexus of veins resulting in abdominal wall collaterals. These appear as dilated subcutaneous veins radiating from the umbilicus and are termed caput medusae (named after the snake-haired *Medusa).*

iv) Retroperitoneal anastomoses: In the retroperitoneum, portocaval anastomoses may be established through the veins of Retzius and the veins of Sappey.

3. SPLENOMEGALY. The enlargement of the spleen in prolonged portal hypertension is called congestive splenomegaly. The spleen may weigh 500-1000 gm and is easily palpable. The spleen is larger in young people and in macronodular cirrhosis than in micronodular cirrhosis.

4. HEPATIC ENCEPHALOPATHY. Porto-systemic venous shunting may result in a complex metabolic and organic syndrome of the brain characterised by disturbed consciousness, neurologic signs and flapping tremors. Hepatic encephalopathy is particularly associated with advanced hepatocellular disease such as cirrhosis.

HEPATIC TUMOURS AND TUMOUR-LIKE LESIONS

The liver is the site for benign tumours, tumour-like lesions, and both primary and metastatic malignant tumours. However, metastatic tumours are much more common than primary tumours and tumour-like lesions. Primary hepatic tumours may arise from *hepatic cells, bile duct epithelium,* or *mesodermal structures*. But first, brief comments on tumour-like lesions occurring in the liver are given below.

TUMOUR-LIKE LESIONS

These include cysts in the liver and focal nodular hyperplasia.

HEPATIC CYSTS

Cysts in the liver may be single or multiple. They are mainly of 3 types – congenital, simple (nonparasitic) and hydatid *(Echinococcus)* cysts.

1. Congenital cysts. These are uncommon. They are usually small (less than 1 cm in diameter) and are lined by biliary epithelium. They may be single, or occur as polycystic liver disease, often associated with polycystic kidney. On occasions, these cysts have abundant connective tissue and numerous ducts, warranting the designation of *congenital hepatic fibrosis.*

2. Simple (non-parasitic) cysts. Simple cysts are solitary non-parasitic cysts seen more frequently in middle-aged women. The cyst is usually large (up to 20 cm in diameter), lying underneath the Glisson's capsule and filled

with serous fluid. The cyst produces a palpable mass and may be associated with jaundice.

Histologically, the cyst wall is composed of compact fibrous tissue and is lined by low columnar to cuboid epithelium and occasionally by squamous lining.

3. Hydatid (echinococcus) cysts.

FOCAL NODULAR HYPERPLASIA

Focal nodular hyperplasia is a well-demarcated tumour-like nodule occurring underneath the Glisson's capsule. The nodules may be single or multiple, measuring about 5 cm in diameter. It may be tan-yellow or bile-stained. The sectioned surface shows a central fibrous scar.

Histologically, it is composed of collagenous septa radiating from the central fibrous scar which separate nodules of normal hepatocytes without portal triads or central hepatic veins. The fibrous septa contain prominent lymphocytic infiltrate.

The *etiology* of focal nodular hyperplasia is not known but these lesions are more common in women taking oral contraceptives.

BENIGN HEPATIC TUMOURS

These are uncommon and some of them are incidental autopsy findings. These include hepatocellular (liver cell) adenoma, bile duct adenoma (cholangioma) and haemangioma.

HEPATOCELLULAR (LIVER CELL) ADENOMA

Adenomas arising from hepatocytes are rare and are reported in women in reproductive age group in association with use of oral contraceptives, sex hormone therapy and with pregnancy. The tumour presents as intrahepatic mass that may be mistaken for hepatocellular carcinoma and may rupture causing severe intraperitoneal haemorrhage.

Pathologic changes. *Grossly,* the tumour usually occurs singly but about 10% are multiple. It is partly or completely encapsulated and slightly lighter in colour than adjacent liver or may be bile-stained. The tumours vary from a few centimeters up to 30 cm in diameter. On cut section, many of the tumours have varying degree of infarction and haemorrhage.

Histologically, liver cell adenomas are composed of sheets and cords of hepatocytes which may be normal-looking or may show slight variation in size and shape but no mitoses. The hepatocytes in adenomas contain greater amount of glycogen than the surrounding liver cells and may sometimes show fatty change. Hepatocellular adenomas lack portal tracts and bile ducts but bile canalculi containing bile-plugs may be present. Numerous blood vessels are generally present in the rumour which may be thrombosed. Thrombosis leads to infarction and may result in rupture with intraperitoneal haemorrhage.

BILE DUCT ADENOMA (CHOLANGIOMA)

Intra-hepatic or extrahepatic bile duct adenoma is a rare benign tumour. The tumour may be small, composed of acini lined by biliary epithelium and separated by variable amount of connective tissue, or are larger cystadenomas having loculi lined by biliary epithelium.

HAEMANGIOMA

Haemangioma is the commonest benign tumour of the liver. Majority of them are asymptomatic and discovered incidentally. Rarely, a haemangioma may rupture into the peritoneal cavity.

Pathologic changes. *Grossly,* haemangiomas appear as solitary or multiple, circumscribed, red-purple lesions, commonly subcapsular and varying from a few millimetres to a few centimetres in diameter. They are commonly cavernous type giving the sectioned surface a spongy appearance. *Histologically,* haemangioma of the liver shows characteristic large, cavernous, blood-filled spaces, lined by a single layer of endothelium and separated by connective tissue. Some haemangiomas may undergo progressive fibrosis and may later get calcified.

PRIMARY MALIGNANT HEPATIC TUMOURS

Among the primary malignant tumours of the liver, hepatocellular (liver cell) carcinoma accounts for approximately 85% of all primary malignant tumours, cholangiocarcinoma for about 5-10%, and infrequently mixed pattern is seen. The remainder are rare tumours that include hepatoblastoma, haemangiosarcoma (angiosarcoma) and embryonal sarcoma. Hepatic haemangiosarcoma and embryonal sarcoma resemble in morphology with their counterparts elsewhere in the body.

HEPATOCELLULAR CARCINOMA

Hepatocellular or liver cell carcinoma (HCC), sometimes termed hepatoma, is the most common primary malignant tumour of the liver. The tumour shows marked geographic variations in incidence which is closely related to hepatitis B virus infection in the region. Whearas the prevalence of HCC is less than 1% of all autopsies in the United States and Europe, the incidence in Africa and South-East Asia is 2-8%. HCC is the leading malignant tumour in South-East Asia. Liver cell cancer is 4-6 times more common in males than in females. The peak incidence occurs in 5th to 6th decades of life but in high incidence areas where HBV infection is prevalent, it occurs a decade or two earlier. The tumour supervenes on cirrhosis, usually post-necrotic macronodular type, in 70-80% of cases.

Etiology. A number of etiologic factors are implicated in the etiology of HCC, most important being HBV *infection (and now HCV infection also) and association with cirrhosis.*

1. *Relation to HBV infection.* Genesis of HCC is linked to prolonged infection with HBV. The evidence in support is both epidemiologic and direct.

i) The incidence of HBsAg positivity is higher in HCC patients. For example, in Taiwan, HBsAg-positive carriers have more than 200 times greater risk of developing HCC than HBsAg-negative patients, particularly when the infection is acquired in early life,

ii) In African and Asian patients, 95% cases of HCC have anti-HBc.

iii) There is more direct evidence of integration of HBV-DNA genome in the genome of tumour cells of HCC.

2. *Relation to HCV infection.* More recent evidence points to long-standing HCV infection as a major factor in the etiology of HCC. The evidences in support are as under:

i) In developed countries where higher incidence of HCC was earlier attributed to endemic infection (e.g. in Japan) has shown a remarkable shift to HCV infection. However, in less developed countries HBV is still the predominant etiologic factor in the pathogenesis of HCC.

ii) The patients having anti-HCV and anti-HBc antibodies together have three times higher risk of developing HCC than in those with either antibody alone.

iii) It is also possible that HBV and HCV infection act synergistically to predispose to HCC.

3. *Relation to cirrhosis.* Cirrhosis of all etiologic types is more commonly associated with HCC but the most frequent association is with macronodular post-necrotic cirrhosis. The mechanism of progression to HCC appears to be chronic regenerative activity in cirrhosis, or that the damaged liver in cirrhosis is rendered vulnerable to carcinogenic influences. *Liver cell dysplasia* identified by cellular enlargement, nuclear hyper-chromatism and multinucleate cells, is found in 60% of cirrhotic livers with HCC and in only 10% of non-cirrhotic livers.

4. *Relation to alcohol.* It has been observed that alcoholics have about four-fold increased risk of developing HCC. It is possible that alcohol may act as co-carcinogen with HBV infection, but alcohol does not appear to be a hepatic carcinogen *perse.*

5. *Mycotoxins.* An important mycotoxin, aflatoxin Bl, produced by a mould *Aspergillusflavus,* can contaminate stored grains or groundnuts, especially in less developed countries. Aflatoxin Bl is carcinogenic; it may act as a co-carcinogen with hepatitis B or may suppress the cellular immune response.

6. Chemical carcinogens. A number of chemical carcinogens can induce liver cancer in experimental animals. These include butter-yellow and nitrosamines used as common food additives.

7. *Miscellaneous factors.* Limited role of various other factors in HCC has been observed. These include:

i) haemochromatosis;

ii) CXL-antitrypsin deficiency;

iii) prolonged immunosuppressive therapy in renal transplant patients;

iv) other types of viral hepatitis;

v) tobacco smoking; and

vi) parasitic infestations such as clonorchiasis and schistosomiasis.

Pathologic changes. *Macroscopically*, the HCC may form one of the following 3 patterns of growth, in decreasing order of frequency: i) *Expanding type:* Most frequently, it forms a *single,* yellow-brown, *large mass,* most often in the right lobe of the liver with central necrosis, haemorrhage and occasional bile-staining. It may be deceptively encapsulated.

ii) *Multifocal type:* Less often, *multifocal, multiple masses,* 3-5 cm in diameter, scattered throughout the liver are seen.

iii) *Infiltrating (Spreading) type:* Rarely, the HCC forms diffusely infiltrating tumour mass. *Microscopically*, the tumour cells in the typical HCC resemble hepatocytes but vary with the degree of differentiation, ranging from well-differentiated to highly anaplastic lesions. Most of the HCC have trabecular growth pattern. The tumour cells have a tendency to invade and grow along blood vessels. Thus important diagnostic features are the *patterns of tumour cells* and their *cytologic features*:

1. Histologic patterns: These include the following:

i) *Trabecular or sinusoidal pattern* is the most common. The trabeculae are made up of 2-8 cell wide layers of tumour cells separated by vascular spaces or sinusoids which are endothelrum-lined.

ii) *Pseudoglandular or acinar pattern* is seen sometimes. The tumour cells are disposed around central cystic space formed by degeneration and breakdown in solid trabeculae.

iii) *Compact pattern* resembles trabecular pattern but the tumour cells form large solid masses with inconspicuous sinusoids.

iv) *Scirrhous pattern* is characterised by more abundant fibrous stroma.

2 Cytologic features: The typical cytologic features in the HCC consist of cells resembling hepatocytes having vesicular nuclei with prominent nucleoli. The cytoplasm is granular and eosinophilic but becomes increasingly basophilic with increasing malignancy. Aside from these features, a few other cytologic variants are: pleomorphism, bizarre giant cell formation, spindle-shaped cells, tumour cells with clear cytoplasm, presence of bile within dilated canaliculi, and intracytoplasmic Mallory's hyalin.

FIBROLAMELLAR CARCINOMA

A clinicopathologic variant of the HCC is fibrolamellar carcinoma of the liver found in young people of both sexes. The tumour forms a single large mass which may be encapsulated and occurs in the absence of cirrhosis.

Histologically, the tumour is composed of eosinophilic polygonal cells (oncocytes) forming cords and nests which are separated by bands of fibrous stroma.

The prognosis of fibrolamellar carcinoma is better than other forms of HCC.

Spread. The HCC can have both intrahepatic and extrahepatic spread which faithfully reproduces the structure of the primary tumour.

• Intrahepatic spread occurs by haematogenous route and forms multiple metastases in the liver.

• Extrahepatic spread occurs via hepatic or portal veins to different sites, chiefly to lungs and bones, and by lymphatic route to regional lymph nodes at the porta hepatis and to mediastinal and cervical lymph nodes.

The causes of death from the HCC are cachexia, massive bleeding from oesophageal varices, and liver failure with hepatic coma.

CHOLANGIOCARCINOMA

Cholangiocarcinoma is the designation used for carcinoma arising from bile duct epithelium within the liver *(peripheral Cholangiocarcinoma).* Carcinomas arising from the large hilar ducts *(hilar Cholangiocarcinoma)* and from extrahepatic ducts are termed *bile duct carcinomas*. None of the etiologic factors related to HCC have any role in the genesis of Cholangiocarcinoma. However, the etiological factors involved in it are exposure to radio-opaque dye thorotrast, anabolic steroids, clonorchiasis and fibrocystic disease. The tumour affects older people and the clinical features are those of HCC but with prominence of jaundice.

Pathologic changes. *Grossly*, the tumour i firm to hard and whitish. *Microscopically*, the tumourhas glandular structure. The tumour cells resemble biliary epithelium but without bile secretion. They form various patterns such as tubular, ductular or papillary. The stroma consists of fibrous tissue with little or no capillary formation. Occasionally, mucinous, signet-ring and adenosquamous type of patterns are found. An uncommon variant is combined hepatocellular-cholangiocarcinoma.

HEPATOBLASTOMA

Hepatoblastoma is a rare malignant tumour arising from primitive hepatic parenchymal cells. It presents before the age of 2 years as progressive abdominal distension with anorexia, failure to thrive, fever and jaundice. It is more common in boys. The concentration of serum AFP is high. The tumour

grows rapidly and causes death by haemorrhage, hepatic failure or widespread metastases.

Pathologic changes, *Grossly,* the tumour is circumscribed and tabulated mass measuring 5-25 cm in size, having areas of cystic degeneration, haemorrhage and necrosis.

Microscopically, hepatoblastoma consists of 2 components:

i) Epithelial component contains 2 types of cells – *'embryonal' hepatocytes* are small with dark-staining, hyperchromatic nuclei and scanty cytoplasm, and *'foetal' hepatocytes* are larger with more cytoplasm that may be granular or clear. The epithelial cells are organised in trabeculae, ribbons or rosettes,

ii) Mesenchymal component includes fibrous connective tissue, cartilage and osteoid of variable degree of maturation. Extramedullary haematopoiesis is a frequent accompaniment.

SECONDARY HEPATIC TUMOURS

Metastatic tumours in the liver are more common than the primary hepatic tumours. Most frequently, they are blood-borne metastases, irrespective of whether the primary tumour is drained by portal vein or systemic veins. Most frequent primary rumours metastasising to the liver, in descending order of frequency, are those of stomach, breast, lungs, colon, oesophagus, pancreas, malignant melanoma and haematopoietic malignancies. Sarcomas rarely metastasise to the liver. Occasionally, metastatic involvement may be present in the absence of obvious evidence of primary tumour. Aside from general features of disseminated malignancy such as anorexia, cachexia and anaemia, the patients have hepatomegaly with nodular free margin. There is little hepatic dysfunction until late in the course of hepatic metastatic disease.

Pathologic changes. *Grossly,* most metastatic carcinomas form multiple, spherical, nodular masses which are of variable size. Liver is enlarged and heavy, weighing 5 kg or more. The tumour deposits are white, well-demarcated, soft or haemorrhagic. The surface of the liver shows characteristic umbilication due to central necrosis of nodular masses.

Histologically, the metastatic tumours generally reproduce the structure of the primary lesions.

PATHOLOGY OF BILIARY SYSTEM

The gallbladder is a pear-shaped organ, *9* cm in length and has a capacity of approximately 50 ml. It consists of the *fundus, body* and *neck* that tapers into the cystic duct. The two hepatic ducts from right and left lobes of the liver unite at the porta hepatis to form the common hepatic duct which is joined by the cystic duct from the gallbladder to form the common bile duct. The common bile duct enters the second part of the duodenum posteriorly. In about 70% of cases, it is joined by the main pancreatic duct to form the combined opening in the duodenum *(ampulla of Vater).* In 30% cases, the common bile duct and the pancreatic duct open separately into the duodenum. The common bile duct in its duodenal portion is surrounded by longitudinal and circular muscles derived from the duodenum forming *sphincter of Oddi.*

Histologically, the gallbladder, unlike the rest of gastrointestinal tract, lacks the muscularis mucosae and submucosa. The wall of the gallbladder is composed of the following 4 layers:

1. Mucosal layer: It has a single layer of tall columnar epithelium which is thrown into permanent folds that are larger and more numerous in the neck of the gallbladder. Beneath the epithelium is delicate lamina propria that contains capillaries, and in the region of the neck, a few acinar glands are present.

2. Smooth muscle layer: External to the lamina propria are smooth muscle bundles in layers –inner longitudinal, middle oblique, and outer circular.

3. Perimuscular layer: Outer to the muscle layer is a zone of fibrous connective tissue with some interspersed

4. Serosal layer: The perimuscular layer is covered by serosa on the peritoneal surface of the gallbladder. The peritoneum covers the gallbladder except in the region of gallbladder fossa where it is embedded in the liver. The *extrahepatic bile ducts* are also lined by tall columnar epithelium that overlies the lamina propria. It is surrounded by dense layer of fibromuscular tissue. The ducts which lie between the lobules of the liver and receive bile from the canaliculi are lined by cuboidal or flattened cells.

The main function of the gallbladder is to store and concentrate the bile secreted by the liver and then deliver it into the intestine for digestion and absorption of fat. The concentrating ability of the gallbladder is due to its absorptive mucosal surface that has numerous folds. Normally, the liver secretes approximately 500 ml of bile per day and the gallbladder concentrates it 5-10 times. The motility, concentration and relaxation of the gallbladder are under the influence of a peptide hormone, cholecystokinin, released from neuro-endocrine cells of the duodenum and jejunum.

CONGENITAL ANOMALIES

Several uncommon congenital anomalies of the biliary system have been described. These include: agenesis, duplication and heterotopic tissue. However, *congenital cystic lesions* of the bile ducts (as also of the liver) are more frequently being diagnosed. These conditions include: congenital intrahepatic biliary dilatation (Caroli's disease), choledochal cysts, polycystic liver disease and congenital hepatic fibrosis. They are found in various combinations and are usually inherited. All of them may be complicated by malignant change.

CHOLELITHIASIS (GALLSTONES)

Gallstones are formed from constituents of the bile (viz. cholesterol, bile pigments and calcium salts) alongwith other organic components. Ac-

cordingly, the gallstones commonly contain cholesterol, bile pigment and calcium salts in varying proportions. They are usually formed in the gallbladder, but sometimes may develop within extrahepatic biliary passages, and rarely in the larger intrahepatic bile duct.

Risk factors. The incidence of gallstones varies markedly indifferent geographic areas, age, sex, diet and various other risk factors. These factors which largely pertain to cholesterol stones can be summed up in the old saying that gallstones are common in 4F's – *'fat, female, fertile (multipara) and forty'*. Some of the risk factors in lithogenesis are explained below:

1. Geography. Gallstones are quite prevalent in almost the entire Western world. American Indians have the highest known prevalence. Black Africans and populations in the Eastern world are relatively free of cholelithiasis.

2. Genetic factors. There is increased frequency of gallstones in family members of patients with cholelithiasis.

3. Age. There is steady increase in the prevalence of gallstones with advancing age which may be related to increased cholesterol content in the bile. The incidence increases above the age of 40 and presentation is usually in the 50s and 60s.

4. Sex. Gallstones are twice more frequent in women than in men. In the United States, autopsy series have shown gallstones in about 20% of women and 8% of men above the age of 40. The incidence is higher in multiparous women than in nulliparous women.

5. Drugs. Women on oestrogen therapy or on birth control pills have higher incidence of gallstones. This is considered to be due to production of more lithogenic bile as a result of cholestatic effect of oestrogen. Similar is the influence of clofibrate used for lowering blood cholesterol.

6. Obesity. Obesity is associated with increased cholesterol synthesis and excretion resulting in higher incidence of gallstones in obese patients.

7. Diet. Deficiency of dietary fibre content in Western countries is linked to higher prevalence of gallstones. A moderate consumption of alcohol, however, seems to protect against gallstones.

8. Gastrointestinal diseases. Certain gastrointestinal disorders such as Crohn's disease, ileal resection, ileal bypass surgery etc are associated with interruption in enterohepatic circulation followed by gallstone formation.

9. Factors in pigment gallstones. All the above factors apply largely to cholesterol stones. Pigment stones, whether pure or mixed type, are more frequently associated with haemolytic anaemias which lead to increased content of unconjugated bilirubin in the bile. Pigment stones are also more frequent in cirrhosis and hepatocellular disease.

Pathogenesis. The mechanism of cholesterol gallstone formation or lithogenesis is determined by 3 major factors – *supersaturation of bile with cholester-*

ol, cholesterol nucleation, and *the hyperfunction of gallbladder.* However, the mechanism of pigment stones is less clear and discussed separately.

1. Supersaturation of bile. Gallstone formation is related to supersaturation of bile with cholesterol due to increased proportion of cholesterol with a decreased proportion of bile acids in it. Normally, water is the major constituent (85-95%) of the bile, while cholesterol present in bile is insoluble in water. It is kept in solution by formation of micelles that have a hydrophilic external surface and a hydrophobic internal surface. Cholesterol is incorporated into the wall of the micelles, thus producing a bile that is supersaturated with cholesterol, termed *lithogenic bile.*

2. Cholesterol nucleation. Initiation of cholesterol stones occurs by nucleation of cholesterol monohydrate crystals. Bile from patients of gallstones contains a potent nucleating factor and the gallbladder mucin secreted by epithelial cells, both of which play a role in cholesterol nucleation. A deficiency of antinucleating factors has also been suggested to play role in nucleation.

3. Gallbladder hyperfunction. Normally, the gallbladder is capable of emptying and clearing any sludge or debris which might initiate stone formation. This takes place under the influence of cholecystokinin secreted from small intestine. However, the motility of gallbladder may be impaired due to decrease in cholecystokinin receptors in the gallbladder resulting in stasis of biliary sludge and lithogenesis.

Pathogenesis of pigment gallstones. The mechanism of pigment stone formation is mainly explained on the basis of increased level of unconjugated bilirubin in the bile as a result of excessive haemolysis of red blood cells. In Oriental countries, pigment stones are associated with parasitic infestations of the biliary tract such as *Clonorchis sinensis* and *Ascaris lumbricoides.*

TYPES OF GALLSTONES. As stated before, gallstones contain cholesterol, bile pigment and calcium carbonate, either in pure form or in various combinations. Accordingly, gallstones are of 3 major types — *pure gallstones, mixed gallstones* and *combined gallstones.* Mixed gallstones are the most common (80%) while pure and combined gallstones comprise 10% each. In general, gallstones are formed most frequently in the gallbladder but may xicur in extrahepatic as well as intrahepatic biliary massages. Gallbladders containing pure stones show no significant inflammatory reaction, whereas chronic rholecystitis is invariably present in gallbladders with nixed and combined gallstones. Presence of calcium salts renders gallstones radio-opaque, while cholesterol stones appear as radiolucent filling defects in the gallbladder.

The salient features of various types of gallstones:

1. Pure gallstones. They constitute about 10% of all gallstones. They are further divided into 3 types according to the component of bile forming them. These are as under:

i) Pure cholesterol gallstones: They are usually solitary, oval and fairly large (3 cm or more) filling the gallbladder. Their surface is hard, smooth, whitish-yellow and glistening. On cut section, the pure cholesterol stone shows radiating glistening crystals. It may result in deposition of cholesterol within the mucosal macrophages of the gallbladder producing *cholesterolosis* which is an asymptomatic condition. Pure cholesterol stones are radiolucent but 10-20% of them have calcium carbonate in them which renders them opaque.

ii) Pure pigment gallstones: These stones composed of bile pigment (calcium bilirubinate) are generally multiple, jet-black and small (less than 1 cm in diameter). They have mulberry like external surface. They are soft and can be easily crushed. The gallbladder usually appears uninvolved.

iii) Pure calcium carbonate gallstones: They are rare. Calcium carbonate gallstones are usually multiple, grey-white, small (less than 1 cm in diameter), faceted and fairly hard due to calcium content. They, too, do not produce any change in the gallbladder wall.

2. Mixed gallstones. Mixed gallstones are the most common (80%). They are always multiple, multifaceted so that they fit together and vary in size from as tiny as sand-grain to 1 cm or more in diameter. On section, they have distinct laminated structure with alternating dark pigment layer and pale-white layer revealing different combinations of cholesterol, bilirubin pigment and calcium carbonate, laid down in layers at different times. Mixed gallstones are invariably accompanied by chronic cholecystitis.

3. Combined gallstones. They comprise about 10% of all gallstones. Combined gallstones are usually solitary, large and smooth-surfaced. It has a *pure gallstone nucleus* (cholesterol, bile pigment or calcium carbonate) and outer shell of mixed gallstone; or a *mixed gallstone nucleus* with pure gallstone shell. Combined gallstones, too, are associated with chronic cholecystitis.

Clinical manifestations and complications. In about 50% cases, gallstones cause no symptoms and may be diagnosed by chance during investigations for some other condition *(silent gallstones).* The future course in such asymptomatic silent cases is controversial, most surgeons advocating cholecystectomy while physicians advising watchful waiting. Follow-up studies, however, show that only about 10% of such cases develop symptoms. Symptomatic gallstone disease appears only when complications develop. These are as under:

1. *Cholecystitis.* The relationship between cholelithiasis and cholecystitis is well known but it is not certain which of the two comes first. The patients with gallstones develop symptoms due to cholecystitis which include typical biliary colic precipitated by fatty meal, nausea, vomiting, fever alongwith leucocytosis and high serum bilirubin.

2. *Choledocholithiasis.* Gallstones may pass down into the extrahepatic biliary passages and the small bowel, or less often they may be formed in the

biliary tree. Patients with gallstone in the common bile duct frequently develop pain and obstructive jaundice. Fever may develop due to bacterial ascending cholangitis.

3. *Mucocele.* Mucocele or hydrops of the gallbladder is distension of the gallbladder by clear, watery mucinous secretion resulting from impacted stones in the neck of the gallbladder.

4. *Biliary fistula.* An uncommon complication of cholelithiasis is formation of fistulae between one part of the biliary system and the bowel, and rarely between the gallbladder and the skin.

5. *Gallstone ileus.* A gallstone in the intestine may be passed in the faeces without causing symptoms.

Occasionally, however, gallstones in the intestine may cause intestinal obstruction called gallstone ileus.

6. *Gallbladder cancer.* There is a small and doubtful risk of development of cancer of the gallbladder in cases with cholelithiasis.

CHOLECYSTITIS

Cholecystitis or inflammation of the gallbladder may be acute, chronic, or acute superimposed on chronic. Though chronic cholecystitis is more common, acute cholecystitis is a surgical emergency.

ACUTE CHOLECYSTITIS

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

Etiopathogenesis. Based on the initiating mechanisms, acute cholecystitis occurs in two types of situations – *acute calculous* and *acute acalculous cholecystitis.*

• Acute calculous cholecystitis. In 90% of cases, acute cholecystitis is caused by obstruction in the neck of the gallbladder or in the cystic duct by a gallstone. The commonest location of impaction of a gallstone is in Hartmann's pouch. Obstruction results in distension of the gallbladder followed by acute inflammation which is initially due to chemical irritation. Later, however, secondary bacterial infection, chiefly by *E. coli* and *Streptococcus faecalis,* supervenes.

• Acute acalculous cholecystitis. The remaining 10% cases of acute cholecystitis do not contain gallstones. In such cases, a variety of causes have been assigned such as previous nonbiliary surgery, multiple injuries, burns, recent childbirth, severe sepsis, dehydration, torsion of the gallbladder and diabetes mellitus. Rare causes include primary bacterial infection like salmonellosis and cholera and parasitic infestations.

Pathologic changes. Except for the presence or absence of calculi, the two forms of acute cholecystitis are morphologically similar. *Grossly,* the

gallbladder is distended and tense. The serosal surface is coated with fibrinous exudate with congestion and haemorrhages. The mucosa is bright red. The lumen is filled with pus mixed with green bile. In cakulous cholecystitis, a stone is generally impacted in the neck or in the cystic duct. When obstruction of the cystic duct is complete, the lumen is filled with purulent exudate and the condition is known as *empyema of the gallbladder*. *Microscopically*, wall of the gallbladder shows marked inflammatory oedema, congestion and neutrophilic exudate. There may be frank abscesses in the wall and gangrenous necrosis with rupture into the peritoneal cavity *(gangrenous cholecystitis).*

CHRONIC CHOLECYSTITIS

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

Etiopathogenesis. The association of chronic cholecystitis with mixed and combined gallstones is virtually always present. However, it is not known what initiates the inflammatory response in the gallbladder wall. Possibly, supersaturation of the bile with cholesterol predisposes to both gallstone formation and inflammation. In some patients, repeated attacks of mild acute cholecystitis result in chronic cholecystitis.

Pathologic changes. *Grossly*, the gallbladder is generally contracted but may be normal or enlarged. The wall of the gallbladder is thickened which on cut section is grey-white due to dense fibrosis or may be even calcified. The mucosal folds may be intact, thickened, or flattened and atrophied. The lumen commonly contains multiple mixed stones or a combined stone. *Histologically,* the features are as under:

1. Thickened and congested mucosa but occasionally mucosa may be totally destroyed.

2. Penetration of the mucosa deep into the wall of the gallbladder up to muscularis layer to form *Rokitansky-Aschoffsm uses*.

3. Variable degree of chronic inflammatory reaction, consisting of lymphocytes, plasma cells and macrophages, present in the lamina propria and subserosal layer.

4. Variable degree of fibrosis in the subserosal and subepithelial layers.

A few morphologic variants of chronic cholecystitis are considered below:

• Cholecystitis glandularis, when the mucosal folds fuse together due to inflammation and result in formation of crypts of epithelium buried in the gallbladder wall.

• Porcelain gallbladder is the pattern when the gallbladder wall is calcified and cracks like an eggshell.

• Acute on chronic cholecystitis is the term used for the morphologic changes of acute cholecystitis superimposed on changes of chronic cholecystitis.

TUMOURS OF BILIARY SYSTEM

Tumours of the biliary tract include benign and malignant tumours and carcinoid of the biliary tract.

BENIGN TUMOURS

Benign tumours such as papilloma, adenoma, adenomyoma, fibroma, lipoma, myxoma, and haemangioma have been described in the biliary tract but all of them are exceedingly rare. *Adenomyoma* is more common benign tumour than the rest. All these tumours resemble their counterparts in morphology elsewhere in the body.

MALIGNANTTUMOURS

Carcinoma of the gallbladder and carcinoma of the bile ducts and ampulla of Vater are among the more frequent malignant tumours of the biliary tract.

CARCINOMA OF THE GALLBLADDER

Primary carcinoma of the gallbladder is more prevalent than other cancers of the extrahepatic biliary tract. Like cholelithiasis and cholecystitis, it is more frequent in women than in men with a peak incidence in 7th decade of life. It is usually slow-growing and may remain undetected until the time it is widely spread and rendered inoperable.

Etiology. A number of etiologic factors have been implicated.

1. *Cholelithiasis and cholecystitis.* The most signin cant association of cancer of the gallbladder is with cholelithiasis and cholecystitis, though there is no definite evidence of causal relationship. Cholelithiasir and cholecystitis are present in about 75% cases of gallbladder cancer. But, on the other hand, the incidence of documented gallbladder cancer in the presence of cholelithiasis and cholecystitis is about 0.5% only. Porcelain gall bladdder is particularly likely to become cancerous.

2. *Chemical carcinogens.* A number of chemical carcinogens structurally similar to naturally-occurring bile acids have been considered to induce gallbladder cancer. These include methyl cholanthrene, various nitrosamines and pesticides. Workers engaged in rubber industry have higher incidence of gallbladder cancer.

3. *Genetic factors.* There is higher incidence of cancer of the gallbladder in certain populations living in the same geographic region suggesting a strong genetic component in the disease. Japanese immigrants and Native Americans of the South-Western America have increased frequency while American Indians and Mexicans have lower incidence.

4. *Miscellaneous.* Patients who have undergone previous surgery on the biliary tract have higher incidence of subsequent gallbladder cancer. Patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease) have high incidence of gallbladder cancer.

Pathologic changes. The commonest site is the fundus, followed next in frequency by the neck of the gallbladder.

Grossly, cancer of the gallbladder is of 2 types – infiltrating and fungating type.

1. Infiltrating type appears as an irregular area of diffuse thickening and induration of the gallbladder wall. It may have deep ulceration causing direct invasion of the gallbladder wall and liver bed. On section, the gallbladder wall is firm due to scirrhous growth.

2. Fungating type grows like an irregular, friable, papillary or cauliflower-like growth into the lumen as well as into the wall of the gallbladder and beyond.

Histologicaltyf the following patterns are observed:

1. Most gallbladder cancers are *adenocarcinomas* (90%). They may be papillary or infiltrative, well-differentiated or poorly-differentiated. Most are non-mucin secreting but some are colloid carcinomas forming mucus pools:

2. About 5% of gallbladder cancers are *squamous cell carcinomas* arising from squamous metaplastic epithelium.

3. A few cases show both squamous and adenocarcinoma pattern of growth called *adenosquamous carcinoma*.

CARCINOMA OF EXTRAHEPATIC BILE DUCTS AND AMPULLA OF VATER

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

Etiology. There is no association between bile duct carcinoma and gallstones. Bile duct cancers are associated with a number of other conditions such as ulcerative colitis, sclerosing cholangitis, parasitic infestations of the bile ducts with *Fasciola hepatica* (liver fluke), *Ascaris lumbricoides* and *Clonorchis sinensis.*

Pathologic changes. Extrahepatic bile duct carcinoma may arise anywhere in the biliary tree but the most frequent sites, in descending order of frequency, are: the ampulla of Vater, lower end of common bile duct, hepatic ducts, and the junction of hepatic ducts to form common bile duct.

Grossly, bile duct carcinoma is usually small, extending for 1-2 cm along the duct, producing thickening of the affected duct.

Histologically, the tumour is usually well-differentiated adenocarcinoma which may or may not be mucin-secreting. Perineural invasion is frequently present.

PATHOLOGY OF PANCREAS

The human pancreas, though anatomically a single organ, histologically and physiologically has 2 distinct parts – the *exocrine* and *endocrine parts.* The endocrine part of the gland is dealt with in Chapter 24 while the exocrine gland is considered here. The whole of pancreas, exocrine and endocrine, is embryologically derived from the foregut endoderm.

The pancreas lies obliquely in the concavity of the duodenum as an elongated structure about 15 cm in length and 100 gm in weight. It is subdivided into 3 topographic zones:

1. The *head* lying in the concavity of the duodenum and the *uncinate process* projecting from the head.
2. The *body* comprises the main part of the gland.
3. The *tail* is the thin, tapering part of the gland towards the hilum of the spleen.

The exocrine pancreas constitutes 80 to 85% of the total gland, while the endocrine pancreas comprises the remaining part.

The exocrine part is divided into rhomboid lobules separated by thin fibrous tissue septa containing blood vessels, lymphatics, nerves and ducts. Each lobule is composed of numerous acini. The acini are lined by pyramid-shaped columnar epithelial cells. These secretory epithelial cells have microvilli projecting into the lumen from their surface. The apical portions of these cells contain zymogen granules in their cytoplasm, while the basal region is deeply basophilic and free of zymogen granules. The zymogen granules are membrane-bound sacs which fuse with the plasma membrane and are then released into the lumina of the acini. The secretions are carried from the acini by fine ductal branches into the small ducts in the lobules and eventually into the main pancreatic duct. The main pancreatic duct is formed by fusion of the ventral duct with the dorsal duct; the latter also called the *duct of Wirsung,* provides the main drainage for pancreatic secretions into the duodenum. The pancreatic secretions are delivered into the second part of the duodenum either by a combined opening of the pancreatic and bile ducts in the ampulla of Vater, or less often both open separately into the duodenum. Occasionally, the proximal part of the dorsal duct persists as the *duct of Santorini.*

The main functions of the exocrine pancreas is the alkaline secretion of digestive enzymes prominent among which are trypsin, chymotrypsin, elastase, amylase, lipase and phospholipase.

DEVELOPMENTAL ANOMALIES

The significant developmental anomalies of the pancreas are ectopic or aberrant pancreatic tissue in Meckel's diverticulum, anomalies of the ducts, and cystic fibrosis. Only the last named requires elaboration here.

Cystic Fibrosis

Cystic fibrosis of the pancreas or fibrocystic disease is a hereditary disorder characterised by viscid mucous secretions in all the exocrine glands of the body *(mucoviscidosis)* and associated with increased concentrations of electrolytes in the eccrine glands. The terms 'cystic fibrosis' and 'fibrocystic disease' are preferable over 'mucoviscidosis' in view of the main pathologic change of fibrosis produced as a result of obstruction of the passages by viscid mucous secretions. The disease is transmitted as an *autosomal recessive*

trait with apparent clinical features in homozygotes only. The genetic defect appears to lie in chromosome 7. It is quite common in the whites (1 per 2000 livebirths). The clinical manifestations may appear at birth or later in adolescence and pertain to multiple organs and systems such as pancreatic insufficiency, intestinal obstruction, steatorrhoea, malnutrition, hepatic cirrhosis and respiratory complications.

Pathologic changes. Depending upon the severity of involvement and the organs affected, the pathologic changes are variable. Most of the changes are produced as a result of obstruction by viscid mucous.

1. Pancreas. The pancreas is almost invariably involved in cystic fibrosis.

Grossly, pancreatic lobules are ovoid rather than rhomboid. Fatty replacement of the pancreas and grossly visible cysts may be seen.

Microscopically the lobular *architecture of pan*creatic parenchyma is maintained. There is increased interlobular fibrosis. The acini are atrophic and many of the acinar ducts contain laminated, eosinophilic concretions. Rarely, inflammation, fat necrosis and cyst formation may be seen. The islet tissue (endocrine pancreas) generally remains intact. Atrophy of the exocrine pancreas may cause impaired fat absorption, steatorrhoea, intestinal obstruction and avitaminosis A.

2. Liver. The bile canaliculi are plugged by viscid mucous which may cause diffuse fatty change, portal fibrosis and ductular proliferation. More severe involvement may cause biliary cirrhosis.

3. Respiratory tract. Changes in the respiratory passages are seen in almost all typical cases of cystic fibrosis. The viscid mucous secretions of the submucosal glands of the respiratory tract cause obstruction, dilatation and infection of the airways. The changes include chronic bronchitis, bronchiectasis, bronchiolitis, bronchiolectasis, peribronchiolar pneumonia and inflammatory nasal polyps.

4. Salivary glands. Pathologic changes in the salivary glands are similar to those in pancreas and include obstruction of the ducts, dilatation, fibrosis and glandular atrophy.

5. Sweat glands. Hypersecretion of sodium and chloride in the sweat observed in these patients may be reflected pathologically by diminished vacuolation of the cells of eccrine glands.

PANCREATITIS

Pancreatitis is inflammation of the pancreas with acinic cell injury. It is classified into acute and chronic forms both of which are two distinct entities.

ACUTE PANCREATITIS

Acute pancreatitis is an acute inflammation of the pancreas presenting clinically with 'acute abdomen'. The severe form of the disease associated

with macroscopic haemorrhages and fat necrosis in and around the pancreas is termed *acute haemorrhagic pancreatitis* or *acute pancreatic necrosis.* The condition occurs in adults between the age of 40 and 70 years and is commoner in females than in males.

The onset of acute pancreatitis is sudden, occurring after a bout of alcohol or a heavy meal. The patient presents with abdominal pain, vomiting and collapse and the condition must be differentiated from other diseases producing acute abdomen such as acute appendicitis, perforated peptic ulcer, acute *cholecystitis, and* infarction of the intestine following sudden occlusion of the mesenteric vessels. Characteristically, there is elevation of *serum amylase* level within the first 24 hours and of *serum lipase* level after 3 to 4 days; the latter being more specific for pancreatic disease. Glucosuria occurs in 10% of cases.

Etiology. The two leading causes associated with acute pancreatitis are *alcoholism* and *cholelithiasis,* both of which are implicated in more than 80% of cases. Less common causes of acute pancreatitis include trauma, ischaemia, shock, extension of inflammation from the adjacent tissues, blood-borne bacterial infection, viral infections, certain drugs (e.g. thiazides, sulfonamides, oral contraceptives), hypothermia, hyperlipoproteinaemia and hypercalcaemia from hyperparathyroidism. Rarely, *familial pancreatitis* is encountered. In a proportion of cases of acute pancreatitis, the etiology remains unknown *(idiopathic pancreatitis).*

Pathogenesis. The destructive changes in the pancreas are attributed to the liberation and activation of pancreatic enzymes. Though more than 20 enzymes are secreted by exocrine pancreas, 3 main groups of enzymes which bring about destructive effects on the pancreas are as under:

1. *Proteases* such as trypsin and chymotrypsin play the most important role in causing proteolysis. Trypsin also activates the kinin system by converting prekallikrein to kallikrein, and thereby the clotting and complement systems are activated. This results in inflammation, thrombosis, tissue damage and haemorrhages found in acute haemorrhagic pancreatitis.

2. *Lipases and phospholipases* degrade lipids and membrane phospholipids.

3. *Elastases* cause destruction of the elastic tissue of the blood vessels.

The activation and release of these enzymes is brought about by one of the following mechanisms:

1. *Acinic cell damage* caused by the etiologic factors such as alcohol, viruses, drugs, ischaemia and trauma result in release of the intracellular enzymes.

2. Duct obstruction caused by cholelithiasis, chronic alcoholism and other obstructing lesions is followed by leakage of pancreatic enzymes from the ductules into the interstitial tissue.

3. *Block in exocytosis* of pancreatic enzymes occurring from nutritional causes results in activation of these intracellular enzymes by pancreatic lysosomal hydrolases.

Pathologic changes. *Macroscopically,* in the early stage, the pancreas is swollen and oedematous. Subsequently, in a day or two, the characteristic variegated appearance of grey-white pancreatic necrosis, chalky-white fat necrosis and blue-black haemorrhages are seen. In typical case, the peritoneal cavity contains blood-stained ascitic fluid and white flecks of fat necrosis in the omentum, mesentry and peripancreatic tissue. The resolved lesions show areas of fibrosis, calcification and ductal dilatation. *Microscopically,* the following features in varying grades are noticeable:

1. Necrosis of pancreatic lobules and ducts.
2. Necrosis of the arteries and arterioles with areas of haemorrhages.
3. Fat necrosis.
4. Inflammatory reaction, chiefly by polymorphs, around the areas of necrosis and haemorrhages.

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

Systemic complications. These are:

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

Local sequelae. These result after widespread involvement of the pancreas. These are:

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

Mortality in acute pancreatitis is high (20-30%). Patients succumb to hypotensive shock, infection, acute renal failure, and DIC.

CHRONIC PANCREATITIS

Chronic pancreatitis or *chronic relapsing pancreatitis* is the progressive destruction of the pancreas due to repeated mild and subclinical attacks of acute pancreatitis. Most patients present with recurrent attacks of severe abdominal pain at intervals of months to years. Weight loss and jaundice are often associated. Later manifestations include associated diabetes mellitus and steatorrhoea. Abdominal radiographs show calcification in the region of pancreas and presence of pancreatic calculi in the ducts.

Etiology. Most cases of chronic pancreatitis are caused by the same factors as for acute pancreatitis. Thus, most commonly, chronic pancreatitis is related to *chronic alcoholism* with protein-rich diet, and less often to *bili-*

ary tract disease. Familial hereditary pancreatitis, though uncommon, is more frequently chronic than the acute form. Other rare causes of chronic pancreatitis are hypercalcaemia, hyperlipidaemia and developmental failure of fusion of dorsal and ventral pancreatic ducts.

Pathogenesis. Acute haemorrhagic pancreatitis seldom develops into chronic pancreatitis, but instead develops pancreatic pseudocysts following recovery. Pathogenesis of alcoholic and non-alcoholic chronic pancreatitis is explained by different mechanisms:

1. Chronic pancreatitis due to *chronic alcoholism* accompanied by a high-protein diet results in increase in protein concentration in the pancreatic juice which obstructs the ducts and causes damage.

2. *Non-alcoholic cases* of chronic pancreatitis seen in tropical countries (tropical chronic pancreatitis) result from protein-calorie malnutrition. Genetic factors play a role in some cases of chronic pancreatitis.

Pathologic changes. *Macroscopically*, the pancreas is enlarged, firm and nodular. The cut surface shows a smooth grey appearance with loss of normal lobulation. Foci of calcification and tiny pancreatic concretions to larger visible stones are frequently found. Pseudocysts may be present. *Microscopically*, depending upon the stage of development, the following changes are seen:

1. Obstruction of the ducts by fibrosis in the wall and protein plugs or stones in the lumina.

2. Squamous metaplasia and dilatation of some inter- and intralobular ducts.

3. Chronic inflammatory infiltrate around the lobules as well as the ducts.

4. Atrophy of the acinar tissue with marked increase in interlobular fibrous tissue.

5. Islet tissue is involved in late stage only.

Complications. Late stage of chronic pancreatitis may be complicated by diabetes mellitus, pancreatic insufficiency with steatorrhoea and malabsorption and formation of pancreatic pseudocysts.

TUMOURS AND TUMOUR-LIKE LESIONS

Tumour-like masses of the exocrine pancreas include *congenital cystic disease* (involving the pancreas, liver and kidney) and *pancreatic pseudocysts.* True pancreatic tumours are classified into benign (e.g. serous cystadenoma, fibroma, lipoma and adenoma) and malignant (i.e. carcinoma of the pancreas). Out of all these, only two pancreatic lesions—pseudocyst and carcinoma of the pancreas, are common and are discussed below.

PANCREATIC PSEUDOCYST

Pancreatic pseudocyst is a localised collection of pancreatic juice, necrotic debris and haemorrhages. It develops following either acute pancreatitis or trauma. The patients generally present with abdominal mass producing pain, intraperitoneal haemorrhage and generalised peritonitis.

Pathologic changes. *Grossly,* the pseudocyst may be present within or adjacent to the pancreas. Usually it is solitary, unilocular, measuring up to 10 cm in diameter with thin or thick wall. *Microscopically,* the cyst wall is composed of dense fibrous tissue with marked inflammatory reaction. There is evidence of preceding haemorrhage and necrosis in the form of deposits of haemosiderin pigment, calcium and cholesterol crystals. The lumen of the cyst contains serous or turbid fluid. The cyst does not show any epithelial lining.

CARCINOMA OF PANCREAS

Pancreatic cancer is the term used for cancer of the exocrine pancreas. It is one of the common cancers, particularly in the Western countries and Japan. In the United States, cancer of the pancreas is the second most common cancer of the alimentary tract after colorectal cancer, and accounts for 5% of all cancer deaths in that country. It is commoner in males than in females and the incidence increases progressively after the age of 50 years.

Etiology. A significant increase in the incidence of pancreatic cancer has been observed in the UK and US during the last 50 years. A number of etiologic factors have been implicated. These include the following:

1. *Smoking:* heavy cigarette smokers have higher incidence than the non-smokers.

2. *Diet:* Diet with high total caloric value and high consumption of animal proteins and fats is related to higher incidence of pancreatic cancer.

3. *Chemical carcinogens:* Individuals exposed to (3 naphthylamine, benzidine and nitrosamines have higher incidence of cancer of the panceras.

4. Diabetes mellirus.

5. Hereditary chronic pancreatitis.

6. Disease of the gallbladder.

Pathologic changes. The most common location of pancreatic cancer is the head of pancreas (70%), followed in decreasing frequency, by the body and the tail of pancreas.

Grossly, carcinoma of the head of pancreas is generally small, homogeneous, poorly-defined, grey-white mass without any sharp demarcation between the tumour and the surrounding pancreatic parenchyma. The tumour of the head extends into the ampulla of Vater, common bile duct and duodenum, producing obstructive biliary symptoms and jaundice early in the course of illness. Carcinomas of the body and tail of the pancreas, on the other hand,

are fairly large and irregular masses and frequently infiltrate the transverse colon, stomach, liver, spleen and regional lymph nodes. *Microscopically*, most pancreatic carcinomas arise from the ductal epithelium which normally comprises less than 4% of total pancreatic cells, whereas carcinoma of the acini constitutes less than 1% of pancreatic cancers. The following histologic patterns of pancreatic carcinoma are seen:

1. *Well-differentiated adenocarcinoma,* both mucinous and non-mucin secreting type, is the most common pattern. Perineural invasion is commonly present and is diagnostic of malignancy.

2. *Adenoacanthoma* consisting of glandular carcinoma and benign squamous elements is seen in a proportion of cases.

3. Rarely, peculiar *tumour giant cell formation* is seen with marked anaplasia, pleomorphism and numerous mitoses.

4. *Acinar cell carcinoma* occurs rarely and reproduces the pattern of acini in normal pancreas.

Generally, the following features are present:

1. *Obstructive jaundice,* more often and early in the course of disease in cases with carcinoma head of the pancreas (80%), and less often in cancer of the body and tail of the pancreas. It is characterised by: dark urine, clay-like stools, pruritus, and very high serum alkaline phosphatase.

2. *Other features.* These include: abdominal pain, anorexia, weight loss, cachexia, weakness and malaise, nausea and vomiting, and migratory thrombophlebitis (Trousseau's syndrome), GI bleeding and splenomegaly.

The prognosis of pancreatic cancer is dismal: median survival is 6 months from the time of diagnosis. Approximately 10% patients survive 1 year and the 5-year survival is poor 1 to 2%.

PATHOLOGY OF KIDNEY AND LOWER URINARY TRACT

The kidneys are bean-shaped paired organs, each weighing about 150 gm in the adult male and about 135 gm in the adult female. The hilum of the kidney is situated at the midpoint on the medial aspect where the artery, vein, lymphatics and ureter are located. The kidney is surrounded by a thin fibrous capsule which is adherent at the hilum.

Cut surface of the kidney is made up of well-demarcated *peripheral cortex and inner medulla.* The cortex is 1.2 to 1.5 cm in thickness and shows faint striations called *medullary rays* formed by the collecting tubules, ascending limbs and straight portions of the proximal convoluted tubules. The medulla is composed of several cone-shaped renal pyramids, the apex of each of which called the *papilla* is related to a calyx. Cortical tissue that extends into the space between adjacent pyramids is called the *renal column (septa) of Berlin.* The pelvis is the funnel-shaped, dilated proximal part of the ureter formed by the union of 2 to 3 *major calyces,* each of which is further subdivided into 3 to 4 minor calyces into which the papillae project.

The parenchyma of each kidney is composed of approximately one million microstructures called nephrons. A nephron, in turn, consists of 5 major parts, each having a functional role in the formation of urine: the glomerular capsule (glomerulus and Bowman's capsule), the proximal convoluted tubule (PCT), the loop of Henle, the distal convoluted tubule (DCT), and the collecting ducts. From point of view of diseases of the kidneys, 4 components of renal parenchyma require further elaboration: renal vasculature, glomeruli, tubules and interstitium.

1. Renal vasculature. Each kidney is supplied with blood by a main *renal artery* which arises from the aorta at the level of the 2nd lumbar vertebra. It usually divides into *anterior and posterior divisions* at the hilum although occasionally these divisions may even arise directly from the aorta. The anterior and posterior divisions divide into *segmental branches* from which interlobar arteries arise. Along their course, they give off the *arcuate arteries* which arch between the cortex and medulla. The arcuate arteries, in turn, give off *interlobular arteries* which lie in the cortex perpendicular to the capsular surface in the part overlying the pyramids and, therefore, are also called *straight arteries*. It is from the interlobular arteries that the *afferent arterioles* take their origin, each one supplying a single glomerulus. From the glomerulus emerge the efferent arterioles. Up to this stage, the arteries and arterioles are end-vessels. The efferent arterioles leaving the glomerulus supply *peritubular capillary plexus* which anastomoses with the capillary plexus of another nephron.

The juxtamedullary glomeruli, however, give off a series of parallel vessels called *vasa recta* which descend to the inner medulla supplying the loop of Henle and collecting ducts and anastomose at all levels throughout the medulla with the ascending vasa recta. These drain into *arcuate veins* and then into the veins that accompany the corresponding arteries and finally through a single renal vein into the inferior vena cava. Lymphatic drainage likewise occurs through lymphatics associated with the intrarenal vasculature leaving the kidney at the hilum and draining to lateral aortic lymph nodes.

The following important derivations can be made from the peculiarities of the renal vasculature:

i) The renal cortex receives about 90% of the total renal blood supply and that the pressure in the glomerular capillaries is high. Therefore, renal cortex is more prone to the effects of hypertension.

ii) The renal medulla, on the other hand, is poorly perfused and any interference in blood supply to it results in medullary necrosis.

iii) The divisions and subdivisions of the renal artery up to arterioles are end-arteries and have no anastomoses. Thus, occlusion of any of the branches results in infarction of the renal parenchyma supplied by it.

iv) Since the tubular capillary beds are derived from the efferent arterioles leaving the glomeruli, diseases affecting the blood flow through glomerular tuft have significant effects on the tubules as well.

2. Glomerulus. The glomerulus consists of invagination of the blind end of the proximal tubule and contains a *capillary tuft* fed by the afferent arteriole and drained by efferent arteriole. The capillary tuft is covered by visceral epithelial cells (podocytes) which are continuous with those of the parietal epithelium at the *vascular pole.* The transition to proximal tubular cells occurs at the *urinary pole* of the glomerulus. The visceral and parietal epithelial cells are separated by the urinary space or *Bowman's space,* into which glomerular filtrate passes.

Subdivisions of capillaries derived from the afferent arterioles result in the formation of *lobules* of which there are not more than eight within a glomerulus. Each lobule of a glomerular tuft consists of a centrilobular supporting stalk composed of mesangium containing *mesangial cells* and *mesangial matrix.* The mesangium is continuous at the hilum with the *lads cells* of the Juxtaglomerular apparatus. Besides their role as supportive cells, mesangial cells are involved in the production of mesangial matrix and glomerular basement membrane; they function in endocytosis of leaked macromolecules and also possibly in the control of glomerular blood flow through contractile elements present in these cells. The major *function* of glomerulus is complex filtration from the capillaries to the urinary space. The barrier to glomerular filtration consists of the following 3 components:

i) Fenestrated endothelial cells lining the capillary loops.

ii) Glomerular basement membrane (GBM) on which the endothelial cells rest and consists of 3 layers – the central lamina densa, bounded by lamina rara interna and lamina rara externa.

iii) Filtration slit pores between the foot processes of the visceral epithelial cells (podocytes) external to GBM.

The barrier to filtration of macromolecules of the size and molecular weight of albumin and larger depends upon the following:

• A normal lamina densa.

• Maintenance of negative charge on both lamina rarae.

• A healthy covering of glomerular epithelial cells.

Juxtaglomerular apparatus. The Juxtaglomerular apparatus QGA) is situated at the vascular pole of the glomerulus and is made up of 3 parts:

i) The *Juxtaglomerular cells* are modified granular smooth muscle cells in the media of the afferent arteriole and contain the hormone, renin.

ii) The *macula densa* is comprised by specialised region of the distal tubule when it returns to the vascular pole of its parent glomerulus. The tubular cells here are taller and narrower than elsewhere with the nuclei lying close together.

iii) The *lads cells* or *non-granular cells* occupy the space between the macula densa and the arterioles and merge with the glomerular mesangium.

The JGA is intimately concerned with sodium metabolism and is the principal source of renin production.

3. Tubules. The tubules of the kidney account for the greatest amount of the renal parenchyma. The structure of renal tubular epithelium varies in different parts of the nephron and is correlated with the functional capacity of that part of the tubule.

i) Proximal convoluted tubule (PCT). This is the first part arising from the glomerulus and is highly specialised part functionally. It is lined by cuboidal cells with a brush border composed of microvilli and contains numerous mitochondria, Golgi apparatus and endoplasmic reticulum. The major functions of PCT are: *active reabsorption* of filtered sodium, potassium, glucose, amino acids, proteins, phosphate, calcium and uric acid, and *passive reabsorption* of 80% of filtered water.

ii) Loop of Henle. The PCT drains into the straight part of loop of Henle that consists of thin, descending and ascending limbs and the actual loop, all of which are found in the medulla. They are lined by a flattened type of epithelium. The thin ascending limb continues as thick ascending limb in the medullary rays. In cross section, the thick ascending limb is nearly of the same size as that of PCT and the lining cells are columnar. The major function of loop of Henle is *active reabsorption* of sodium and chloride, and *passive diffusion* of water resulting in urinary concentration.

iii) Distal convoluted tubule (DCT). The DCT represents a transition from thick ascending limb from the point where the ascending limb meets the vascular pole of the glomerulus of its origin, to the early collecting ducts. The lining cells are cuboidal which are lower than those of PCT. The epithelial cells at the point of beginning of DCT are taller, narrower and more closely packed to form the macula densa of JGA as already described. The DCT further contributes to urinary concentration and acidification, while the macula densa of JGA is the source of renin and has a role in sodium metabolism.

iv) Collecting ducts. The system of collecting ducts is the final pathway by which urine reaches the tip of renal papilla. The cells lining the collecting ducts are cuboidal but lack the brush border.

4. Interstitium. In health, the renal cortical interstitium is scanty and consists of a small number of fibroblast-like cells. But the medullary interstitium is more plentiful and contains stellate interstitial cells which are considered to produce an antihypertensive agent and are involved in the metabolism of prostaglandins.

In general, the kidney performs the following vital functions in the body:

1. *Excretion of waste products* resulting from protein metabolism.

2. *Regulation of acid-base balance* by excretion of H^+ ions (acidification) and bicarbonate ions.

3. Regulation of salt-water balance by hormones secreted both intra- and extrarenally.

4. *Formation of renin and erythropoietin* and thereby playing a role in the regulation of blood pressure and erythropoiesis respectively.

To confirm the diagnosis of renal disease renal biopsy is performed. Renal biopsy is ideally fixed in alcoholic Bouin's solution and examined morphologically supported by special stains and further studies as under:

1. *Periodic acid-Schiff* stain for highlighting glomerular basement membrane.

2. *Silver impregnation* to outline the glomerular and tubular basement membrane.

3. *Immunofluorescence* to localise the antigens, complements and immunoglobulins.

4. *Electron microscopy* to see the ultrastructure of glomerular changes.

Traditionally, diseases of the kidneys are divided into 8 major groups according to the predominant involvement of corresponding morphologic components:

1. *Glomerular diseases* (Glomerulopathies)*:* These are most often immunologically-mediated and may be acute or chronic, acquired and congenital, inflammatory and noninflammatory;

2. *Tubular diseases* (Tubulopathies)*:* These are acquired and congenital, necrotized and obstructive and more likely to be caused by toxic or infectious agents and may be acute or chronic;

3. Interstitial diseases: These are likewise commonly due to toxic or infectious agents and quite often involve interstitium as well as tubules (tubulo-interstitial diseases);

4. *Vascular diseases:* These include changes in the nephron as a consequence of increased intra-glomerular pressure such as in hypertension or impaired blood flow;

5. Obstructive uropathy (including urolithiasis);

6. Tumours;

7. Congenital malformations (anomalies);

8. Nephrosclerosis (kidney shrinkage). It is classified into primary and secondary.

The major morphologic involvements of the kidneys in the initial stage is confined to one component (glomeruli, tubules, interstitium or blood vessels), but eventually all components are affected leading to *end-stage kidneys.*

Regardless of cause, renal disease usually results in the evolution of one of the two major pathological syndromes: *acute renal failure* and *chronic renal failure.* The term *'azotaemia'* is used for biochemical abnormality characterised by elevation of the blood urea nitrogen (BUN) and creatinine levels, while *'uraemia'* is defined as association of these biochemical abnormalities with clinical signs and symptoms. The pathophysiological aspects of acute and chronic renal failure are briefly discussed below.

PATHOPHYSIOLOGY OF RENAL DISEASE (RENAL FAILURE)

ACUTE RENAL FAILURE (ARF)

Acute renal failure (ARF) is a syndrome characterised by rapid onset of renal dysfunction, chiefly oliguria or anuria, and sudden increase in metabolic waste-products (urea and creatinine) in the blood with consequent development of uraemia.

Etiopathogenesis. The causes of ARF may be classified as pre-renal, intra-renal and post-renal i nature.

1. Pre-renal causes. Pre-renal diseases are those which cause sudden decrease in blood flow to the nephron. Renal ischaemia ultimately results in functional disorders or depression of GFR, or both. These causes include inadequate cardiac output and hypovolaemia or vascular disease causing reduced perfusion of the kidneys.

2. Intra-renal causes. Intra-renal disease is characterised by disease of renal tissue itself. These include vascular disease of the arteries and arterioles within the kidney, diseases of glomeruli, acute tubular necrosis due to ischaemia, or the effect of a nephrotoxin, acute tubulointerstitial nephritis and pyelonephritis.

3. Post-renal causes. Post-renal disease is characteristically caused by obstruction to the flow of urine anywhere along the renal tract distal to the opening of the collecting ducts. This may be caused by a mass within the lumen or from wall of the tract, or from external compression anywhere along the tract – ureter, bladder neck or urethra.

It is important to note that ARF originating in pre-and post-renal disease, such as by renal ischaemia or renal infection eventually leads to intra-renal disease. Thus, full-blown ARF reflects some degree of nephron damage.

Clinical features. The clinical features will depend to a large extent on the underlying cause of ARF and on the stage of the disease at which the patient presents. However, one of the following three major patterns usually emerge:

1. Syndrome of acute nephritis. This is most frequently associated with acute post-streptococcal glomerulonephritis and rapidly progressive glomerulonephritis. Renal dysfunction results from extensive proliferation of epithelial cells in the glomeruli with consequent mild increase in glomerular permeability and decrease in GFR. The characteristic features are: mild proteinuria, haematuria, oedema and mild hypertension. Fluid retention in acute nephritis syndrome appears to be due to both diminished GFR and increased salt and water reabsorption in distal nephron.

2. Syndrome accompanying tubular pathology. When the ARF is caused by destruction of the tubular cells of the nephron as occurs in acute tubular necrosis, the disease typically progresses through 3 characteristic stages from oliguria to diuresis to recovery.

i) *Oliguric phase:* The initial oliguric phase lasting on an average from 7 to 10 days is characterised by urinary output of less than 400 ml per day. The decline in formation of the urine leads to accumulation of waste products of protein metabolism in the blood and resultant azotaemia, metabolic acidosis, hyperkalaemia, hypernatraemia and hypervolaemia due to secondary effects of circulatory overload and pulmonary oedema. The specific gravity of the urine is low but the concentration of sodium in urine tends to be elevated.

ii) *Diuretic phase:* With the onset of healing of tubules, there is improvement in urinary output. This is believed to occur due to drawing of water and sodium by preceding high levels of creatinine and urea as they move through the nephron so as to be excreted. Since tubular cells have not regained normal functional capacity, the urine is of low or fixed specific gravity.

iii) *Phase of recovery:* Full recovery with healing of tubular epithelial cells occurs in about half the cases, while others terminate in death. The process of healing may take up to one year with restoration of normal tubular function.

3. Pre-renal syndrome. The ARF occurring secondary to disorders in which neither the glomerulus nor the tubules are damaged, results in pre-renal syndrome. Most typically, this pattern is seen in marginal ischaemia caused by renal arterial obstruction, hypovolaemia, hypotension or cardiac insufficiency. Due to depressed renal blood flow, there is decrease in GFR causing oliguria, azotaemia (elevation of BUN and creatinine)

and possible fluid retention and oedema. Since the tubular cells are functioning normally, the nephron retains its ability to concentrate the glomerular filtrate according to the adaptive needs.

CHRONIC RENAL FAILURE (CRF)

Chronic renal failure is a syndrome characterised by progressive and irreversible deterioration of renal function due to slow destruction of renal parenchyma, eventually terminating in death when sufficient number of nephrons have been damaged. Acidosis is the major problem in CRF with development of biochemical azotaemia and clinical uraemia syndrome.

Etiopathogenesis. All chronic nephropathies can lead to CRF. The diseases leading to CRF can generally be classified into two major groups: *those causing glomerular pathology,* and *those causing tubulointerstitial pathology.* Though this classification is useful to facilitate study, the disease rarely remains confined to either glomeruli or tubulointerstitial tissue alone. In the final stage of CRF, all parts of the nephron are involved.

1. Diseases causing glomerular pathology. A number of glomerular diseases associated with CRF have their pathogenesis in immune mechanisms. Glomerular destruction results in changes in filtration process and leads to development of the nephrotic syndrome characterised by proteinuria, hypoalbuminaemia and oedema. The important examples of chronic glomerular diseases causing CRF are covered under two headings: primary and systemic.

i) *Primary glomerular pathology:* The major cause of CRF is chronic glomerulonephritis, usually initiated by various types of *glomerulonephritis* such as membranous glomerulonephritis, membranoproliferative glomerulonephritis, lipoid nephrosis (minimal change disease) and anti-glomerular basement membrane nephritis.

ii) *Systemic glomerular pathology:* Certain conditions originate outside the renal system but induce changes in the nephrons secondarily. Major examples of this type are systemic lupus erythematosus, serum sickness nephritis and diabetic nephropathy.

2. Diseases causing tubulointerstitial pathology.

Damage to tubulointerstitial tissues results in alterations in reabsorption and secretion of important constituents leading to excretion of large volumes of dilute urine. Tubulointerstitial diseases can be categorised according to initiating etiology into 4 groups: vascular, infectious, toxic and obstructive.

i) *Vascular causes:* Long-standing primary or essential hypertension produces characteristic changes in renal arteries and arterioles referred to as nephrosclerosis. Nephrosclerosis causes progressive renal vascular occlusion terminating in ischaemia and necrosis of renal tissue.

ii) *Infectious causes: A* good example of chronic renal infection causing CRF is chronic pyelonephritis. The chronicity of process results in progressive damage to increasing number of nephrons leading to CRF.

iii) *Toxic causes:* Some toxic substances induce slow tubular injury, eventually culminating in CRF. The most common example is intake of high doses of analgesics such as phenacetin, aspirin and acetaminophen (chronic analgesic nephritis). Other substances that can cause CRF after prolonged exposure are lead, cadmium and uranium.

iv) *Obstructive causes:* Chronic obstruction in the urinary tract leads to progressive damage to the nephron due to fluid back-pressure. The examples of this type of chronic injury are stones, blood clots, rumours, strictures and enlarged prostate.

Clinical features. Regardless of the initiating cause, CRF evolves progressively through 4 stages:

1. Decreased renal reserve. At this stage, damage to renal parenchyma is marginal and the kidneys remain functional. The GFR is about 50% of normal, BUN and creatinine values are normal and the patients are usually asymptomatic except at times of stress.

2. Renal insufficiency. At this stage, about 75% of functional renal parenchyma has been destroyed. The GFR is about 25% of normal accompanied by elevation in BUN and serum creatinine. Polyuria and nocturia occur due to tubulointerstitial damage. Sudden stress may precipitate uraemic syndrome.

3. Renal failure. At this stage, about 90% of functional renal tissue has been destroyed. The GFR is approximately 10% of normal. Tubular cells are essentially nonfunctional. As a result, the regulation of sodium and water is lost resulting in oedema, metabolic acidosis, hypocalcaemia, and signs and symptoms of uraemia.

4. End-stage kidney. The GFR at this stage is less than 5% of normal and results in complex clinical picture of uraemic syndrome with progressive primary (renal) and secondary systemic (extra-renal) symptoms.

Clinical manifestations of full-blown CRF culminating in uraemic syndrome are thus described under 2 main headings: primary (renal) uraemic manifestations and secondary (systemic or extra-renal) uraemic manifestations.

A. Primary uraemic (renal) manifestations. Primary symptoms of uraemia develop when there is slow and progressive deterioration of renal function. The resulting imbalances cause the following manifestations:

1. Metabolic acidosis. As a result of renal dysfunction, acid-base balance is progressively lost. Excess of hydrogen ions occurs, while bicarbonate level declines in the blood, resulting in metabolic acidosis. The clinical symptoms of metabolic acidosis include: compensatory Kussmaul breathing, hyperkalaemia and hypercalcaemia.

2. Hyperkalaemia. A decreased GFR results in excessive accumulation of potassium in the blood since potassium is normally excreted mainly in the urine. Hyperkalaemia is further worsened by metabolic acidosis. The clinical features of hyperkalaemia are: cardiac arrhythmias, weakness, nausea, intestinal colic, diarrhoea, muscular irritability and flaccid paralysis.

3. Sodium and water imbalance. As GFR declines, sodium and water cannot pass sufficiently into Bowman's capsule leading to their retention. Release of renin from juxtaglomerular apparatus further aggravates sodium and water retention. The main symp-

toms referable to sodium and water retention are: hypervolaemia and circulatory overload with congestive heart failure.

4. Hvperuricaemia. Decreased GFR results in excessive accumulation of uric acid in the blood.

Uric acid crystals may be deposited in joints and soft tissues resulting in gout.

5. Azotaemia. The waste-products of protein metabolism fail to be excreted resulting in elevation in the blood levels of urea, creatinine, phenols and guanidines causing biochemical abnormality, azotaemia. The secondary manifestations of uraemia are related to toxic effects of these metabolic waste-products.

B. *Secondary uraemic (extra-renal) manifestations.* A number of extra-renal systemic manifestations develop secondarily following fluid-electrolyte and acid-base imbalances. These include the following:

1. Anaemia. Decreased production of erythropoietin by diseased kidney results in decline in erythropoiesis and anaemia. Besides, gastrointestinal bleeding may further aggravate anaemia.

2. Integumentary system. Deposit of urinary pigment such as urochrome in the skin causes sallow-yellow colour. The urea content in the sweat as well as in the plasma rises. On evaporation of the perspiration, urea remains on the facial skin as powdery *'uraemic frost'*.

3. Cardiovascular system. Fluid retention secondarily causes cardiovascular symptoms such as increased workload on the heart due to the hypervolaemia and eventually congestive heart failure.

4. Respiratory system. Hypervolaemia and heart failure cause pulmonary congestion and pulmonary oedema due to back pressure. Radiologically, uraemic pneumonitis shows characteristic central, butterfly-pattern of oedema and congestion in the chest radiograph.

5. Digestive system. Azotaemia directly induces mucosal ulcerations in the lining of the stomach and intestines. Subsequent bleeding can aggravate the existing anaemia. Gastrointestinal irritation may cause nausea, vomiting and diarrhoea.

6. Skeletal system. The skeletal manifestations of renal failure are referred to as *renal osteodystrophy*. Two major types of skeletal disorders may occur:

i) *Osteomalacia* occurs from deficiency of a form of vitamin D which is normally activated by the kidney. Since vitamin D is essential for absorption of calcium, its deficiency results in inadequate deposits of calcium in bone tissue.

ii) *Osteitis fibrosa* occurs due to elevated levels of parathormone. How parathormone excess develops in CRF is complex. As the GFR is decreased, increasing levels of phosphates accumulate in the extracellular fluid which, in turn, cause decline in calcium levels. Decreased calcium level triggers the secretion of parathormone which mobilises calcium from bone and increases renal lubular reabsorption of calcium thereby conserving it. However, if the process of resorption of calcium phosphate from bone continues for sufficient time, hypercalcaemia may be induced with deposits of excess calcium salts in joints and soft tissues and weakening of bones (renal osteodystrophy).

CONGENITAL MALFORMATIONS

Approximately 10% of all persons are born with potentially significant malformations of the urinary system. These range in severity from minor anomalies which may not produce clinical manifestations to major anomalies

which are incompatible with extrauterine life. About half of all patients with malformations of the kidneys have coexistent anomalies either elsewhere in the urinary tract or in other organs.

Malformations of the kidneys are classified into 3 broad groups:

I. Abnormalities in amount of renal tissue. These include: anomalies with deficient renal parenchyma (e.g. unilateral or bilateral renal hypoplasia) or with excess renal tissue (e.g. renomegaly, supernumerary kidneys).

II. Anomalies of position, form and orientation. These are: renal ectopia (pelvic kidney), renal fusion (horseshoe kidney) and persistent foetal lobation.

III. Anomalies of differentiation. This group consists of the more important and common morphologic forms covered under the heading of *'cystic diseases of the kidney'* described in detail below.

CYSTIC DISEASES OF KIDNEY

Cystic lesions of the kidney may be *congenital or acquired, non-neoplastic or neoplastic.* Majority of these lesions are congenital non-neoplastic. Cystic lesions in the kidney may occur at any age, extending from foetal (detected on ultrasonography) to old age. Their clinical presentation may include: abdominal mass, infection, respiratory distress (due to accompanied pulmonary hypoplasia), haemorrhage, and neoplastic transformation.

Potter divided developmental renal cystic lesions into three types – I, II and III.

I. RENAL CYSTIC DYSPLASIA

The term 'renal cystic dysplasia' or Potter type II is used for defective renal differentiation with persistence of structures in the kidney not represented in normal nephrogenesis such as presence of undifferentiated mesenchyme containing smooth muscle or cartilage and immature collecting ducts. Renal dysplasia is thus diagnosed on the basis of histologic features. The condition is fairly common in the newborn and infants. The pathogenesis of renal dysplasia is unknown. Since renal dysplasia is commonly associated with obstructive abnormalities of the ureter and lower urinary tract, it is hypothesised that the condition results from intrauterine obstruction and disorganised metanephrogenic differentiation.

Pathologic changes. Unilateral renal dysplasia is frequently discovered in newborn or infants as a flank mass. Often, renal dysplasia is associated with other congenital malformations and syndromes such as ventricular septal defect, tracheo-esophageal fistula, lumbosacral meningomyelocele and Down's syndrome. The prognosis of unilateral renal dysplasia following removal of the abnormal kidney is excellent while bilateral renal dysplasia results in death in infancy.

Renal dysplasia may be unilateral or bilateral. The dysplastic process may involve the entire renal mass or a part of it. *Grossly,* the dysplastic kidney is almost always cystic. The kidney is replaced by disorderly mass of multiple cysts that is not reniform but resembles a bunch of grapes. No normal renal parenchyma is recognisable, and calyces and pelvis are not present. The ureter is invariably abnormal, being either absent or atretic. *Histologically,* the characteristic feature is the presence of undifferentiated mesenchyme that contains smooth muscle or cartilage. The cysts are dilated tubules lined by flattened epithelium surrounded by concentric layers of connective tissue. Glomeruli are scanty or absent.

II. POLYCYSTIC KIDNEY DISEASE

Polycystic disease of the kidney (PKD) is a disorder in which major portion of the renal parenchyma is converted into cysts of varying size. The disease occurs in two forms:

A. An *adult type* inherited as an *autosomal dominant* disease; and

B. An *infantile type* inherited as an *autosomal recessive* disorder.

A. Adult Polycystic Kidney Disease

Adult (autosomal dominant) polycystic kidney disease (ADPKD) is relatively common and is the cause of end-stage renal failure in approximately 10% of haemodialysis patients. The pattern of inheritance is *autosomal dominant* having high penetrance with variable expressivity. Family history of renal disease may be present. The condition occurs due to mutation in chromosome 16. The true adult polycystic renal disease is always bilateral and diffuse. Though the kidneys are abnormal at birth, renal function is retained, and symptoms appear in adult life, mostly between the age of 30 and 50 years.

Pathologic changes. *Grossly,* kidneys in ADPKD are always bilaterally enlarged, usually symmetrically, heavy (weighing up to 4 kg) and cystic. The cut surface shows cysts throughout the renal parenchyma varying in size from tiny cysts to 4-5 cm in diameter. The contents of the cysts vary from clear straw-yellow fluid to reddish-brown material. The renal pelvis and calyces are present but are greatly distorted by the cysts. The cysts, however, do not communicate with the pelvis of the kidney – a feature that helps to distinguish polycystic kidney from hydronephrotic kidney on sectioned surface.

Histologically, the cysts arise from all parts of nephron. It is possible to find some cysts containing recognisable glomerular tufts reflecting their origin from Bowman's capsule, while others have epithelial lining like that of distal or proximal tubules or collecting ducts. The intervening tissue between the cysts shows some normal renal parenchyma. With advancement of age of

the patient, acquired lesions such as pyelonephritis, nephrosclerosis, fibrosis and chronic inflammation are increasingly seen.

The condition may become clinically apparent at any age but most commonly manifests in 3rd to 5th decades of life. The most frequent and earliest presenting feature is a dullache in the lumbar regions. In others, the presenting complaints are haematuria or passage of blood clots in urine, renal colic, hypertension, urinary tract infections and progressive CRF with polyuria and proteinuria.

About a third of patients with adult polycystic kidney disease have cysts of the liver. Other associated congenital anomalies seen less frequently are cysts in the pancreas, spleen, lungs and other organs. Approximately 15% of patients have one or more intracranial berry aneurysms of the circle of Willis. Any acquired renal disease is more prone to occur in polycystic kidneys.

B. Infantile Polycystic Kidney Disease

The infantile (autosomal recessive) form of polycystic kidney disease (ARPKD) is distinct from the adult form. Infantile polycystic kidney disease is rare. It is transmitted as an autosomal recessive trait and the family history of similar disease is usually not present. The condition occurs due to a mutation in chromosome 6. It is invariably bilateral. The age at presentation may be perinatal, neonatal, infantile or juvenile, but frequently serious manifestations are present at birth and result in death from renal failure in early childhood.

Pathologic changes. *Grossly,* the kidneys are bilaterally enlarged with smooth external surface and retained normal shape. Cut surface reveals small, fusiform or cylindrical cysts formed from dilatation of collecting tubules which extend radially to the outer cortex. This gives the sectioned surface of the kidney *sponge-like appearance.* No normal renal parenchyma is grossly recognised. Pelvis, calyces and ureters are normal.

Histologically, the total number of nephrons is normal but all the collecting tubules show cylindrical or saccular dilatations and are lined by cuboidal to low columnar epithelium. Many of the glomeruli are also cystically dilated.

Almost all the cases of infantile polycystic kidney disease have associated multiple epithelium-lined cysts in the liver or proliferation of portal bile ductules. In older children, these associated hepatic changes develop into what is termed *congenital hepatic fibrosis* which may lead to portal hypertension and splenomegaly.

III. GLOMERULOCYSTIC KIDNEY DISEASE

Many cystic diseases of kidney may have both glomerular as well as tubular cysts e.g. in renal cystic dysplasia, ADPKD. In glomerulocystic kidney disease, exclusive glomerular cysts appear due to dilatation of Bowman's space.

Pathologic changes. *Grossly,* there is marked bilateral enlargement of kidneys. Cut surface shows tiny cysts, 2-3 mm in size.

Microscopically, glomerular cysts are lined by flattened to cuboidal epithelium and have compressed glomerular tuft.

IV. MEDULLARY CYSTIC DISEASE

Cystic disease of the renal medulla has two main types:

A. *Medullary sponge kidney,* a relatively common and innocuous condition; and

B. *Nephronophthiasis-medullary cystic disease complex,* a common cause of chronic renal failure in juvenile age group.

A. Medullary Sponge Kidney

Medullary sponge kidney consists of multiple cystic dilatations of the papillary ducts in the medulla. The condition occurs in adults and may be recognised as an incidental radiographic finding in asymptomatic cases, or the patients may complain of colicky flank pain, dysuria, haematuria and passage of sandy material in the urine. Renal function remains largely normal or may be mildly impaired in long-standing disease with secondary complications of infection and calculus formation.

Pathologic changes. *Grossly,* the kidneys may be enlarged, normal or shrunken in size depending upon the extent of secondary pyelonephritis. On cut surface, the characteristic feature is the presence of several, small (less than 0.5 cm diameter), cystically dilated papillary ducts, which may contain spherical calculi.

Microscopically, the cysts are lined by tall columnar, cuboidal, transitional or squamous epithelium. Renal cortex may show secondary pyelonephritis but cortical cysts are never a component of medullary sponge kidney.

B. Nephronophthiasis-Medullary Cystic Disease Complex

This form of medullary cystic disease, also called *juvenile nephronophthiasis or uraemic sponge kidney,* is a progressive renal disease that makes its appearance in childhood. Familial occurrence is common and both patterns of inheritance occur, recessive transmission being more common than dominant transmission. The clinical manifestations are due to impaired urinary concentration consequent upon the medullary lesions and consist of polyuria, polydipsia and enuresis. Other features include renal osteodystrophy, growth retardation, anaemia and progressive renal failure leading to uraemia.

Pathologic changes. *Grossly,* the kidneys are moderately reduced in size and granular and have narrow cortices. Cut surface reveals minute cysts, majority of which are present at the cortico-medullary junction.

Microscopically, the cysts are lined by flattened or cuboidal epithelium. There is widespread nonspecific chronic inflammatory infiltrate and interstitial

fibrosis. Many glomeruli are hyalinised but tubular atrophy is more pronounced due to marked thickening of tubular basement membrane.

V. Simple Renal Cysts

Simple renal cysts are a very common postmortem finding. They are seen in about half of all persons above the age of 50 years. Since these cysts are rare in infants and children, they appear to be acquired rather than congenital lesions. Simple cysts of the kidneys are rarely responsible for symptoms. However, symptoms may result from rupture, haemorrhage or infection. The association between simple cysts and hypertension is common.

Pathologic changes. *Grossly,* simple renal cysts are usually solitary but may be multiple. They are commonly located in the cortex. Their size varies from a few millimeters to 10 cm in diameter. The wall of cyst is characteristically yellowish-white and translucent. The cyst usually contains clear straw-coloured fluid which may become rust-coloured due to haemorrhage.

Microscopically, the lining of the cyst is by flattened epithelium. The cyst wall contains variable amount of collagenised fibrous tissue which may occasionally have deposits of haemosiderin or calcium salts.

VI. Acquired Renal Cysts

A number of acquired conditions give rise to renal cysts. These include the following:

1. Patients with end-stage renal disease on prolonged dialysis (dialysis-associated cystic disease).
2. Hydatid (echinococcal) cyst.
3. Tuberculosis of the kidney.
4. Cystic degeneration in carcinoma of kidney.
5. Traumatic intrarenal haematoma.
6. Drug-induced cystic disease in experimental animals.

VII. Pararenal Cysts

Cysts occurring adjacent to a kidney are termed pararenal cysts. These include the following:

1. Pyelocalyceal cysts
2. Hilar lymphangiectatic cysts
3. Retroperitoneal cysts
4. Perinephric pseudocysts from trauma.

GLOMERULAR DISEASES

Glomerular diseases encompass a large and clinically significant group of renal diseases. Glomerulonephritis (GN) or Bright's disease is the term used for diseases that primarily involve the renal glomeruli. It is convenient to classify glomerular diseases into 2 broad groups:

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

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

Though this division is widely followed, it is somewhat arbitrary since many primary forms of glomerulonephritis have systemic effects, and many systemic diseases may initially present with glomerular involvement.

Clinical manifestations

The clinical presentation of glomerular disease is quite variable but in general four features – proteinuria, haematuria, hypertension and disturbed excretory function, are present in varying combinations depending upon the underlying condition. A firm diagnosis, however, can be established by examination of renal biopsy under light, electron and immunofluorescence microscopy.

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

- nephritic and nephrotic syndromes;
- acute and chronic renal failure;
- asymptomatic proteinuria and haematuria.

These are briefly described below.

I. ACUTE NEPHRITIC SYNDROME. This is the acute onset of haematuria, proteinuria, hypertension, oedema and oliguria following an infective illness about 10 to 20 days earlier.

1. The haematuria is generally slight giving the urine smoky appearance and erythrocytes are detectable by microscopy or by chemical testing for haemoglobin. Appearance of red cell casts is another classical feature of acute nephritic syndrome.

2. The proteinuria is mild (less than 3 gm per 24 hrs) and is usually non-selective *(nephritic range proteinuria).*

3. Hypertension is variable depending upon the severity of the glomerular disease but is generally mild.

4. Oedema in nephritic syndrome is usually mild and results from sodium and water retention.

5. Oliguria is variable and reflects the severity of glomerular involvement.

The underlying causes of acute nephritic syndrome may be primary glomerulonephritic diseases (classically acute glomerulonephritis and rapidly progressive glomerulonephritis) or certain systemic diseases.

II. NEPHROTIC SYNDROME Nephrotic syndrome is a group of diseases having different pathogenesis and characterised by clinical findings of massive proteinuria, hypoalbuminaemia, oedema, hyperlipidaemia, lipiduria, and hypercoagulability.

1. Heavy proteinuria (protein loss of more than 3 gm per 24 hrs) is the chief characteristic of nephrotic syndrome *(nephrotic range proteinuria).* In children, protein loss is correspondingly less. A small amount of protein (20 to 150 mg/day) normally passes through the glomerular filtration barrier and is reasorbed by the tubules. But in case of increased glomerular permeability to plasma proteins, excess of protein is filtered out exceeding the capacity of tubules for reabsorption and, therefore, appears in the urine. Another feature of protein loss is its 'selectivity'. A *highly-selective proteinuria* consists mostly of loss of low molecular weight proteins, while a *poorly-selective proteinuria* is loss of high molecular weight proteins in the

urine. In nephrotic syndrome, proteinuria mostly consists of loss of albumin (molecular weight 66,000) in the urine.

2. Hypoalbuminaemia is produced primarily consequent to urinary loss of albumin, and partly due to increased renal catabolism and inadequate hepatic synthesis of albumin. Often, the plasma albumin level is 1 to 3 gm/dl (normal 3.5 to 5.5 gm/dl) and there is reversed albumin-globulin ratio. The concentration of other proteins in the plasma such as immunoglobulins, clotting factors and antithrombin may fall rendering these patients more vulnerable to infections and thrombotic and thromboembolic complications.

3. Oedema in nephrotic syndrome appears due to fall in colloid osmotic pressure consequent upon hypoalbuminaemia. Sodium and water retention further contribute to oedema. Nephrotic oedema is usually peripheral but in children facial oedema may be more prominent.

4. Hyperlipidaemia is a frequent accompaniment of nephrotic syndrome. The exact mechanism of its genesis is not clear. It is hypothesised that the liver faced with the stress of massive protein synthesis in response to heavy urinary protein loss, also causes increased synthesis of lipoproteins. There are increased blood levels of total lipids, cholesterol, triglycerides, VLDL and LDL but decrease in HDL. Low blood level of HDL is partly due to its loss in the urine.

5. Lipiduria occurs following hyperlipidaemia due to excessive leakiness of glomerular filtration barrier.

6. Hypercoaguability. Patients with nephrotic syndrome may develop spontaneous arterial or venous thrombosis, renal vein thrombosis and pulmonary embolism as a result of various factors. These include: increased urinary loss of antithrombin III, hyperfibrinogenaemia due to increased synthesis in the liver, decreased fibrinolysis, increased platelet aggregation and altered levels of protein C and S.

The morphology of individual types is described later. But it must be mentioned here that:

• In *children,* primary glomerulonephritis is the cause in majority of cases of the nephrotic syndrome, most frequently *lipoid nephrosis (65%).*

• *In adults,* on the other hand, systemic diseases (diabetes, amyloidosis and SLE) are more frequent causes of nephrotic syndrome. The most common primary glomerular disease in adults is *membranous glomerulonephritis* (40%).

III.ACUTE RENAL FAILURE.

IV. CHRONIC RENAL FAILURE. These cases have advanced renal impairment progressing over years and is detected by significant proteinuria, haematuria, hypertension and azotaemia. Such patients generally have small contracted kidneys as a result of chronic glomerulonephritis.

V. ASYMPTOMATIC PROTEINURIA. Presence of proteinuria unexpectedly in a patient may be unrelated to renal disease (e.g. exercise-induced, extreme lordosis and orthostatic proteinuria), or may indicate an underlying mild glomerulonephritis. Association of asymptomatic haematuria, hypertension or impaired renal function with asymptomatic proteinuria should raise strong suspicion of underlying glomerulonephritis.

VI. ASYMPTOMATIC HAEMATURIA. Asymptomatic microscopic haematuria is common in children and young adolescents and has many diverse causes such as diseases of the glomerulus, renal intersritium, calyceal system, ureter, bladder, prostate, urethra, and underlying bleeding disorder, congenital abnormalities of the kidneys or neoplasia. Glomerular haematuria is indicated by the presence of red blood cells, red cell casts and haemoglobin in the urine. Glomerular haematuria is frequently associated with asymptomatic proteinuria.

Pathogenesis of glomerular injury

It is widely believed that most forms of primary GN and many of the secondary glomerular diseases in human beings have immunopathogenetic mechanisms. This view is largely based on immunofluorescence studies of GN in humans which have revealed glomerular deposits of immunoglobulins and complement in patterns that closely resemble those of experimental models. Non-immunologic mechanisms, however, play some role in certain forms of glomerular damage as discussed later.

The consequences of injury at different sites within the glomerulus can be assessed when compared with the normal physiologic role of the main cells involved i.e. *endothelial, mesangial, visceral epithelial,* and *parietal epithelial cells* as well as of the GBM.

Immunologic mechanisms underlying glomerular injury are primarily *antibody-mediated* (immune-complex disease). However, more recently there has been evidence to suggest that *cell-mediated immune reactions* in the form of delayed type hypersensitivity can cause glomerular injury. In addition, a few secondary mechanisms are involved in the pathogenesis of GN in human beings.

I. Immunologic mechanisms

Experimental studies and observations in man have revealed that immunologic mechanisms, most importantly antigen-antibody complexes, underlie most forms of glomerular injury. The general principles of these mechanisms in different forms of glomerular diseases are discussed below, while more specific features are described under the specific types of GN.

A. Antibody-Mediated Glomerular Injury

1. Immune complex disease. Majority of cases of glomerular disease result from deposits of immune complexes (antigen-antibody complexes). The immune complexes are represented by *irregular or granular glomerular deposits* of immunoglobulins (IgG, IgM and IgA) and complement (mainly C3). Based on the experimental models and studies in human beings, the following 3 patterns of glomerular deposits of immune complexes in various glomerular diseases have been observed:

i) *Exclusive mesangial deposits* are characterised by very mild form of glomerular disease.

ii) *Extensive subendothelial deposits* along the GBM are accompanied by severe hypercellular sclerosing glomerular lesions.

iii) *Subepithelial deposits* are seen between the outer surface of the GBM and the podocytes.

Deposits may be located at one or more of the above sites in any case of glomerular. injury. It was widely believed earlier that glomerular deposits result from circulating immune complexes. Now, it has been shown that glomerular deposits are formed by one of the following two mechanisms:

i) *Local immune complex deposits.* Formation of glomerular deposits of immune complex *in situ* occurs as a result of combination of antibodies with autologous non-basement membrane antigens or nonglomerular antigens planted on glomeruli. Currently, this mechanism is considered responsible for most cases of immune complex GN. Classic experimental model of *in situ* immune complex GN is *Hermann nephritis* (autologous immune complex nephritis) induced in rats by immunising animals with homologous preparations of proximal tubular brush border. The rats develop antibodies to brush border antigens and thereby membranous GN that closely resembles human membranous GN. The examples of *planted nonglomerular antigens* are cationic proteins, lectins, DNA, bacterial products (e.g. a protein of group A streptococci), viral and parasitic products and drugs.

ii) *Circulating immune complex deposits.* This mechanism used to be considered very important for glomerular injury but now it is believed that circulating immune complexes cause glomerular damage under certain circumstances only. These situations are: their presence in high concentrations for prolonged periods, or when they possess special properties that cause their binding to glomeruli, or when host mechanisms are defective and fail to eliminate immune complexes. The antigens evoking antibody response may be endogenous (e.g. in SLE) or may be exogenous (e.g. Hepatitis B virus, *Treponema pallidum, Plasmodium falciparum* and various tumour antigens). The antigen-antibody complexes are formed in the circulation and then trapped in the glomeruli where they produce glomerular injury after combining with complement.

Immune complex GN is observed in the following human diseases:

i) *Primary GN* e.g. acute diffuse proliferative GN, membranous GN, membranoproliferative GN, IgA nephropathy and some cases of rapidly progressive GN and focal GN.

ii) *Systemic diseases* e.g. glomerular disease in SLE, malaria, syphilis, hepatitis, Henoch-Schonlein purpura and idiopathic mixed cryoglobulinaemia.

2. Anti-GBM disease. Less than 5% cases of human GN are associated with anti-GBM antibodies. The constituent of GBM acting as antigen appears to be a component of collagen IV of the basement membrane. The experimental model of anti-GBM disease is *Masugi nephritis* (nephrotoxic serum nephritis) produced in rats by injection of heterologous antibodies against GBM prepared in rabbits by immunisation with rat kidney tissue.

Anti-GBM disease is classically characterised by *interrupted linear deposits* of anti-GBM antibodies (mostly IgG; rarely IgA and IgM) and complement (mainly C3) along the glomerular basement membrane. These deposits are detected by immunofluorescence microscopy or by electron microscopy.

Anti-GBM disease is characteristically exemplified by glomerular injury in Goodpasture's syndrome in some cases of rapidly progressive GN. About half to two-third of the patients with renal lesions in Goodpasture's syndrome have pulmonary haemorrhage mediated by cross-reacting autoantibodies against alveolar basement membrane.

3. *Alternate pathway disease.* As apparent from the above mechanisms, the complement system, in particular C3, contributes to glomerular injury in most forms of GN. Deposits of C3 are associated with the early components Cl, C2 and C4 which are evidence of classic pathway activation of complement. But in alternate pathway activation, there is decreased serum C3 level, decreased serum levels of factor B and properdin, normal serum levels of Cl, C2 and C4 but C3 and properdin are found deposited in the glomeruli without immunoglobulin deposits, reflecting activation of alternate pathway of complement. Such patients have circulating anti-complementary nephritic factor called C3NeF which is an IgG antibody and acts as an auto-antibody to the alternate C3 convertase and enhances alternate pathway activity.

The deposits in alternate pathway disease are characteristically electron-dense under electron microscopy, glomerular lesions in such cases are referred to as *dense-deposit disease.*

Alternate pathway disease occurs in most cases of type II membranoproliferative GN, some patients of rapidly progressive GN, acute diffuse proliferative GN, IgA nephropathy and in SLE.

4. *Other mechanisms of antibody-mediated injury.* A few autoantibodies have been implicated in some patients of glomerulonephritis. These include the following:

i) Anti-neutrophil cytoplasmic antibodies (ANCA).

About 40% cases of rapidly progressive GN are deficient in immunoglobulins in glomeruli and are positive for ANCA against neutrophil cytoplasmic antigens in their circulation. ANCA causes endothelial injury by generation of reactive oxygen radicals.

ii) Anti-endothelial cell antibodies (AECA). Auto-antibodies against endothelial antigens have been detected in circulation is several inflammatory vasculitis and glomerulonephritis. These antibodies increase the adhesiveness of leucocytes to endothelial cells.

B. Cell-mediated Glomerular Injury (Delayed-type Hypersensitivity)

Recent evidence suggests that cell-mediated immune reactions may be involved in causing glomerular injury, particularly in cases with deficient immunoglobulins (pauci-immune glomerulonephritis). Cytokines and other mediators released by activated T cells stimulate cytotoxicity, recruitment of more leucocytes and fibrogenesis. CD4 + T lymphocytes recruit more mac-

rophages while CDS + cytotoxic T lymphocytes and natural killer cells cause further glomerular cell injury. However, cell-mediated injury, is yet less clear than antibody-mediated glomerular injury.

C. Secondary Pathogenetic Machanisms (Mediators of Immunologic Injury)

Secondary pathogenetic mechanisms are a number of mediators of immunologic glomerular injury operating in man and in experimental models. These include the following:

1. *Neutrophils.* Neutrophils are conspicuous in certain forms of glomerular disease such as in acute diffuse proliferative GN, and may also be present in membranoproliferative GN and lupus nephritis. Neutrophils can mediate glomerular injury by activation of complement as well as by release of proteases, arachidonic acid metabolites and oxygen-derived free radicals. These agents cause degradation of GBM and cell injury.

2. *Mononuclear phagocytes.* Many forms of human and experimental proliferative GN are associated with glomerular infiltration by monocytes and macrophages. Accumulation of mononuclear phagocytes is considered an important constituent of hypercellularity in these forms of GN aside from proliferation of rnesangial and endothelial cells. Activated macrophages release a variety of biologically active substances which take part in glomerular injury.

3. *Complement system*. The pathogenetic role of classical and alternate pathway of activation of complement has already been highlighted above. Besides the components of complement which mediate glomerular injury via neutrophils already mentioned, C5b9 is capable of inducing damage to GBM directly.

4. *Platelets.* Platelet aggregation and release of mediators play a role in the evolution of some forms of GN. Increased intrarenal platelet consumption has been found to occur in some forms of glomerular disease.

5. *Mesangial cells.* There is evidence to suggest that rnesangial cells present in the glomeruli may be stimulated to produce mediators of inflammation and take part in glomerular injury.

6. *Coagulation system.* The presence of fibrin in early crescents in certain forms of human and experimental GN suggests the role of coagulation system in glomerular damage. Fibrinogen may leak into Bowman's space and act as stimulus for cell proliferation. Crescents usually transform into scar tissue under the influence of fibronectin which is regularly present in crescents in human glomerular disease.

II. Non-immunologic mechanisms

Though most forms of GN are mediated by immunologic mechanisms, a few examples of glomerular injury by non-immunologic mechanisms are found. These are:

1. *Metabolic glomerular injury* e.g. diabetic nephropathy, Fabry's disease.

2. *Haemodynamic glomerular injury* e.g. systemic hypertension.

3. *Deposition diseases* e.g. cryoglobulinaemia, amyloidosis.

4. *Infectious diseases* e.g. HBV, HCV, HIV, E. *coil-derived* nephrotoxin.

5. Inherited glomerular diseases e.g. Alport's syndrome, nail-patella syndrome.

The evolution of end-stage renal failure is explained on the basis of adaptive glomerular hypertrophy of unaffected glomeruli that results in increased glomerular blood flow and increased glomerular capillary pressure inducing intraglomerular hypertension. These events lead to increased deposition of mesangial matrix and proliferation of mesangial cells, endothelial and epithelial cell injury, and eventually to progressive glomerulosclerosis and end-stage renal failure.

So, **GLOMERULONEPHRITIS** can be classifide according to:

I. Primary and secondary

II. Etiology:

1. Of determined etiology,
2. Of undetermined etiology

III. Pathogenesis:

1. With immune mechanisms of development (antibodies and immune complexes),
2. Without immune changes.

IV. Character of course:

1. Acute,
2. Subacute,
3. Chronic

V. Morphological criteria:

- topography of process:
  1) intracapillary, 2) extracapillary,
- character of inflammation:
  1) exudative, 2) proliferative, 3) mixed,
- spreading of process:
  1) diffuse, 2) focal.

PRIMARY GLOMERULONEPHRITIS

ACUTE GLOMERULONEPHRITIS(SYNONYMS: ACUTE DIFFUSE PROLIFERATIVE GN, DIFFUSE ENDOCAPILLARY GN)

Acute GN is known to follow acute infection and characteristically presents as acute nephritic syndrome. Based on etiologic agent, acute GN is subdivided into 2 main groups: acute post-streptococcal GN and acute non-streptococcal GN, the former being more common.

ACUTE POST-STREPTOCOCCAL GN

Acute post-streptococcal GN is fairly common form of GN, seen most commonly in children 6 to 16 years of age but adolescents and adults may also be affected. The onset of disease is generally sudden after 1-2 weeks of streptococcal infection, most frequently of the throat and sometimes of the skin.

Etiopathogenesis. The relationship between strep tococcal infection and this form of GN is now well established. Particularly nephritogenic are types 12,4,1 and Red Lake of group A β-haemolytic streptococci. The glomerular lesions appear to result from deposition of immune complexes in the glomeruli. The evidences cited in support are as under:

i) There is *epidemiological* evidence of preceding streptococcal sore throat or skin infection about 1-2 weeks prior to the attack.

ii) The *latent period* between streptococcal infection and onset of clinical manifestations of the disease is compatible with the period required for building up of antibodies.

iii) Streptococcal infection may be identified by *culture* or may be inferred from elevated titres of *antibodies* against streptococcal antigens. These include:

- anti-streptolysin O (ASO);
- anti-deoxyribonuclease B (anti-DNAse B);
- anti-streptokinase (ASKase);
- anti-nicotinyl adenine dinucleoridase (anti-NADase); and
- anti-hyaluronidase (AHase).

iv) There is usually *hypocomplementaemia* indicating involvement of complement in the glomerular deposits,

v) More recently, it has been possible to identify antigenic component of streptococci which is cytoplasmic antigen, *endostreptosin.*

Pathologic changes. *Grossly,* the kidneys are symmetrically enlarged, weighing one and a half to twice the normal weight. The cortical as well as sectioned surface show petechial haemorrhages giving the characteristic appearance of flea-bitten kidney.

i) Glomeruli – The glomeruli are affected diffusely. They are enlarged and hypercellular. The diffuse hypercellulariry of the tuft is due to proliferation of mesangial, endothelial and occasionally epithelial cells *(acute proliferative lesions)* as well as by infiltration of leucocytes, chiefly polymorphs and sometimes monocytes. There may be small deposits of fibrin within the capillary lumina and in the mesangium.

ii) Tubules – Tubular changes are not very striking. There may be swelling and hyaline droplets in tubular cells, and tubular lumina may contain red cell casts.

iii) Interstitium – There may be sorm degree of interstitial oedema and leucocytic infiltration.

iv) Vessels – Changes in arteries and arterioles are seldom present in acute GN.

Electron microscopic findings, aside from confirming the light microscopic findings, are the characteristic electron-dense irregular deposits *Chumps'* on the epithelial side of the GBM. These deposits represent the immune complexes. *Immunofluorescence microscopy* reveals that the irregular deposits along the GBM consist principally of IgG and complement C3.

Prognosis varies with the age of the patient. Children almost always (95%) recover completely with reversal of proliferative glomerular changes. Complications arise moie often in adults and occasionally in children. These include development of rapidly progressive GN, chronic GN, uraemia and chronic renal failure.

ACUTE NON-STREPTOCOCCAL GN

About one-third cases of acute GN are caused by organisms other than haemolytic streptococci. These include other bacteria (e.g. staphylococci, pneumococci, meningococci, *Salmonella* and *Pseudomonas)*, viruses (e.g. hepatitis B virus, mumps, infectious mononucleosis and varicella), parasitic infections (e.g. malaria, toxoplasmosis and schistosomiasis) and syphilis. The appearance of renal biopsy by light microscopy, EM and immunofluorescence microscopy is similar to that seen in acute post-streptococcal GN. The prognosis of non-streptococcal GN is not as good as that of streptococcal GN.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (SYNONYMS; RPGN, CRESCENTIC GN, EXTRACAPILLARY GN)

RPGN presents with an acute reduction in renal function resulting in acute renal failure in a few weeks or months.

It is characterised by formation of 'crescents' *(crescentic GN)* outside the glomerular capillaries *(extracapillary GN). 'Crescents'* are formed from the proliferation of parietal epithelial cells lining Bowman's capsule with contribution from visceral epithelial cells and the invading mononuclear cells. The stimulus for crescent formation appears to be the presence of fibrin in the capsular space. RPGN occurs most frequently in adults, with a slight male preponderance. Prognosis of RPGN in general is dismal.

Etiopathogenesis. A number of primary glomerular and systemic diseases are characterised by formation of crescents. Based on the etiologic agents and pathogenetic mechanism, patients with RPGN are divided into 3 groups:

- RPGN in systemic diseases (anti-GBM type);
- post-infectious RPGN (immune-complex type); and

• pauci-immune RPGN.

There are three main serologic markers in RPGN:

i) serum C3 level,

ii) anti-GBM antibody; and

iii) anti-neutrophil cytoplasmic antibody (ANCA).

Type I RPGN: Anti-GBM disease. A number of systemic diseases such as Goodpasture's syndrome, SLE, vasculitis, Wegener's granulomatosis, Henoch-Schonlein purpura and idiopathic mixed cryoglobulinaemia are associated with crescentic GN.

Goodpasture's syndrome. Goodpasture's syndrome is characterised by acute renal failure due to RPGN and pulmonary haemorrhages. The condition is more common in males in 3rd decade of life. The disease results from damage to the glomeruli by anti-GBM antibodies which cross-react with alveolar basement membrane and hence, produce renal as well as pulmonary lesions. The evidences in support are the characteristic linear deposits of anti-GBM antibodies consisting of IgG and complement along the GBM, detection of circulating anti-GBM antibodies and induction of glomerular lesions with injection of anti-GBM antibodies experimentally in monkeys. Pulmonary lesions can be experimentally induced if the lungs are previously injured by viral or bacterial infection or exposed to hydrocarbons. The Goodpasture's antigen appears to be a component of collagen type IV.

Type II RPGN: Immune complex disease. A small proportion of cases of post-streptococcal GN, particularly in adults and sometimes of non-streptococcal origin, develop RPGN. The evidences in support of post-infectious RPGN having immune complex pathogenesis are granular deposits of immune complexes of IgG and C3 along the glomerular capillary walls, lowering of blood complement levels and demonstration of circulating complexes.

Type III RPGN: Pauci-immune type. These include cases of Wegener's granulomatosis and polyarteritis. The pathogenesis of pauci-immune GN is yet not fully defined. However, majority of these patients are ANCA-positive, implying a defect in humoral immunity. Serum complement levels are normal and anti-GBM antibody is negative. There is little or no glomerular immune deposit (i.e. pauci-immune).

Pathologic *changes*. *Grossly,* the kidneys are usually enlarged and pale with smooth outer surface *(large white kidney).* Cut surface shows pale cortex and congested medulla.

Light Microscopic findings vary according to the cause but in general following features are present:

i) *Glomeruli.* Irrespective of the underlying etiology, all forms of RPGN show pathognomonic *'crescents'* on the inside of Bowman's capsules.

These are collections of pale-staining polygonal cells which commonly tend to be elongated. Eventually, crescents obliterate the Bowman's space and compress the glomerular tuft. Fibrin deposition is invariably present alongside crescents. Besides the crescents, glomerular tufts may show increased cellularity as a result of proliferation of endothelial and rnesangial cells and leucocytic infiltration. Fibrin thrombi are frequently present in the glomerular tufts.

ii) *Tubules*. Tubular epithelial cells may show hyaline droplets. Tubular lumina may contain casts, red blood cells and fibrin.

iii) *Interstitium.* The interstitium is oedematous and may show early fibrosis. Inflammatory cells, usually lymphocytes and plasma cells, are commonly distributed in the interstitial tissue.

iv) *Vessels.* Arteries and arterioles may show no change, but cases associated with hypertension usually show severe vascular changes.

Electron microscopic findings vary according to the type of RPGN. Post-infectious RPGN cases show electron-dense subepithelial granular deposits similar to those seen in acute GN, while cases of RPGN in Goodpasture's syndrome show characteristic linear deposits along the GBM.

Immunofluorescence microscopy shows:

• linear pattern of RPGN in Goodpasture's syndrome (type I RPGN), containing IgG accompanied by C3 along the capillaries

• granular pattern of post-infectious RPGN (type II RPGN) consisting of IgG and C3 along the capillary wall; and

• scanty or no deposits of immunoglobulin and C3 in pauci-immune GN (type III RPGN).

Prognosis of all forms of RPGN is poor. However, post-infectious cases have somewhat better outcome and may show recovery.

MEMBRANOUS GLOMERULONEPHRITIS (SYNONYM: EPIMEMBRANOUS NEPHROPATHY)

Membranous GN is characterised by wide-spread thickening of the glomerular capillary wall and is the most common cause of nephrotic syndrome in adults. In about 15% of cases, membranous GN is secondary to an underlying condition (e.g. SLE, malignancies, infections such as chronic hepatitis B and C, syphilis, malaria and drugs), while in the majority of cases (85%) it is truly idiopathic.

Etiopathogenesis. *Idiopathic membranous GN* is an immune complex disease. The deposits of immune complex are formed locally because circulating immune complexes are detected in less than a quarter of cases. Since leucocytic infiltration is not a feature of membranous GN, damage to the GBM is mediated directly by complement. While nephritogenic antigen against which autoantibodies are formed in *idiopathic membranous* GN is not

known yet, the antigen in cases of *secondary membranous GN* is either an endogenous (e.g. DNA in SLE) or exogenous one (e.g. hepatitis B virus, tumour antigen, treponema antigen etc).

Pathologic changes. *Grossly,* the kidneys are enlarged, pale and smooth.

Light microscopy shows the following findings:

i) *Glomeruli.* The characteristic finding is diffuse thickening of the glomerular capillary walls with all the glomeruli being affected more or less uniformly. As the disease progresses, the deposits are incorporated into enormously thickened basement membrane, producing 'duplication' of GBM which is actually formation of a new basement membrane. These basement membrane changes are best appreciated by silver impregnation stains (black colour) or by periodic acid-Schiff stain (pink colour).

There is no cellular proliferation in the glomerular tufts.

ii) *Tubules.* The renal tubules remain normal except in the early stage when lipid vacuolation of the proximal convoluted tubules may be seen.

iii) *Interstitium.* The interstitium may show fine fibrosis and scanty chronic inflammatory cells.

iv) *Vessels*. In the early stage, vascular changes are not prominent, while later hypertensive changes of arterioles may occur.

Electron microscopy shows electron-dense deposits situated in the epithelial side of the GBM. The basement membrane material protrudes between deposits as *'spikes'*. *Immunofluorescence microscopy* reveals granular deposits of immune complexes consisting of IgG associated with complement C3. In secondary cases of membranous GN the relevant antigen such as hepatitis B or tumour antigen may be seen.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS *(SYNONYMS: MPGN, MESANGIOCAPILLARY GN)*

Membranoproliferative GN is another important cause of nephrotic syndrome in children and young adults. As the name implies, it is characterised by two histologic features increase in cellularity of the mesangium associated with increased lobulation of the tuft, and irregular thickening of the capillary wall.

Etiopathogenesis. Etiology of MPGN is unknown though in some cases there is evidence of preceding streptococcal infection. Based on ultrastructural, immunofluorescence and pathogenetic mechanisms, three types of MPGN are recognised:

• Type I or classic form is an example of immune complex disease and comprises more than 70% cases. It is characterised by immune deposits in the subendothelial position.

• Type II or dense deposit disease is the example of alternate pathway disease and constitutes about 30% cases. The capillary wall thickening is due to the deposition of electron-dense material in the lamina densa of the GBM.

• Type III is rare and shows features of type I MPGN and membranous nephropathy in association with systemic diseases or drugs.

Pathologic changes. Grossly and by light microscopy, all the three types of MPGN are similar.

Grossly, the kidneys are usually pale in appearance and firm in consistency.

By light microscopy, the features are as under:

i) *Glomeruli.* Glomeruli show highly characteristic changes. They are enlarged with accentuated lobular pattern. The enlargement is due to variable degree of mesangial cellular proliferation and increase in mesangial matrix. The GBM is considerably thickened, which with silver stains shows two basement membranes with a clear zone between them. This is commonly referred to as *'double contour', splitting, or 'tram track'* appearance.

ii) *Tubules.* Tubular cells may show vacuolation and hyaline droplets.

iii) *Interstitium.* There may be scattered chronic inflammatory cells and some finely granular foam cells in the interstitium.

iv) *Vessels.* Vascular changes are prominent in cases in which hypertension develops.

By electron microscopy and immunofluorescence microscopy, the changes are different in the three types of MPGN:

Type I: It shows *electron-dense deposits* in subendothelial location conforming to immune-complex character of the disease. These deposits reveal positive fluorescence for C3 and slightly fainter staining for IgG.

Type II: The hallmark of type II MPGN is the presence of *dense amorphous deposits* within the lamina densa of the GBM and in the mesangium. Immunofluorescence studies reveal the universal presence of C3 and properdin in the deposits but the immunoglobulins are usually absent.

Type III: This rare form has *electron-dense deposits* within the GBM as well as in subendothelial and subepithelial regions of the GBM. Immunofluorescence studies show the presence of C3, IgG and IgM.

FOCAL GLOMERULONEPHRITIS (SYNONYMS: FOCAL SEGMENTAL GN, FOCAL PROLIFERATIVE GN)

Focal GN is characterised by pathologic changes in certain number of glomeruli *(focal),* and often confined to one or two lobules of the affected glomeruli *(segmental),* while other glomeruli are normal. Focal GN is, thus, a pathologic diagnosis. It may occur as a primary glomerular disease or may be a part of a number of systemic diseases such as SLE, Henoch-Schonlein pur-

pura, subacute bacterial endocarditis, Wegener's granulomatosis, vasculitis, Goodpasture's syndrome and IgA nephropathy.

Etiopathogenesis. The diverse settings under which focal GN is encountered make it unlikely that there are common etiologic agents or pathogenetic mechanisms. However, the observation of mesangial deposits of immunoglobulins and complement suggest immune complex disease and participation of the mesangium.

Pathologic changes. *By light microscopy,* the single most important feature in focal GN is the abnormality seen in certain number of glomeruli and generally confined to one or two lobules of the affected glomeruli i.e. *focal and segmental glomerular involvement*. The pathologic change most frequently consists of focal and segmental cellular proliferation but sometimes necrotising changes can be seen. The condition must be distinguished from focal and segmental glomerulosclerosis (discussed below).

By immunofluorescence microscopy, widespread mesangial deposits of immunoglobulins (mainly IgA with or without IgG), complement (C3) and fibrin are demonstrated in most cases of focal GN.

MINIMAL CHANGE DISEASE (SYNONYMS: LIPOID NEPHROSIS, FOOT PROCESS DISEASE, NIL DEPOSIT DISEASE)

Minimal change disease is a condition in which the nephrotic syndrome is accompanied by no apparent change in glomeruli by light microscopy. Its other synonyms, lipoid nephrosis and foot process disease, are descriptive terms for fatty changes in the tubules and electron microscopic appearance of flattened podocytes respectively. Minimal change disease accounts for 80% cases of nephrotic syndrome in children under 16 years of age with preponderance in boys (ratio of boys to girls 2:1).

Etiopathogenesis. The etiology and pathogenesis of minimal change disease remain elusive, and majority of cases are idiopathic but the following features point to possible immunologic mechanisms:

i) Absence of deposits by electron microscopy.

ii) Normal circulating levels of complement but presence of circulating immune complexes in many cases.

iii) Clinical association, relapses and immunisation of the disease with respiratory infections.

iv) Universal satisfactory response to steroid therapy.

v) HLA association of the disease as with other forms of GN.

vi) Increased suppressor T cell activity as evidenced by association of lipoid nephrosis with Hodgkin's disease.

The proteinuria of nephrotic syndrome in minimal change disease in children is characteristically *selective* (albuminuria). The basis for selective proteinuria appears to be:

i) reduction of normal negative charge on GBM due to loss of heparan sulfate proteoglycan from the GBM; and

ii) change in the shape of epithelial cells producing foot process flattening due to reduction of sialoglycoprotein cell coat.

Adults having MCD, however, have non-selective proteinuria, suggesting more extensive membrane permeability defect.

Pathologic changes. *Grossly,* the kidneys are of normal size and shape.

By light microscopy, the findings are as under:

i) *Glomeruli.* The most characteristic feature is no apparent abnormality in the glomeruli except for slight increase in the mesangial matrix at the most.

ii) *Tubules.* There is presence of fine lipid vacuolation and hyaline droplets in the cells of proximal convoluted tubules and, hence, the older name of the condition as 'lipoid nephrosis'.

iii) *Interstitium.* There may be oedema of the interstitium.

iv) *Vessels.* Blood vessels do not show any significant change (minimal change).

By electron microscopy, the most characteristic feature of the disease is identified which is diffuse flattening of foot processes of the visceral epithelial cells (podocytes) and, hence, the name foot process disease. Unlike other forms of GN, no deposits are seen and the GBM is normal. *By immunofluorescence microscopy,* no deposits of complement or immunoglobulins are recognised (nil deposit disease).

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (SYNONYMS: FOCAL SCLEROSIS, FOCAL HYALINOSIS)

Focal segmental glomerulosclerosis is a condition in which there is sclerosis and hyalinosis of some glomeruli and portions of their tuft, while the other glomeruli are normal by light microscopy i.e. involvement is focal and segmental.

Etiopathogenesis. Focal segmental glomerulosclerosis was previously believed to be a variant of minimal change disease with accentuation of epithelial damage in the form of hyalinosis and sclerosis. Currently, the condition is divided into 3 groups:

i) *Idiopathic type*. It is found in children and young adults with presentation of nephrotic syndrome. It differs from minimal change disease in having non-selective proteinuria, in being steroid-resistant, and may progress to

chronic renal failure. Immunofluorescence microscopy reveals deposits of IgM and C3 in the sclerotic segment.

ii) *With superimposed primary glomerular disease*. There may be cases of focal segmental glomerulosclerosis with superimposed minimal change disease or IgA nephropathy. Those associated with minimal change disease show good response to steroid therapy and progression to chronic renal failure may occur after a long time.

iii) *Secondary type.* This group consists of focal segmental sclerotic lesions as a secondary manifestation of certain diseases such as AIDS, reflux nephropathy and analgesic nephropathy. Infection with HIV, particularly in blacks, has been found associated with a variant of focal segmental glomerulosclerosis which is characterised by *collapsing sclerosis.*

Pathologic changes. *By light microscopy*, depending upon the severity of the disease, variable number of glomeruli are affected focally and segmentally, while others are normal. The affected glomeruli show solidification or *sclerosis* of one or more lobules of the tuft. *Hyalinosis* refers to collection of eosinophilic, homogeneous, PAS-positive, hyaline material present on the inner aspect of a sclerotic peripheral capillary loop. Mesangial hypercellularity is present in appreciable number of cases.

HTV-associated nephropathy is characterised by focal sclerosis that may be segmental or global, having collapsed capillaries in the tuft. Besides glomerular changes, there is interstitial fibrosis and infiltration by mononuclear leucocytes, and tubular epithelial cell atrophy and degeneration.

By electron microscopy, diffuse loss of foot processes as seen in minimal change disease is evident but, in addition, there are electron-dense deposits in the region of hyalinosis and sclerosis which are believed to be immune complexes.

By Immunofluorescence microscopy, the deposits in the lesions are shown to contain IgM and C3.

IgA Nephropathy (Synonyms: Berger's Disease, IgA GN)

IgA nephropathy is characterised by aggregates of IgA, deposited principally in the mesangium. The condition was first described by Berger, a French physician in 1968.

Etiopathogenesis. The etiology and pathogenetic mechanism are not quite clear. A number of theories have been proposed:

i) In view of exclusive mesangial deposits of IgA and elevated serum levels of IgA and IgA-immune complexes, IgA nephropathy has been considered to arise from *entrapment* of these complexes in the mesangium.

ii) There is absence of early components of the complement but presence of C3 and properdin in the mesangial deposits, which point towards activation of complement system by *alternate pathway.*

iii) Since there is close association between mucosal infections (e.g. of the respiratory, gastrointestinal or urinary tract), it is suggested that IgA deposited in the mesangium could be of *mucosal origin.*

iv) Another possibility is *genetically-determined* abnormality of the immune system producing an increase in circulating IgA.

Pathologic changes. *By light microscopy,* the pattern of involvement varies. These include: focal proliferative GN, focal segmental glomerulosclerosis, membranoproliferative GN, and rarely RPGN. *By electron microscopy,* finely granular electron-dense deposits are seen in the mesangium. *By immunofluorescence microscopy,* the diagnosis is firmly established by demonstration of mesangial deposits of IgA, with or without IgG, and usually with C3 and properdin.

CHRONIC GLOMERULONEPHRITIS *(SYNONYM: END-STAGE KIDNEY)*

Chronic GN is the final stage of a variety of glomerular diseases which result in irreversible impairment of renal function. The conditions which may progress to chronic GN, in descending order of frequency, are as under:

i) Rapidly progressive GN (90%)

ii) Membranous GN (50%)

iii)) Membranoproliferative GN (50%)

iv) Focal segmental glomerulosclerosis (50%)

v) IgA nephropathy (40%)

vi) Acute post-streptococcal GN (1%)

However, about 20% cases of chronic GN are *idiopathic* without evidence of preceding GN of any type.

Pathologic changes. *Grossly,* the kidneys are usually small and contracted weighing as low as 50 gm each. The capsule is adherent to the cortex. The cortical surface is generally diffusely granular. On cut section, the cortex is narrow and atrophic, while the medulla is unremarkable.

Microscopically, the changes vary greatly depending upon the underlying glomerular disease. In general, the following changes are seen:

i) *Glomeruli.* Glomeruli are reduced in number and most of those present show completely hyalinised tufts, giving the appearance of acellular, eosinophilic masses which are PAS-positive. Evidence of underlying glomerular disease may be present,

ii) *Tubules.* Many tubules completely disappear and there may be atrophy of tubules close to scarred glomeruli. Tubular cells show hyaline-droplets, degeneration and tubular lumina frequently contain eosinophilic, homogeneous casts.

iii) *Interstitium.* There is fine and delicate fibrosis of the interstitial tissue and varying number of chronic inflammatory cells are often seen.

iv) *Vessels.* Advanced cases which are frequently associated with hypertension show conspicuous arterial and arteriolar sclerosis.

Patients of end-stage kidney disease on dialysis show a variety of dialysis associated changes that include acquired cystic disease, occurrence of adenomas and adenocarcinomas of the kidney, calcification of tufts and deposition of calcium oxalate crystals in tubules.

II. SECONDARY GLOMERULAR DISEASES

Glomerular involvement may occur secondary to certain systemic diseases or a few hereditary diseases. In some of these, renal involvement may be the initial presentation, while in others clinical evidence of renal disease appears long after other manifestations have appeared.

DIABETIC NEPHROPATHY

Renal involvement is an important complication of diabetes mellitus. End-stage kidney with renal failure accounts for deaths in more than 10% of all diabetics. Renal complications are more severe and develop early in juvenile-onset diabetes (insulin-dependent diabetes) than in maturity-onset diabetes (non-insulin dependent diabetes). A variety of clinical syndromes are associated with diabetic nephropathy that includes asymptomatic proteinuria, nephrotic syndrome, progressive renal failure and hypertension.

Pathologic changes. Diabetic nephropathy is the term that encompasses 4 types of renal lesions in diabetes mellitus: diabetic glomerulosclerosis, vascular lesions, diabetic pyelonephritis and tubular lesions (Armanni-Ebstein lesions).

1. *Diabetic glomerulosclerosis.* Glomerular lesions in diabetes mellitus are particularly common and account for majority of abnormal findings referable to the kidney. These may take one of the 2 forms: diffuse or nodular lesions:

i) *Diffuse glomerulosclerosis.* Diffuse glomerular lesions are the most common. There is involvement of all parts of glomeruli. The pathologic changes consist of thickening of the GBM and diffuse increase in mesangial matrix with mild proliferation of mesangial cells. Various exudative lesions such as capsular hyaline drops and fibrin caps may also be present *Capsular drop* is an eosinophilic hyaline thickening of the parietal layer of Bowman's capsule and bulges into the glomerular space. *Fibrin cap* is homogeneous, brightly eosinophilic material appearing on the wall of a peripheral capillary of a lobule.

ii) *Nodular glomerulosclerosis.* Nodular lesions of diabetic glomerulosclerosis are also called as *Kinimelstiel-Wilson (KW) lesions* or *intercapillary glomerulosclerosis.* These lesions are specific for juvenile-onset diabetes or islet cell antibody-positive diabetes mellitus. The pathologic changes consist of

one or more nodules in a few or many glomeruli. *Nodule* is an ovoid or spherical, laminated, hyaline, acellular mass located within a lobule of the glomerulus. The nodules are surrounded peripherally by glomerular capillary loops which may have normal or thickened GBM. The nodules are PAS-positive and contain lipid and fibrin. As the nodular lesions enlarge, they compress the glomerular capillaries and obliterate the glomerular tuft. As a result of glomerular and arteriolar involvement, renal ischaemia occurs leading to tubular atrophy and interstitial fibrosis and grossly small, contracted kidney.

Pathogenesis. The pathogenesis of diffuse or nodular diabetic glomerulosclerosis is closely linked with the pathogenesis of diabetic microangiopathy. Available evidences support a role for metabolic defect in diabetes in the form of insulinopenia, hyperglycaemia and glycosuria, increased synthesis of collagen types IV, fibronectin, and haemodynamic changes, in causing diabetic glomerulosclerosis.

2. *Vascular lesions*. Atherosclerosis of renal arteries is very common and severe in diabetes mellitus. Hyaline arteriolosclerosis affecting the afferent and efferent arterioles of the glomeruli is also often severe in diabetes. These vasrular lesions are responsible for renal ischaemia that results in tubular atrophy and interstitial fibrosis.

3. *Diabetic pyelonephritis*. Poorly-controlled diabetics are particularly susceptible to bacterial infections. Papillary necrosis (necrotising papillitis is an important complication of diabetes that may result in acute pyelonephritis. Chronic pyelonephritis is 10 to 20 times more common in diabetics than in others.

4. Tubular lesions (armanni-ebstein lesions). In untreated diabetics who have extremely high blood sugar level, the epithelial cells of the proximal convoluted tubules develop extensive glycogen deposits appearing as vacuoles. These are called Armanni-Ebstein lesions. The tubules return to normal on control of hyperglycaemic state.

HEREDITARY NEPHRITIS

A group of hereditary diseases principally involving the glomeruli are termed hereditary nephritis. These include the following:

1. Alport's syndrome
2. Fabry's disease
3. Nail-patella syndrome

1. Alport's syndrome. Out of various hereditary nephritis, Alport's syndrome is relatively more common and has been extensively studied. This is an X-linked dominant disorder with variable penetrance and affects males more severely than females. The syndrome consists of sensorineural deafness and ophthalmic complications (lens dislocation, posterior cataracts and corneal dystrophy) associated with hereditary nephritis. The condition is slowly progressive,

terminating in end-stage kidney in the 2nd to 3rd decades of life. The common presenting features are persistent or recurrent haematuria accompanied by erythrocyte casts, proteinuria and hypertension.

By *light microscopy*, the glomeruli have predominant involvement and show segmental proliferation of mesangial cells with increased mesangial matrix and occasional segmental sclerosis. Another prominent feature is the presence of *lipid-laden foam cells* in the intersritium. As the disease progresses, there is increasing sclerosis of glomeruli, tubular atrophy and interstitial fibrosis.

Electron microscopy reveals characteristic basement membrane splitting or lamination in the affected parts of glomeruli.

Immunofluorescence studies fail to show deposits of immunoglobulins or complement components.

2. Fabry's disease, another hereditary nephritis is characterised by accumulation of neutral glycosphingolipids in lysosomes of glomerular, tubular, vascular and interstitial cells.

3. Nail-patella syndrome or osteonychodysplasia is a rare hereditary disease associated with multiple osseous defects of elbows, knees and nail dysplasia. About half the cases develop nephropathy.

TUBULAR DISEASES

Acute tubular necrosis is the pathologic entity that affects exclusively renal tubules. Many other diseases involve the tubules secondarily, or the tubular involvement is accompanied by interstitial involvement as well and are described later under the heading of 'tubulo-interstitial diseases.'

ACUTE TUBULAR NECROSIS

Acute tubular necrosis (ATN) is the term used for acute renal failure (ARF) resulting from destruction of tubular epithelial cells. ATN is the most common and most important cause of ARF characterised by sudden cessation of renal function. Here, the two distinct forms of ATN – ischaemic and toxic, are discussed.

ISCHAEMIC ATN

Ischaemic ATN, also called tubulorrhectic ATN, lower nephron nephrosis, or shock kidney, occurs due to hypoperfusion of the kidneys resulting in focal damage to the tubules.

Etiopathogenesis. Ischaemic ATN is more common than toxic ATN and accounts for more than 80% cases of tubular injury. Ischaemia may result from a variety of causes such as:

1. Shock (post-traumatic, surgical, burns, dehydration, obstetrical and septic type).

2. Crush injuries.

3. Non-traumatic rhabdomyolysis induced by alcohol, coma, muscle disease or extreme muscular exertion (myoglobinuric nephrosis).

4. Mismatched blood transfusions, black-water fever (haemoglobinuric nephrosis).

The *pathogenetic mechanism* of ischaemic ATN resulting in ARF is explained on the basis of the following 4 factors, which may be operating singly or in combination:

- Arteriolar vasoconstriction induced by reninangiotensin system.
- Tubular obstruction by casts in the lumina or by interstitial oedema.
- Back-leak of tubular fluid into the interstitium.
- Abnormal glomerular permeability.

Pathologic changes. *Grossly,* the kidneys are enlarged and swollen. On cut section, the cortex is often widened and pale, while medulla is dark. *Histologically,* predominant changes are seen in the tubules, while glomeruli are normal. Interstitium shows oedema and mild chronic inflammatory cell infiltrate. Tubular changes are as follows:

1. Dilatation of the proximal and distal convoluted tubules.
2. Focal tubular necrosis at different points along the nephron.
3. Flattened epithelium lining the tubules suggesting epithelial regeneration.
4. Eosinophilic hyaline casts or pigmented haemoglobin and myoglobin casts in the tubular lumina.
5. Disruption of tubular basement membrane adjacent to the cast (tubulorrhexis).

Prognosis of ischaemic ATN depends upon the underlying etiology. In general, cases that follow severe trauma, surgical procedures, extensive burns and sepsis have much worse outlook than the others.

TOXIC ATN

Toxic or nephrotoxic ATN occurs as a result of direct damage to tubular cells by ingestion, injection or inhalation of a number of toxic agents.

Etiopathogenesis. The toxic agents causing toxic ATN are:

1. General poisons such as mercuric chloride, carbon tetrachloride, ethylene glycol, mushrooms and insecticides.
2. Heavy metals (mercury, lead, arsenic, phosphorus and gold).
3. Drugs such as sulfonamides, certain antibiotics (gentamycin, cephalosporin), anaesthetic agents (methoxyflurane, halothane), barbiturates, salicylates.
4. Radiographic contrast material.

The *pathogenetic mechanism* producing ARF in toxic ATN is in principle similar to that for ischaemic ATN and involves interplay of four factors:

arteriolar vasoconstriction, tubular obstruction, back-leak of tubular fluid and abnormal glomerular permeability.

Pathologic changes. Poisoning with mercuric chloride provides the best example that produces widespread and readily discernible tubular necrosis *(acute mercury nephropathy).*

Grossly, the kidneys are enlarged and swollen. On cut section, the cortex is pale and swollen, while the medulla is slightly darker than normal. *Histologically,* the appearance varies according to the cause of toxic ATN but, in general, involves the segment of tubule diffusely (unlike ischaemic ATN where the involvement of nephron is focal). In mercuric chloride poisoning, the features are as follows:

1. Epithelial cells of mainly proximal convoluted tubules are necrotic and desquamated into the tubular lumina.
2. The desquamated cells may undergo dystrophic calcification.
3. Tubular basement membrane is generally intact.
4. The regenerating epithelium, which is flat and thin with few mitoses, may be seen lining the tubular basement membrane.

Prognosis of toxic ATN is good if there is no serious damage to other organs such as heart and liver.

TUBULOINTERSTITIAL DISEASE

The term tubulointerstitial nephritis is used for inflammatory process that predominantly involves the renal interstitial tissue and is usually accompanied by some degree of tubular damage. A number of primary glomerular, tubular, vascular and obstructive diseases are secondarily associated with interstitial reaction. However, the term *interstitial nephritis* is reserved for those cases where there is no primary involvement of glomeruli, tubules or blood vessels. The older nomenclature, interstitial nephritis, is currently used syronymously with *tubulointerstitial nephritis or tubulr interstitial nephropathy.*

ACUTE PYELONEPHRITIS

Acute pyelonephritis is an acute suppurativg inflammation of the kidney caused by pyogenic bacteria.

Etiopathogenesis. Most cases of acute pyelonephritis follow infection of the lower urinary tract. The most common pathogenic organism in urinary tract infection (UTI) is *Escherichia coli* (in 90% of cases), followed in decreasing frequency, by *Enterobacter, Klebsiella, Pseudomonas* and *Proteus.* The bacteria gain entry into the urinary tract, and thence into the kidney by one of the two routes: ascending infection and haematogenous infection:

1. *Ascending infection.* This is the most common route of infection. The common pathogenic organisms are inhabitants of the colon and may

cause faecal contamination of the urethral orifice, especially in females in reproductive age group. This has been variously attributed to shorter urethra in females liable to faecal contamination, hormonal influences facilitating bacterial adherence to the mucosa, absence of prostatic secretions which have antibacterial properties, and urethral trauma during sexual intercourse. The last named produces what is appropriately labelled as *'honeymoon pyelitis'*. Ascending infection may occur in a normal individual but the susceptibility is increased in patients with diabetes mellitus, pregnancy, urinary tract obstruction or instrumentation. Bacteria multiply in the urinary bladder and produce asymptomatic bacteriuria found in many of these cases. After having caused urethritis and cystitis, the bacteria in a small proportion of cases ascend further up into the ureters against the flow of urine, extend into the renal pelvis and then the renal cortex. The role of vesico-ureteral reflux is primarily of importance in the pathogenesis of chronic pyelonephritis but not in acute pyelonephritis.

2. *Haematogenous infection.* Less often, acute pyelonephritis may result from blood-borne spread of infection. This occurs more often in patients with obstructive lesions in the urinary tract, and in debilitated or immunosuppressed patients.

Pathologic changes. *Grossly,* well-developed cases of acute pyelonephritis show enlarged and swollen kidney mat bulges on section. The cut surface shows small, yellow-white abscesses with a haemorrhagic rim. These abscesses may be several millimetres across and are situated mainly in the cortex.

Microscopically, acute pyelonephritis is characterised by extensive acute inflammation involving the interstitium and causing destruction of the tubules. Generally, the glomeruli and renal blood vessels show considerable resistance to infection and are spared. The acute inflammation may be in the form of large number of neutrophils in the interstitial tissue and bursting into tubules, or may form focal neutrophilic abscesses in the renal parenchyma.

Complications. Complications of acute pyelonephritis are encountered more often in patients with diabetes mellitus or with urinary tract obstruction. There are 3 important complications of acute pyelonephritis. These are as under:

1. Papillary necrosis. Papillary necrosis or necrotising papillitis develops more commonly in analgesic abuse nephropathy and in sickle cell disease but may occur as a complication of acute pyelonephritis as well. It may affect one or both kidneys.

Grossly, the necrotic papillae are yellow to grey-white, sharply-defined areas with congested border and resemble infarction. The pelvis may be dilated. *Microscopically,* necrotic tissue is separated from the viable tissue by a dense zone of polymorphs. The necrotic area shows characteristic coagulative necrosis as seen in renal infarcts.

2. Pyonephrosis. Rarely, the abscesses in the kidney in acute pyelonephritis are extensive, particularly in cases with obstruction. This results in inability of the abscesses to drain and this transforms the kidney into a multilocular sac filled with pus called as pyonephrosis or renal carbuncle.

3. Perinephric abscess. The abscesses in the kidney may extend through the capsule of the kidney into the perinephric tissue and form perinephric abscess.

CHRONIC PYELONEPHRITIS

Chronic pyelonephritis is a chronic tubulointerstitial disease resulting from repeated attacks of inflammation and scarring.

Etiopathogenesis. Depending upon the etiology and pathogenesis, two types of chronic pyelonephritis are described—reflux nephropathy and obstructive pyelonephritis.

1. *Reflux nephropathy.* Reflux of urine from the bladder into one or both the ureters during micturition is the major cause of chronic pyelonephritis. *Vesicoureteric reflux* is particularly common in children, especially in girls, due to congenital absence or shortening of the intravesical portion of the ureter so that ureter is not compressed during the act of micturition. Reflux results in increase in pressure in the renal pelvis so that the urine is forced into renal tubules which is eventually followed by damage to the kidney and scar formation. Vesicoureteric reflux is more common in patients with urinary tract infection, whether symptomatic or asymptomatic, but reflux of sterile urine can also cause renal damage.

2. *Obstructive pyelonephritis.* Obstruction to the outflow of urine at different levels predisposes the kidney to infection. Recurrent episodes of such obstruction and infection result in renal damage and scarring. Rarely, recurrent attacks of acute pyelonephritis may cause renal damage and scarring.

Pathologic changes. *Grossly,* the kidneys show rather characteristic appearance. The kidneys are usually small and contracted (weighing less than 100 gm) showing unequal reduction so as to distinguish it from other forms of contracted kidney. The surface of the kidney is irregularly scarred; the capsule can be stripped off with difficulty due to adherence to scars. These scars are of variable size and show characteristic U-shaped depressions on the cortical surface. There is generally dilatation of pelvis and blunted calyces.

Microscopically, predominant changes are seen in interstitium and tubules:

i) *Interstitium.* There is chronic interstitial inflammatory reaction, chiefly composed of lymphocytes, plasma cells and macrophages with pronounced interstitial fibrosis. *Xanthogranulomatous pyelonephritis* is an uncommon variant characterised by collection of foamy macrophages admixed with other inflammatory cells and giant cells.

ii) *Tubules.* The tubules show varying degree of atrophy and dilatation. Dilated tubules may contain eosinophilic colloid casts producing thyroidisarion of tubules. A few tubules may contain neutrophils.

iii) *Pelvicalyceal system.* The renal pelvis and calyces are dilated. The walls of pelvis and calyces show marked chronic inflammation and fibrosis. Lymphoid follicles with germinal centres may be present in the pelvicalyceal walls.

iv) *Blood vessels.* Blood vessels entrapped in the scarred areas show obliterative endarteritis. There may be changes of hypertensive hyaline arteriolosclerosis.

v) *Glomeruli.* Though glomerular tuft in the scarred area is usually intact, there is often periglomerular fibrosis. In advanced cases, there may be hyalinisation of glomeruli.

TUBERCULOUS PYELONEPHRITIS

Tuberculosis of the kidney occurs due to haematogenous spread of infection from another site, most often from the lungs. Less commonly, it may result from ascending infection from tuberculosis of the genitourinary system such as from epididymis or Fallopian tubes. The renal lesions in tuberculosis may be in the form of tuberculous pyelonephritis or appear as multiple miliary tubercles.

Pathologic changes. *Grossly,* the lesions in tuberculous pyelonephritis are often bilateral, usually involving the medulla with replacement of the papillae by caseous tissue. Obstruction may result in tuberculous pyonephrosis in which thinned out renal parenchyma surrounds dilated pelvis and calyces filled with caseous material. *Histologically,* typical granulomatous reaction is seen. Acid-fast bacilli can often be demonstrated in the lesions.

MYELOMA NEPHROPATHY

Renal involvement in multiple myeloma is referred to as myeloma nephropathy or myeloma kidney. Functional renal impairment in multiple myeloma is a common manifestation, developing in about 50% of patients. The pathogenesis of myeloma kidney is related to excess filtration of Bence-Jones proteins through the glomerulus, usually *kappa (κ)* light chains. These light chain proteins are precipitated in the distal convoluted tubules in combination with Tamm-Horsfall proteins, the urinary glycoproteins. The precipitates form tubular casts which are eosinophilic and often laminated. These casts may induce peritubular interstitial inflammatory reaction. Not all light chains are nephrotoxic and their toxicity occurs under acidic pH of the tubular fluid.

Pathologic changes. *Grossly,* the kidneys may be normal or small and shrunken. *Histologically*, there are some areas of tubular atrophy while many other tubular lumina are dilated and contain characteristic bright pink laminated casts. These casts are surrounded by peritubular interstitial inflammatory reaction including the presence of nonspecific inflammatory cells and some multinucleate giant cells induced by tubular casts.

NEPHROCALCINOSIS

Nephrocalcinosis is a diffuse deposition of calcium salts in renal tissue in a number of renal diseases, in hypercalcaemia, hyperphosphataemia and renal tubular acidosis. Most commonly, it develops as a complication of severe hypercalcaemia such as due to hyperparathyroidism, hypervitaminosis D, excessive bone destruction in metastatic malignancy, hyperthyroidism, excessive calcium intake such as in milk-alkali syndrome and sarcoidosis. Clinically, patients of hypercalcaemia and nephrocalcinosis may have renal colic, band keratopathy due to calcium deposits in the cornea, visceral metastatic calcification, polyuria and renal failure.

Pathologically, nephrocalcinosis due to hypercalcaemia characteristically shows deposition of calcium in the tubular epithelial cells in the basement membrane, within the mitochondria and the cytoplasm. These concretions may produce secondary tubular atrophy, interstitial fibrosis and nonspecific chronic inflammation in the interstitium. As the calcification occurs intracellularly, radiological evidence is usually not present until fairly late in the disease. The calcium deposits are first visible as small opacities in the renal papillae.

RENAL VASCULAR DISEASES

Renal blood vessels which enormously perfuse the kidney are affected secondarily in majority of renal diseases. Renal blood flow is controlled by systemic and local haemodynamic, hormonal and intrinsic intra-renal mechanisms. Diseases which disturb these controlling mechanisms give rise to primary renal vascular lesions. These diseases are as under:

I. Most importantly, *hypertensive vascular disease* and its consequent renal manifestations in the form of benign and malignant nephrosclerosis.

II. *Thrombotic microangiopathy.*

III. *Renal cortical necrosis.*

IV. *Renal infarcts.*

I. Hypertensive vascular disease (see above)

II. Thrombotic microangiopathy

Thrombotic renal disease encompasses a group of diseases having in common the formation of thrombi composed by platelets and fibrin in arterioles and glomeruli of the kidney and culminating clinically in acute renal failure.

The common clinical manifestations include micro-angiopathic haemolytic anaemia, thrombocytopenia, DIC, and eventually renal failure.

Pathogenesis. In all such cases, endothelial injury appears to be the trigger for vascular changes. The injured endothelial surface causes the following effects:

• Passage of plasma constituents to the subendothelial zone of microvasculature.

• Promotes thrombosis.

Morphologically, the lesions closely resemble those of malignant nephrosclerosis. The features include:

• Fibrinoid necrosis of arterioles.

• Thrombi in renal microvasculature.

• Oedema of intima of arterioles.

• Consolidation, necrosis and congestion of glomeruli.

If the renal lesions are massive, the prognosis is generally lethal.

III. Renal cortical necrosis

Renal cortical necrosis is infarction of renal cortex varying from microscopic foci to a situation where most of the renal cortex is destroyed. The medulla, the juxtamedullary cortex and a rim of cortex under the capsule are usually spared. The condition develops most commonly as an obstetrical emergency (e.g. in eclampsia, preeclampsia, premature separation of the placenta). Other causes include septic shock, poisoning, severe trauma etc.

The lesions may be present focally, patchily or diffusely. The gross and microscopic characteristics of infarcts of cortex are present. Patients present with sudden oliguria or anuria and haematuria. If the process has involved renal cortex extensively, acute renal failure and uraemia develop and prognosis is grave.

OBSTRUCTIVE UROPATHY

Obstruction in the urinary tract is common and important because it increases the susceptibility to infection and stone formation. Obstruction can occur at any age and in either sex. The cause of obstruction may lie at any level of the urinary tract – renal pelvis, ureters, urinary bladder and urethra.

The obstruction may be unilateral or bilateral, partial or complete, sudden or insidious. Complete bilateral obstruction may result in irreversible renal failure, whereas long-standing chronic partial obstruction may cause various functional abnormalities and anatomic changes. There are three important anatomic sequelae of obstruction, namely: *hydronephrosis, hydroureter and hypertrophy of the bladder.* But before describing these conditions, an account of the most common and important cause of obstructive uropathy, *urolithiasis,* is given below.

UROLITHIASIS

Urolithiasis or formation of urinary calculi at any level of the urinary tract is a common condition. Urinary calculi are worldwide in distribution but are particularly common in some geographic locales such as in parts of the United States, South Africa, India and South-East Asia. It is estimated that approximately 2% of the population experiences renal stone disease at some-time in their life with male-female ratio of 2:1. The peak incidence is observed in 2nd to 3rd decades of life. Renal calculi are characterised clinically by colicky pain *(renal colic)* as they pass down along the ureter and manifest by haematuria.

Types of Urinary Calculi

There are 4 main types of urinary calculi – calcium containing, mixed (struvite), uric acid and cystine stones, and a small number of rare types.

1. CALCIUM STONES. Calcium stones are the most common comprising about *75%* of all urinary calculi. They may be pure stones of calcium oxalate (50%) or calcium phosphate (5%), or mixture of calcium oxalate and calcium phosphate (45%).

Etiology of calcium stones is variable.

i) About 50% of patients with calcium stones have *idiopathic hypercalciuria without hypercalcaemia.*

ii) Approximately 10% cases are associated with *hypercalcaemia* and *hypercalciuria*, most commonly due to hyperparathyroidism or a defect in the bowel (i.e. absorptive hypercalciuria) or in the kidney (i.e. renal hypercalciuria).

iii) About 15% of patients with calcium stones have *hyperuricosuria with a normal blood uric acid level* and without any abnormality of calcium metabolism.

iv) In about 25% of patients with calcium stones, the cause is unknown as there is no abnormality in urinary excretion of calcium, uric acid or oxalate and is referred to as *'idiopathic calcium stone disease'.*

Pathogenesis. The mechanism of calcium stone formation is explained on the basis of imbalance between the degree of super saturation of the ions forming the stone and the concentration of inhibitors in the urine. Most likely site where the crystals of calcium oxalate and/or calcium phosphate are precipitated is the tubular lining or around some fragment of debris in the tubule acting as nidus of the stone. The stone grows, as more and more crystals are deposited around the nidus. A number of other predisposing factors contributing to formation of calcium stones are alkaline urinary pH, decreased urinary volume and increased excretion of oxalate and uric acid.

Morphology. Calcium stones are usually small (less than a centimeter), ovoid, hard, with granular rough surface. They are dark brown due to old

blood pigment deposited in them as a result of repeated trauma caused to the urinary tract by these sharp-edged stones.

2. MIXED (STRUVITE) STONES. About 15% of urinary calculi are made of magnesium-ammonium-calcium phosphate, often called *struvite.* That is why mixed stones are also called as *'struvite stones'* or 'triple phosphate stones'.

Struvite stones are formed as a result of infection of the urinary tract with urea-splitting organisms that produce urease such as by species of *Proteus,* and occasionally *Klebsiella, Pseudomonas* and *Enterobacter.* These are, therefore, also known as infection-induced stones. However, *E. coli* does not form urease.

Morphology. Struvite stones are yellow-white or grey. They tend to be soft and friable and irregular in shape. 'Staghorn stone' which is a large, solitary stone that takes the shape of the renal pelvis where it is often formed is an example of struvite stone.

3. URIC ACID STONES. Approximately 6% of urinary calculi are made of uric acid. Uric acid calculi are radiolucent unlike radio-opaque calcium stones.

Uric acid stones are frequently formed in cases with hyperuricaemia and hyperuricosuria such as due to primary gout or secondary gout due to myeloproliferative disorders (e.g. in leukaemias), especially those on chemotherapy, and administration of uricosuric drugs (e.g. salicylates, probenacid).

Pathogenesis. The solubility of uric acid at pH of *7* is 200 mg/dl while at pH of 5 is 15 mg/dl. Thus, as the urine becomes more acidic, the solubility of uric acid in urine decreases and precipitation of uric acid crystals increases favouring the formation of uric acid stones. Hyper uricosuria is the most important factor in the production of uric acid stones, while hyper uricaemia is found in about half the cases.

Morphology. Uric acid stones are smooth, yellowish-brown, hard and often multiple. On cut section, they show laminated structure.

4. CYSTINE STONES. Cystine stones comprise less than 2% of urinary calculi.

Cystine stones are associated with cystinuria due to a genetically-determined defect in the transport of cystine and other amino acids across the cell membrane of the renal tubules and the small intestinal mucosa.

Pathogenesis. The resultant excessive excretion of cystine which is least soluble of the naturally-occurring amino acids leads to formation of crystals and eventually cystine calculi.

Morphology. Cystine stones are small, rounded, smooth and often multiple. They are yellowish and waxy.

5. OTHER CALCULI. Less than 2% of urinary calculi consist of other rare types such as due to inherited abnormality of xanthine metabolism resulting in xanthinuria and consequently xanthine stones.

HYDRONEPHROSIS

Hydronephrosis is the term used for dilatation of renal pelvis and calyces due to partial or intermittent obstruction to the outflow of urine. Hydronephrosis develops if one or both the pelviureteric sphincters are incompetent, as otherwise there will be dilatation and hypertrophy of the urinary bladder but no hydronephrosis. Hydroureter nearly always accompanies hydronephrosis. Hydronephrosis may be *unilateral or bilateral.*

Unilateral Hydronephrosis

This occurs due to some form of ureteral obstruction at the level of pelviureteric junction (PUJ). The causes are:

1. Intraluminal e.g. a calculus in the ureter or renal pelvis.

2. Intramural e.g. congenital PUJ obstruction, atresia of ureter, inflammatory stricture, trauma, neoplasm of ureter or bladder.

3. Extramural e.g. obstruction of upper part of ureter by inferior renal artery or vein, pressure on ureter from outside such as carcinoma cervix, prostate, rectum, colon or caecum and retroperitoneal fibrosis.

Bilateral Hydronephrosis

This is generally the result of some form of urethral obstruction but can occur from the various causes listed above if the lesions involve both sides. The causes are:

1. Congenital e.g. atresia of the urethral meatus, congenital posterior urethral valve.

2. Acquired e.g. bladder tumour involving both ureteric orifices, prostatic enlargement, prostatic carcinoma and prostatitis, bladder neck stenosis, inflammatory or traumatic urethral stricture and phimosis.

Pathologic changes. The pathologic changes vary depending upon whether the obstruction is sudden and complete, or incomplete and intermittent. The latter situation is more common.

*Grossly***,** the kidneys may have moderate to marked enlargement. Initially, there is *extrarenal hydronephrosis* characterised by dilatation of renal pelvis medially in the form of a sac. As the obstruction persists, there is progressive dilatation of pelvis and calyces and pressure atrophy of renal parenchyma. Eventually, the dilated pelvi-calyceal system extends deep into the renal cortex so that a thin rim of renal cortex is stretched over the dilated calcyes and the external surface assumes lobulated appearance. This advanced stage is called as *intmrenal hydronephrosis.* An important point of distinction

between the sectioned surface of advanced hydronephrosis and polycystic kidney disease is the direct continuity of dilated cystic spaces (i.e. dilated calcyes) with the renal pelvis in the former.

Microscopically, the wall of hydronephrotic sac is thickened due to fibrous scarring and chronic inflammatory cell infiltrate. There is progressive atrophy of tubules and glomeruli alongwith interstitial fibrosis. Stasis of urine in hydronephrosis causes infection *(pyelitis)* resulting in filling of the sac with pus, a condition called *pyonephrosis.*

TUMOURS OF KIDNEY

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

BENIGN TUMOURS

Benign renal tumours are usually small and are often an incidental finding at autopsy or nephrectomy.

CORTICAL ADENOMA

Cortical tubular adenomas are more common than other benign renal neoplasms. They are frequently multiple and associated with chronic pyelonephritis or benign nephrosclerosis.

Grossly, these tumours may form tiny nodules up to 3 cm in diameter. They are encapsulated and white or yellow.

Microscopically, they are composed of tubular cords or papillary structures projecting into cystic space. The cells of the adenoma are usually uniform, cuboidal with no atypicality or mitosis. However, size of the tumour rather than histologic criteria is considered more significant parameter to predict the behaviour of the tumour — those larger than 3 cm in diameter are potentially malignant and metastasising.

ONCOCYTOMA

Oncocytoma is a benign epithelial tumour arising from collecting ducts.

Grossly, The tumour is encapsulated and has variable size. Cut section is homogeneous and has characteristic mahogany-brown or tan colour.

Microscopically, the tumour cells are plump with abundant, finely granular, acidophilic cytoplasm and round nuclei. Electron microscopy demonstrates numerous mitochondria in the cytoplasm.

OTHER BENIGN TUMOURS

• **Angiomyolipoma** is a hamartoma of the kidney that contains differentiated tissue element derived from blood vessels, smooth muscle and fat.

• **Mesoblastic nephroma** is a congenital benign tumour.

Grossly, the tumour resembles a uterine leiomyoma in having whorled appearance.

Microscopically, it shows cellular growth of spindle cells derived from secondary mesenchyme.

• **Multicystic nephroma** is another uncommon tumour of early infancy.

Grossly, it is a solitary, unilateral well demarcated tumour of varying size. Cut surface shows characteristic multilocular appearance.

Microscopically, the cysts are lined by tubular epithelium while the stroma between the cysts contains mesenchymal tissue with some immature blastemal or abortive tubules. Some authors consider this entity as fully-differentiated variant of Wilms' tumour. However, clinically multicystic nephroma is always benign compared to Wilms' tumour.

• **Medullary interstitial cell tumour** is a tiny nodule in the medulla composed of fibroblast-like cells in hyalinised stroma. These tumours used to be called *renal fibromas* but electron microscopy has revealed that the tumour cells are not fibrocytes but are medullary interstitial cells.

• **Juxtaglomerular tumour or reninoma** is a rare rumour of renal cortex consisting of sheets of epithelioid cells with many small blood vessels. The tumour secretes excessive quantities of renin and, thus, the patients are likely to have hypertension.

MALIGNANT TUMOURS

The two most common primary malignant tumours of the kidney are *adenocarcinoma* and *Wilms' tumour. A* third less common tumour is *urothelial carcinoma* of renal pelvis which is described in the next section alongwith similar tumours of the lower urinary tract.

ADENOCARCINOMA OF KIDNEY *(Synonyms: Renal cell carcinoma, Hypernephroma, Grawitz tumour)*

Hypernephroma is an old misnomer under the mistaken belief that the tumour arises from adrenal rests because of the resemblance of the tumour cells with clear cells of the adrenal cortex. It is now known that the renal cell carcinoma (RCC) is an adenocarcinoma arising from tubular epithelium. This cancer comprises 70 to 80% of all renal cancers and occurs most commonly in 50 to 70 years of age with male preponderance (2:1).

Etiology and pathogenesis. Various etiologic factors implicated in the etiology of RCC are as follows:

1. Tobacco. Tobacco is the major risk factor for RCC, whether chewed or smoked. Cigarette smokers have 2-times higher risk of developing RCC.

2. Additional risk factors. These include:

i) Exposure to asbestos, heavy metals and petrochemical products.

ii) In women, obesity and oestrogen therapy.

iii) Hereditary and acquired cystic diseases of the kidney.

iv) Analgesic nephropathy.

v) Hereditary and family history are associated with 4-5 times higher risk.

vi) Hypertension.

Majority of cases of RCC are sporadic but about 5% cases are inherited in which carcinogenesis has been studied in detail. Carcinongenesis in hereditary RCC is explained on the basis of 3 distinct syndromes:

1. V*on Hippel-Lindau (VHL) disease:* It is an autosomal dominant cancer syndrome that includes: haemangioblastoma of the cerebellum, retinal angiomas, multiple RCC (clear cell type) and pheochromocytoma and cysts in different organs.

2. *Hereditary clear cell RCC:* These are cases of RCC of clear cell type confined to the kidney without other manifestations of VHL but having autosomal dominant inheritance.

3. *Hereditary papillary RCC:* This form of RCC is characterised by bilateral and multifocal cancer with papillary growth pattern.

Classification. Based on cytogenetics of sporadic and familial rumours, RCC has been reclassified recently into clear cell, papillary, granular cell, chromophobe, sarcoma toid and collecting duct type.

Pathologic changes. *Grossly,* the RCC commonly arises from the poles of the kidney as a solitary and unilateral tumour, more often in the upper pole. The tumour is generally large, golden yellow and circumscribed. Papillary tumours may be multifocal and bilateral, besides grossly visible papillae. Cut section of the tumour commonly shows large areas of ischaemic necrosis, cystic change and foci of haemorrhages. Another significant characteristic is the frequent presence of tumour thrombus in the renal vein which may extend into the vena cava.

Histologically, the features of various types of RCC are as under:

1. *Clear cell type RCC (70%):* This is the most common pattern. The clear cytoplasm of tumour cells is due to removal of glycogen and lipid from the cytoplasm during processing of tissues. The tumour cells have a variety of patterns: solid, trabecular and tubular, separated by delicate vasculature. Majority of clear cell rumours are well differentiated.

2. *Papillary type RCC (15%):* The tumour cells are arranged in papillary pattern over the fibrovascular stalks. The tumour cells are cuboidal with small round nuclei. Psammoma bodies may be seen.

3. *Granular cell type RCC (8%):* The tumour cells have abundant acidophilic cystoplasm. These tumours have more marked nuclear pleomorphism, hyperchromatism and cellular atypia.

4. *Chromophobe type RCC (5%):* This type shows admixture of pale clear cells with perinuclear halo and acidophilic granular cells. The cytoplasm of these tumour cells contains many vesicles.

5. *Sarcomatoid type RCC (1.5%):* This is the most anaplastic and poorly differentiated form. The tumour is characterised by whorls of atypical spindle tumour cells.

6. Collecting duct type RCC (0.5%): This is a rare type that occurs in the medulla. It is composed of a single layer of cuboidal tumour cells arranged in tubular and papillary pattern.

The prognosis in renal cell carcinoma depends upon the extent of tumour involvement at the time of diagnosis. The overall 5-year survival rate is about 45%. Presence of metastases lowers the survival rate.

WILMS' TUMOUR (SYNONYM: NEPHROBLASTOMA)

Nephroblastoma, or Wilms' tumour is an embryonic tumour derived from primitive renal epithelial and mesenchymal components. It is the most common abdominal malignant tumour of young children, seen most commonly between 1 to 6 years of age with equal sex incidence.

Pathologic changes. *Grossly*, the tumour is usually quite large, spheroidal, replacing most of the kidney. It is generally solitary and unilateral but 5-10% cases may have bilateral rumour. On cut section, the tumour shows characteristic variegated appearance – soft, fishflesh-like grey-white to cream-yellow tumour with foci of necrosis and haemorrhages and grossly identifiable myxomatous or cartilaginous elements. Invasion into renal vein is grossly evident in half the cases.

Microscopically, nephroblastoma shows mixture of primitive epithelial and mesenchymal elements. Most of the tumour consists of small, round to spindled, anaplastic, sarcomatoid tumour cells. In these areas are present abortive tubules and poorly-formed glomerular structures. Sometimes, mesenchymal elements such as smooth and skeletal muscle, cartilage and bone, fat cells and fibrous tissue, may be seen.

SECONDARY TUMOURS

Leukaemic infiltration of the kidneys is a common finding, particularly in chronic myeloid leukaemia. Kidney is a common site for blood-borne metastases from different primary sites, chiefly from cancers of lungs, breast and stomach.

LOWER URINARY TRACT

The lower urinary tract consists of *ureters, urinary bladder* and *urethra.*

Ureters are tubular structures, 30 cm in length and half a centimeter in diameter, and extend from the renal pelvis (pelvi-ureteric junction) to the urinary bladder (vesico-ureteric junction). Normally they enter obliquely into the bladder, so that ureter is compressed during micturition, thus preventing vesico-ureteric reflux. Ureters lie retroperitoneally throughout their course.

Histologically, ureter has an outer fibrous investing layer which overlies a thick muscular layer and is lined internally by transitional epithelium or urothelium similar to the lining of the renal pelvis above and bladder below.

Urinary bladder lies extraperitoneally and the peritoneum is reflected on its superior surface. Normally, the capacity of bladder is about 400 to 500 ml without overdistension. Micturition is partly a reflex and partly a voluntary act under the control of sympathetic and parasympathetic innervation.

Histologically, the greater part of the bladder wall is made up of muscular layer (detrusor muscle) having 3 coats – internal, middle and external. The *trigone* muscle is derived from the prolongation of the longitudinal muscle layer of each ureter. The inner layer of bladder consists of urothelium up to 6 layers in thickness.

Urethra runs from the bladder up to the external meatus. The *male urethra* consists of 3 parts – prostatic, membranous and penile. It is lined in the prostatic part by urothelium but elsewhere by stratified columnar epithelium except near its orifice where the epithelium is stratified squamous. The urethral mucosa rests on$_t$ highly vascular submucosa and outer layer of striated muscle. There are numerous small mucous glands in the urethral mucosa. *The female urethra* is shorter and runs from the bladder parallel with the anterior wall of the vagina. The mucous membrane in female urethra is lined throughout by columnar epithelium except near the bladder where the epithelium is transitional. The other layers and mucous glands are similar to those in male urethra.

CONGENITAL ANOMALIES

Double Ureter. This is a condition in which the entire ureter or only the upper part is duplicated. Double ureter is invariably associated with a double renal pelvis, *one* in the upper part and the *other* in the lower part of the kidney. If double ureter affects the entire length, then there are two separate openings into the bladder on one side but more commonly they are joined in the intravesical portion and open by a single ureteric orifice.

Ureterocele. Ureterocele is cystic dilatation of the terminal part of the ureter which lies within the bladder wall. The cystic dilatation lies beneath the bladder mucosa and can be visualised by cystoscopy.

Ectopia vesicae (exstrophy). This is a rare condition owing to congenital developmental deficiency of anterior wall of the bladder and is associated with splitting of the overlying anterior abdominal wall. This results in exposed interior of the bladder. There may be prolapse of the posterior wall of the bladder through the defect in the anterior bladder and abdominal wall. The condition in males is often associated with *epispadias* in which the ure-

thra opens on the dorsal aspect of penis. If the defect is not properly repaired, the exposed bladder mucosa gets infected repeatedly and may undergo squamous metaplasia with increasing tendency to develop carcinoma of the bladder.

Urachal abnormalities. Rarely, there may be persistence of urachus in which urine passes from the bladder to the umbilicus. More often, part of urachus remains patent which may be the umbilical end, bladder end, or central portion. Persistence of central portion gives rise to *urachal cyst* lined by transitional or squamous epithelium. Adenocarcinoma may develop in urachal cyst.

INFLAMMATIONS

Urinary tract infection (UTI) is common, especially in females and has been described already alongwith its morphologic consequences. Inflammation of the tissues of urinary tract (ureteritis, cystitis and urethritis) are considered here.

URETERITIS

Infection of the ureter is almost always secondary to pyelitis above, or cystitis below. Ureteritis is usually mild but repeated and longstanding infection may give rise to chronic ureteritis.

CYSTITIS

Inflammation of the urinary bladder is called cystitis. Primary cystitis is rare since the normal bladder epithelium is quite resistant to infection. Cystitis may occur by spread of infection from upper urinary tract as seen following renal tuberculosis, or may spread from the urethra such as in instrumentation. Cystitis is caused by a variety of bacterial and fungal infections as discussed in the etiology of pyelonephritis. The most common pathogenic organism in urinary tract infection is E. *coli,* followed in decreasing frequency by *Enterobacter, Klebsiella, Pseudomonas* and *Proteus.* Infection with *Candida albicans* may occur in the bladder in immunosuppressed patients. Besides bacterial and fungal organisms, parasitic infestations such as with *Schistosoma haematobium* is common in the Middle-East countries, particularly in Egypt. *Chlamydia* and *Mycoplasma* may occasionally cause cystitis. In addition, radiation, direct exposure to chemical irritant, foreign bodies and local trauma may all initiate cystitis.

Cystitis, like UTI, is more common in females than in males because of the shortness of urethra which is liable to faecal contamination and due to mechanical trauma during sexual intercourse. In males, prostatie obstruction is a frequent cause of cystitis. All forms of cystitis are clinically characterised by a *triad* of symptoms – *frequency* (repeated urination), *dysuria* (painful or

burning micturition) and *low abdominal pain.* There may, however, be systemic manifestations of bacteraemia such as fever, chills and malaise.

Pathologic changes. Cystitis may be acute or chronic.

Acute cystitis. *Grossly,* the bladder mucosa is red, swollen and haemorrhagic. There may be suppurative exudate or ulcers on the bladder mucosa. *Microscopically,* this form of cystitis is characterised by intense neutrophilic exudate admixed with lymphocytes and macrophages. There is oedema and congestion of mucosa.

Chronic cystitis. Repeated attacks of acute cystitis lead to chronic cystitis. *Grossly,* the mucosal epithelium is thickened, red and granular with formation of polypoid masses. Long-standing cases result in thickened bladder wall and shrunken cavity.

Microscopically, there is patchy ulceration of the mucosa with formation of granulation tissue in the regions of polypoid masses. Submucosa and muscular coat show fibrosis and infiltration by chronic inflammatory cells. A form of chronic cystitis characterised by formation of lymphoid follicles in the bladder mucosa is termed *cystitis follicularis.*

A few other special forms of cystitis having distinct clinical and morphological appearance are described below.

Interstitial cystitis (Runner's ulcer). This variant of cystitis occurs in middle-aged women. The patients get repeated attacks of severe and excruciating pain on distension of the bladder, frequency of micturition and great decrease in bladder capacity. Cystoscopy often reveals a localised ulcer. The *etiology* of the condition is unknown but it is thought to be neurogenic in origin.

Microscopically, the submucosa and muscle coat show increased fibrosis and chronic inflammatory infiltrate, chiefly lymphocytes, plasma cells and eosinophils.

Cystitis cystica. As a result of long-standing chronic inflammation, there occurs a downward projection of epithelial nests known as *Brunn's nests* from the deeper layer of bladder mucosa. These epithelial cells may appear as small cystic inclusions in the bladder wall, or may actually develop columnar metaplasia with secretions in the lumen of cysts.

Malakoplakia. This is a rare condition most frequently found in the urinary bladder but can occur in the ureters, kidney, testis and prostate, and occasionally in the gut. The *etiology* of the condition is unknown but probably results from persistence of chronic inflammation with defective phagocytic process by the macrophages. Malakoplakia occurs more frequently in immunosuppressed patients and recipients of transplants.

Grossly, the lesions appear as soft, flat, yellowish, slightly raised plaques on the bladder mucosa. They may vary from 0.5 to 5 cm in diameter.

Microscopically, the plaques are composed of massive accumulation of foamy macrophages with occasional multinucleate giant cells and some lymphocytes. These macrophages have granular PAS-positive cytoplasm and some of them contain cytoplasmic laminated concretions of calcium phosphate called *Michaelis-Gutmann bodies.* These bodies ultrastructurally represent lysosomes filled with partly digested debris of bacteria phagocytosed by macrophages which have not been digested fully by them due to defective phagocytosis.

Polypoid cystitis. Polypoid cystitis is characterised by papillary projections on the bladder mucosa due to submucosal oedema and can be confused with transitional cell carcinoma. The condition occurs due to indwelling catheters and infection.

URETHRITIS

Urethritis may be *gonococcal* or *non-gonococcal.*

• Gonococcal (gonorrhoeal) urethritis is an acute suppurative condition caused by gonococci *(Neisseria gonorrhoeae).* The mucosa and submucosa are eventually converted into granulation tissue which becomes fibrosed and scarred resulting in urethral stricture.

• Non-gonococcal urethritis is more common and is most frequently caused by E. *coli.* The infection of urethra often accompanies cystitis in females and prostatitis in males. Urethritis is one of the components in the triad of Reiter's syndrome which comprises arthritis, conjunctivitis and urethritis. The pathologic changes are similar to inflammation of the lower urinary tract elsewhere but strictures are less common than following gonococcal infection of the urethra.

TUMOURS

The urinary bladder and renal pelvis are more common sites for urinary tract tumours than the ureters and urethra. Majority of urinary tract tumours are epithelial. Both benign and malignant tumours occur; the latter being more common.

EPITHELIAL (UROTHELIAL) BLADDER TUMOURS

More than 90% of bladder tumours arise from transitional epithelial (urothelium) lining of the bladder in continuity with the epithelial lining of the renal pelvis, ureters, and the major part of the urethra. Though many workers consider all transitional cell tumours as transitional cell carcinoma, others distinguish true transitional cell papilloma from grade I transitional cell carcinoma.

Bladder cancer comprises about 3% of all cancers. Most of the cases appear beyond 5th decade of life with preponderance in males.

Etiopathogenesis. Urothelial tumours in the urinary tract are typically multifocal and the pattern of disease becomes apparent over a period of years. A number of environmental and host factors are associated with increased risk of bladder cancer. These are as under:

1. Industrial occupations. Workers in industries that produce aniline dyes, rubber, plastic, textiles, and cable have high incidence of bladder cancer. Bladder cancer may occur in workers in these factories after a prolonged exposure of about 20 years. The carcinogenic substances responsible for bladder cancer in these cases are the metabolites of J3-naphthylamine and benzene.

2. Schistosomiasis. There is increased risk of bladder cancer, particularly squamous cell carcinoma, in patients having bilharzial infestation *(Schistosoma haematobium)* of the bladder. Schistosomiasis is common in Egypt and accounts for high incidence of bladder cancer in that country. It is thought to induce local irritant effect and initiate squamous metaplasia followed by squamous cell carcinoma.

3. Dietary factors. Certain carcinogenic metabolites of tryptophan are excreted in urine of patients with bladder cancer. These metabolites have been shown to induce bladder cancer in experimental animals. The role of artificial sweeteners like saccharin, coffee or caffeine and chronic alcoholism in the etiology of bladder cancer in man is controversial.

4. Local lesions. A number of local lesions in the bladder predispose to the development of bladder cancer. These include ectopia vesicae (extrophied bladder), vesical diverticulum, leukoplakia of the bladder mucosa and urinary diversion in defunctionalised bladder. All these conditions are associated with squamous metaplasia and high incidence of bladder cancer.

5. Smoking. Tobacco smoking is associated with 2 to3 fold increased risk of developing bladder cancer, probably due to increased urinary excretion of carcinogenic substances.

6. Drugs. Immunosuppressive therapy with cyclophosphamide and patients having analgesic-abuse (phenacetin) nephropathy have high risk of developing bladder cancer.

Pathologic changes. *Grossly,* urothelial tumours may be single or multiple. About 90% of the rumours are papillary (non-invasive or invasive), whereas the remaining 10% are flat indurated (non-invasive or invasive). The papillary tumours have free floating fern-like arrangement with a broad or narrow pedicle. The non-papillary tumours are bulkier with ulcerated surface. More common locations for either of the two types are the trigone, the region of ureteral orifices and on the lateral walls.

Histologically, urothelial tumours are of 3 cell types – transitional cell, squamous cell, and glandular.

A. Transitional Cell Tumours. Approximately 90% of all epithelial tumours of the bladder are transitional cell tumours. As stated before, transitional cell papilloma is distinguished by some workers from grade I transitional cell carcinoma (TCC), whereas others do not consider this as a distinct entity. Here, we follow the widely accepted classification of Mostofi (1960) adopted by the American Bladder Tumour Registry that divides TCC into 3 grades.

1. Transitional cell papilloma. Papillomas may occur singly or may be multiple. They are generally small, less than 2 cm in diameter, papillary with branching pattern. Each papilla is composed of fibrovascular stromal core covered by normal-looking transitional cells having normal number of layers (not more than six) in thickness. The individual cells resemble the normal transitional cells and do not vary in size and shape. Mitoses are absent and basal polarity is retained. It must be emphasised that the designation transitional cell papilloma is purely a histological diagnosis but does not imply an innocent biologic behaviour. In fact, it may recur and behave in a malignant manner.

2. Transitional cell carcinoma. This is the commonest cancer of the bladder and is divided into 3 grades depending upon 2 features: the *degree of anaplasia* and the *extent of invasion.*

• The *criteria for anaplasia* are: increased cellularity, nuclear crowding, deranged cellular polarity, failure of normal orientation from base to the surface, variation in cell and shape, variation in nuclear chromatin pattern, mitotic figures and giant cells.

• The *criteria for invasion* in papillary as well as non-papillary tumours are: penetration of the basement membrane of bladder mucosa.

Based on these salient features, the characteristics of three grades of transitional cell carcinoma are as under:

Grade I: The tumour cells are clearly transitional type but show increased number of layers of cells *(c.f.* transitional cell papilloma). The individual cells are generally regular but are slightly larger and show mild hyperchromatism.

Grade II: The tumour cells are still recognisable as of transitional cell origin and the number of layers of cells is increased. The individual tumour cells are less regular, larger in size, and show pronounced nuclear hyperchromatism, mitotic activity and loss of polarity. The tumour may or may not be invasive.

Grade III: This is the anaplastic or undifferentiated grade of the tumour which is always invasive extending into the bladder wall to variable depth depending upon the clinical stage (described later). The tumour cells are no longer recognisable as of transitional origin. The individual tumour

cells show pronounced features of anaplasia such as marked pleomorphism, hyperchromatism, total loss of polarity with loosened surface cells exfoliated in the bladder lumen.

There may be foci of squamous or glandular metaplasia in any grade of the tumour.

B. Carcinoma In Situ. Foci of epithelial hyperplasia, dysplasia and carcinoma in situ are seen in other parts of the bladder in non-invasive as well as in invasive carcinomas. Similar foci may be present in the ureters and renal pelvis. The malignant potential of epithelial hyperplasia and dysplasia is uncertain but carcinoma *in situ* is certainly precancerous and is currently included as grade 0 transitional cell carcinoma. Carcinoma *in situ* is characterised by highly anaplastic malignant cells confined to layers superficial to basement membrane of the bladder mucosa. These pathologic changes can be induced in experimental animals by chemical carcinogens. Therefore, it is reasonable to assume that these stages are precursors of invasive bladder cancer.

C. Squamous Cell Carcinoma. Squamous cell carcinoma comprises about 5% of the bladder carcinomas. Unlike transitional cell carcinomas which are mostly papillary and non-ulcerating, most squamous carcinomas of the bladder are sessile, nodular, infiltrating and ulcerating. Association of squamous carcinoma and schistosomiasis has already been highlighted. The carcinoma may be well-differentiated with keratin pearl formation, or may be anaplastic.

D. Adenocarcinoma. Adenocarcinoma of the bladder is rare. Adenocarcinoma has association with exostrophy of the bladder with glandular metaplasia, or may arise from urachal rests, periurethral and periprostatic glands, or from cystitis cystica. The tumour is characterised by glandular and tubular pattern with or without mucus production.

E. Mixed Carcinoma. About 50% of epithelial tumours of the bladder show mixed pattern, usually of transitional and squamous cell combination.

Staging of bladder cancer. The clinical behaviour and prognosis of bladder cancer can be assessed by the following simple staging system:

Stage O: Carcinoma confined to the mucosa.
Stage A: Carcinoma invades the lamina propria but not the muscularis.
Stage Bl: Carcinoma invades the superficial muscle layer.
Stage B2: Carcinoma invades the deep muscle layer.
Stage C: Carcinoma invades the perivesical tissues.
Stage Dl: Carcinoma shows regional metastases.
Stage D2: Carcinoma shows distant metastases.

NON-EPITHELIAL BLADDER TUMOURS

These may be benign or malignant.

Benign. The most common benign mesenchymal tumour of the bladder is leiomyoma. Other less common examples are neurofibroma, haemangioma and granular cell myoblastoma.

Malignant. Rhabdomyosarcoma is the most frequent malignant mesenchymal tumour. It exists in 2 forms:

Adult form occurring in adults over 40 years of age and resembles the rhabdomyosarcoma of skeletal muscle.

Childhood form occurring in infancy and childhood and appears as large polypoid, soft, fleshy, grapelike mass and is also called *sarcoma botryoides* or *embryonal rhabdomyosarcoma.* It is morphologically characterised by masses of embryonic mesenchyme consisting of masses of highly pleomorphic stellate cells in myxomatous background. Similar tumours occur in the female genital tract.

TUMOURS OF RENAL PELVIS AND URETERS

Almost all the tumours of the renal pelvis and ureters are of epithelial origin. They are of the same types as are seen in the urinary bladder. However, tumours in the ureters are quite rare.

TUMOURS OF URETHRA

Tumours of the urethra are rare except for the urethral caruncle which is a tumour-like lesion.

Urethral caruncle. Urethral caruncle is not uncommon. It is an inflammatory lesion present on external urethral meatus in elderly females.

Grossly, the caruncle appears as a solitary, 1 to 2 cm in diameter, pink or red mass, protruding from urethral meatus. It is quite friable and ulcerated.

Microscopically, the mass may be covered by squamous or transitional epithelium or there may be ulcerated surface. The underlying tissues show proliferating blood vessels, fibroblastic connective tissue and intense acute and chronic inflammatory infiltrate. Thus the histologic appearance closely resembles a *pyogenic granuloma.*

Urethral carcinoma. Carcinoma of the urethra is uncommon. In most cases it occurs in the distal urethra near the external meatus and thus is commonly squamous cell carcinoma. Less often, there may be transitional cell carcinoma or adenocarcinoma arising from periurethral glands.

ENDOCRINE PATHOLOGY

PATHOLOGY OF THE PITUITARY GLAND

Acromegaly, gigantism, Itsenko-Cushing disease, hypophyseal nanism, cerebro-hypophyseal cachexia, diabetes insipidus, tumors are the most frequent.

ACROMEGALY AND GIGANTISM usually develop in eosinophil-cell tumors, adenocarcinoma of pituitary anterior lobe. Excess of STH stimulates all mesenchymal derivatives (bones, cartilages, connective tissue). If the disease occurs at a young age, it is called gigantism; if at an older age, it is called acromegaly (the bones does not grow but ears, nose, lower jaw, feet and hands enlarge).

The other glands are also involved by the process (goiter, atrophy of insulin apparatus of pancreas, thymus and epiphysis hyperplasia, adrenal cortex hyperplasia, sexual glands atrophy occur).

ITSENKO-CUSHING DISEASE occurs in adenomas from basophilic cells of anterior lobe of the pituitary or adenocarcinoma in rare cases. Increased ACTH production causes cortex hyperplasia as well as increased production of glucocorticoids. It results in obesity of face and body, elevation of arterial pressure, diabetes mellitus, sexual gland dysfunction. Osteoporosis, nephrolithiasis and chronic pyelonephritis may also develop.

The disease should be differentiated from Itsenko-Cushing syndrome. Its clinical manifestations are the same as in the disease (obesity of the upper part of the body), but the other signs are not clearly marked. The causes of these states are different. The syndrome is characterized by adrenals damage (tumor of zona fasciculata) which causes increased production of glucocorticoids. Cushingoid can be caused by administration of hormones (cortisole, prednisolone, hydrocortisone).

Pituitary nanism develops in congenital hypoplasia of the pituitary body or its necrosis in children. General underdevelopment of the organism with preserved proportions is observed.

SIMMONDS` DISEASE (CEREBRO-HYPOPHYSEAL CACHEXIA) is caused by necrosis of pituitary anterior lobe. It may occur after childbirth due to vascular embolism as well as due to syphilis, tuberculosis, tumor. It manifests by cachexia, inner organ atrophy, sexual dysfunction.

DIABETES INSIPIDUS is caused by tumors, inflammation, sclerosis, trauma of the posterior lobe of pituitary. It manifests by increased urine excretion due to deficiency of antidiuretic hormone.

PATHOLOGY OF THE ADRENAL GLANDS

Adrenal glands consist of cortex and medullar substance. There are 3 zones in the cortex: glomerular zone which produces mineralocorticoids (e.g. aldosterone), zona fasciculata (produces glucocorticoids), reticular zone (produces sexual hormones).

The adrenal medulla is derived embryologically from neural crest ectoderm and is a part of the sympathetic nervous system. It synthesizes and secretes vasoactive amines, adrenaline and noradrenaline (epinephrine and norepinephrine).

Excessive production of adrenal cortical hormones usually results from hyperplasia or tumour. Production of adrenal cortical hydrocortisone and sex steroids is controlled by ACTH secreted by the pituitary gland; aldosterone secretion is controlled by renin production by the juxtaglomerular apparatus in the kidney.

Excessive ACTH production, for example by an ACTH-secreting adenoma of the pituitary, stimulates an increase in the number, size and secretory activity of the adrenal cortical cells, leading to adrenal cortical hyperplasia. The uncontrolled excessive production of adrenal cortical hormones may produce Cushing's syndrome. Excessive production of adrenal cortical hormones usually results from hyperplasia or a tumour. When a tumor develops in a definite zone of the cortex the following conditions develop respectively:

a) in glomerular zone — hyperaldosteronism syndrome;
b) in zona fasciculata — Cushing's syndrome;
c) in reticular zone — reduction in sexual function;
d) in medullar substance — pheochromocytoma.

ADRENAL CORTICAL ADENOMA is a well-circumscribed, yellow tumour in the adrenal cortex, which is usually 2—5 cm in diameter. The colour of the tumour is yellow (as in the adrenal cortex) due to the stored lipid (mainly cholesterol), from which the cortical hormones are synthesized. These tumours are frequent incidental findings at postmortem examination without significant metabolic disorders; only a very small percentage produce Cushing's syndrome. Nevertheless, these apparently «non-functioning» adenomas are most often encountered in elderly obese people. There is some debate that they may really represent nodules in diffuse nodular cortical hyperpiasia.

Very occasionally, a true adrenal cortical adenoma is associated with the clinical manifestations of Conn's syndrome, and can be shown to be excreting mineralocorticoids.

ADRENAL CORTICAL CARCINOMA is rare and usually is associated with excessive production of hormones (usually glucocorticoids and sex steroids). As a result the patients usually have features of Cushing's syn-

drome mixed with androgenic effects, which are particularly noticeable in women. The tumours are usually large and yellowish- white. Llocal invasion and metastatic spread are common.

ACUTE ADRENAL CORTICAL FAILURE is usually due hemorrhagic Infarction, but may be iatrogenic.

Bilateral hemorrhagic necrosis of the adrenal is usually associated with disseminated intravascular coagulation. It is a feature of sepsis (particularly meningococcal septicemia) and is known as the Waterhouse-Friderichsens` syndrome. It manifests by hypovolemic and hypotensive shock, hypoglycemia, and high risk of sudden death.

Jatrogenic acute adrenal cortical failure may occur when prolonged high-dose therapeutic corticosten therapy is abraptly stopped. Prolonged corticosteron therapy leads to suppression of normal endogenic steroid production by the adrenal cortex, which becomes markedly atrophied.

Cessation of exogenic steroid therapy produces acute adrenal cortical failure (adrenal crisis), with hypovolemic and hypotensive shock, hypoglycemia, and risk of sudden death.

Tumours of the adrenal medulla may produse excess of adrenaline/noradrenaline or their breakdown products.

The two principal types of tumour of the adrenal medulla are pheochromocytomas (occurring in adul and neuroblastomas (occurring in children).

PHEOCHROMOCYTOMA is a tumour of the adrenaline and noradrenaline (epinephrine and norepinephrine) secreting cells of the adrenal medulla.

It produces high levels of both hormones and their breakdown products, Vanillylmandelic Acid (VMA) and Homovanillic Acid (HVA), both of which are excreted in the urine and can be estimated as a diagnostic test.

Macroscopically, the tumour is usually spherical and less than 5 cm in diameter. It has a pale, creamy cut surface that changes to dark brown almost instantly when exposed to air, due to oxygenation of tumour pigments. Despite the fact that the tumour is usually small and non-metastatic, it is a hazardous condition with high perioperative mortality.

The excessive amine production produces hypertension that is often initially paroxysmal and associated with severe headaches, but the hypertension eventually becomes constant. There may be intractable, and often unexplained, cardiac failure. Pheochromocytoma is one of the causes of surgically treatable systemic hypertension.

ADDISON'S DISEASE was described in 1849 by Addison and is also called bronze disease. It develops in bilateral lesion of adrenal cortex with the development of acorticism (absence of hormones) or hypoadrenocorticosis.

The causes of Addison's disease are divided into two groups. One of them causes primary Addison's disease (genetic autoimmune disturbances). Secondary Addison's disease is caused by metastases into the adrenal glands, amyloidosis, hemorrhage, tuberculosis, necrosis due to vascular thrombosis, damage of the pituitary body (decreases ACTH or cortlcotro releasing factor).

It manifests by: 1) hyperpigmenfation of skin and mucous membrane due to excessive production of melanin stimulating hormone, 2) myocardial atrophy, 3) changes of the lumen in the aorta and large vessels, 4) hyperplasia of the Langerhans island cells in the pancreas (hypoglycemia), 5) gastric mucosa atrophy, 6) hyperplasia of thymus and lymphatic peripheral tissue.

The cause of death: 1) acute adrenal failure, 2) cachexia (suprarenal cachexia), 3) cardiovascular insufficiency.

PATHOLOGY OF THE THYROID GLAND

GOITROUS HYPOTHYROIDISM

There are a number of conditions in which thyroid enlargement (goiter) is associated with hypothyroidism. The causes are diverse, but in all cases goiter is a compensatory response to the lack of adequate secretion of thyroid hormone. The etiology of Goitrous hypothyroidism includes iodine deficiency, antithyroid agents (drugs or dietary goitrogens), chronic iodide intake, and a number of hereditary defects in the synthesis of thyroid hormone. The evolution of the pathologic changes in goitrous hypothyroidism is similar to that described earlier for nontoxic goiter.

ENDEMIC GOITER

Endemic goiter refers to the goitrous hypothyroidism of dietary iodine deficiency in locales with a high prevalence of the disease. In areas far from salt water and seafood, which are rich sources of iodides, goiters are (or were) common. The Great Lakes region of the United States, alpine Europe, central Africa, and the Himalayas are such places. Iodized salt is an effective preventive dietary measure, and its wide availability has essentially eliminated endemic goiter in many areas. Nevertheless, it has been estimated that more than 200 million persons worldwide are still afflicted with the disease.

The pathologic evolution of endemic goiter is comparable to that of nontoxic goiter discussed earlier. However, in contrast to the latter, endemic goiter rarely eventuates in hyperthyroidism, presumably because iodine protects against this complication. Although the administration of iodine may reverse the early, diffuse stage of endemic goiter, such therapy has little effect on a fully developed multinodular goiter. Replacement therapy with thyroid hormone is indicated, and surgical resection may be necessary if local symptoms are severe.

ENDEMIC GRETINISM

Endemic cretinism refers to congenital hypothyroidism in areas of endemic goiter. Both parents are usually goitrous. The disease encompasses two overlapping clinical presentations, a neurologic syndrome and a Predominantly hypothyroid one.

Neurologic cretinism features mental retardation, ataxia, spasticity, and deaf-mutism. In the pure form of neurologic cretinism, the children may be of normal stature and virtually euthyroid. Thus, it is postulated that iodine deficiency in the first trimester of pregnancy may damage the developing nervous system independently of its effect on thyroid hormone production.

Hypothyroid cretinism is thought to arise from iodine deficiency in late fetal life and in the neonatal period. The clinical course in these children is similar to that of other forms of congenital hypothyroidism.

GOITER INDUCED BY ANTITHYROID AGENTS

There are a number of drugs and naturally occurring chemicals in foods that are goitrogenic, owing to their suppression of thyroid hormone synthesis. Such goiters may or may not be associated with hypothyroidism. The most commonly used goitrogenic drug is lithium, which is employed in the management of manic-depressive states. Women older than the age of 40 years are at particular risk for lithium-induced hypothyroidism, with as many as one third being affected. Other common goitrogenic drugs include phenylbutazone and ρ-aminosalicylic acid. Certain cruciferous vegetables (turnips, rutabaga, cassava) contain goitrogens, and their ingestion can potentiale an iodine-deficient diet to produce goitrous hypothyroidism.

IODINE-INDUCED GOITER

Goiter and hypothyroidism, or either alone, may occur in persons who consume large amounts of iodine, either as a medicinal component (potassium iodine-containing expectorans) or in foods particularly rich in this halide (e.g., seaweed in Japan). In most cases, iodine-induced goiter develops in the context of preexisting thyroid disease, such as thyroiditis. Women given large doses of iodine during pregnancy may be delivered if goitrous infants.

HEREDITARY DEFECTS IN THYROID HORMONE SYNTHESIS

Goitrous hypothyroidism secondary to inherited defects in the synthesis of thyroid hormone is rare. These abnormalities include (1) defective iodide transport, (2) an inability of the thyroid to iodinate thyroglobulin, (3) impaired deiodination of iodotyrosines, and (4) abnormal secretion of iodoproteins. In addition, there exist several syndromes in which peripheral tissues are resistant to the action of thyroid hormone.

HYPERTHYROIDISM

Hyperthyroidism refers to the clinical consequences of an excessive amount of circulating thyroid hormone. In general, the signs and symptoms of hyperthyroidism reflect a hypermetabolic state of the target tissues. Prolonged hypersecretion of thyroid hormone can result from (1) an excess production of THS (rare), (2) the presence of an abnormal thyroid stimulator (Graves disease), and (3) intrinsic disease of the thyroid gland (toxic multinodular goiter of functional adenoma). Rare instances of hyperthyroidism follow the release of preformed thyroid hormone during a bout of thyroiditis or the production of thyroid hormone by ectopic thyroid tissue.

GRAVES DISEASE

Graves disease, also known as Basedow disease in continental Europe, is an autoimmune disorder characterized by diffuse goiter, hyperthyroidism, and exophthalmos. In the US, Graves disease is the most frequent cause of hyperthyroidism in patients younger than age 40 years, affecting as many as 0.4% of the population. Taken together, autoimmune disease of the thyroid (e.g., Graves disease, Hashimoto thyroiditis) are as common as diabetes mellitus.

Pathogenesis: the etiology of Graves disease is not fully understood and seems to involve an interplay between immune mechanism, heredity, sex, and possibly emotional factors, in addition, it is clear that the mechanisms underlying Graves ophthalmopathy are distinct from those that mediate hyperthyroidism.

Immune mechanisms: patients with graves disease are hyperthyroid owing to the presence of IgG antibodies directed against components of the plasma membrane of thyroid follicular epithelium, presumably the TSH receptor. These antibodies function as agonists, that is, they stimulate the TSH receptor, thereby activating adenylyl cyclase and increasing thyroid hormone secretion. Under this continued stimulation, the thyroid becomes diffusely hyperplastic and excessively vascular. The autoantibodies of Graves disease were originally termed long-acting thyroid stimulator (LATS), because the peak secretion of thyroid hormone occurs 16 hours after the exposure of thyroid tissue to antibody, compared with 2 hours for TSH.

Graves autoantibodies are actually heterogeneous, and those that stimulate thyroid hormone secretion represent only one component. Other antibodies seem to be cytotoxic and may account for the thyroid failure that often follows long-stanting Graves disease. There is also a suggestion that sensitized T lymphocytes may stimulate B cells to elaborate thyroid-activating immunoglobulins.

The mechanism underlying the origin of the autoantibodies in Graves disease remains unclear, but there is evidence that sensitization to antigens of Yersinia enterocolitica plays a role. This gram-negative enteric pathogen displays a TSH binding site that also binds Graves autoantibodies, suggesting that antibodies to Y.enterocolitica may cross-reach with thyroid tissue. There is reason to believe that an abnormality of T suppressor cell function permits the persistence of sensitized B cell clones. Another theory holds that an antibody to anti-TSH antibody (anti-idiotypic antibody) mimics TSH and, thereby, stimulates the TSH receptor.

Genetic factors: Graves disease exhibits a higher concordance rate in monozygotic twins than in dizygotic ones. Moreover, patients with Graves disease and their relatives have a considerably higher incidence of other autoimmune diseases, including pernicious anemia and Hashimoto thyroiditis. Some asymptomatic, first-degree relatives of these patients also have an increased uptake of iodine-131. White patients with Graves disease display an increased frequency of HLA-B8 and HLA-DR3, whereas Chinese patients are more likely to manifest HLA-Bw46 and Japanese ones to exhibit HLA-Bw35.

Sex: Like other autoimmune diseases, Graves disease is far more common (7 to 10 times) in women than in men. Interestingly, the disorder tends to arise during periods of hormonal imbalance, including puberty, pregnancy, and menopause. Men with Graves disease are usually older, and although the degree of thyroid hyperfunction is often greater than in women, the symptoms tend to be less severe.

Emotional influences: Quantitative data are lacking, but endocrinologists have long observed that the onset of Graves disease often follows a period of emotional stress, such as separation anxiety, death of a loved one, or near injury in an accident.

Ophthalmopathy: Although exophthalmos is a common complication of Graves disease, its occurrence and severity correlate poorly with the levels of thyroid hormone. It seems likely that a combination of humoral and cell-mediated immune mechanisms are involved. T lymphocytes that are sensitized to antigens shared by thyroid follicular cells and orbital fibroblasts accumulate around the eye, where they secrete cytokines that activate fibroblasts. There is also evidence for the systemic or local production of antibodies that stimulate orbital fibroblasts to proliferate and produce collagen and glycosaminoglycans.

Pathology: The thyroid in Graves disease is symmetrically enlarged, usually weighing 35 to 40 g. The cut surface is firm and dark red. The tan translucence of the normal cut surface of the thyroid, attributable to stored colloid, is notably absent. Microscopically, the thyroid is diffusely hyperplastic and highly vascular. The epithelial cells are tall and columnar and are often ar-

ranged as papillae that project into the lumen of the follicles. The colloid tends to be depleted and presents a scalloped or "moth-eaten" appearance where it abuts the epithelial cells. Scattered lymphocytes and plasma cells infiltrate the interstitial tissue and may even aggregate to form germinal follicles.

Treatment of Graves disease with iodine, which is only rarely employed today, causes involutional changes in the thyroid. The vascularity is diminished, and dilated, colloid-containing follicles appear. These effects are often not uniform, and some hyperplastic areas persist. Therapy with antithyroid medication (e.g., methimazole or propylthiouracil) commonly results in increased thyroid hyperplasia and a complete absence of colloid.

Exophthalmos is caused by enlargement of the extraocular muscles within the orbit. The muscles themselves are normal, but they are swollen by mucinous edema, the accumulation of fibroblasts, and infiltration by lymphocytes. The increased orbital contents cause forward displacement of the eye (proptosis).

Clinical features: patients with Graves disease note the gradual onset of nonspecific symptoms, such as nervousness, emotional lability, tremor, weakness, and weight loss. They are intolerant of heat, seek cooler environments, and tend to sweat profusely. Almost all patients exhibit tachycardia, and many complain of palpitations. In patients with preexisting heart disease, congestive heart failure may ensue. Women develop oligomenorrhea, which may progress to amenorrhea.

Physical examination reveals a symmetrically enlarged thyroid, often with an audible bruit and a palpable thrill. Protrusion of the eyeball and retraction of the eyelids expose the sclera above the superior margin of the limbus. The skin is warm and moist, and some patients exhibit Graves dermopathy, a peculiar pretibial edema caused by the accumulation of fluid and glycosaminoglycans. The diagnosis of Graves disease is documented by an increased uptake of radioactive iodine by the thyroid and elevated serum levels of T_4 and T_3.

The course of Graves disease is characterized by exacerbations and remissions. In untreated cases hyperthyroidism may eventually be replaced by progressive thyroid failure and hypothyroidism, presumably as a result of chronic thyroiditis. Treatment of the disorder depends on many individual factors and includes the use of anti-thyroid medication, destruction of thyroid tissue with radioactive iodine, and adjunctive therapy with corticosteroids and adrenergic antagonists. Surgical ablation is not commonly performed today. Unfortunately, despite successful relief of hyperthyroidism, exophthalmos often persists and may even worsen.

TOXIC MULTINODULAR GOITER

Many patients with nontoxic multinodular goiter, usually older than the age of 50 years, eventually develop functional autonomy of the nodules and a toxic form of the disease. Like its precursor disease, toxic goiter is ten times as frequent in women as in men.

Pathogenesis and pathology: The precise mechanisms by which a nontoxic multinodular goiter assumes functional autonomy are not clear, but two patterns are noted.

In some patients, the uptake of iodine is diffuse and not affected by the administration of thyroid hormone. Microscopic examination of the thyroid shows groups of small hyperplastic follicles mixed with other nodules of varying size that appear to be inactive.

The second pattern is characterized by focal accumulation of radiolabeled iodine in one or more nodules. Hyperfunction of these nodules suppresses the function of the remainder of the thyroid. As in the first type of toxic multinodular goiter, exogenous thyroid hormone produces no further suppression of iodine uptake, although the previously inactive areas will respond to TSH by sequestering iodine. On microscopic examination, the functional nodules are clearly demarcated from the inactive areas and consist of large hyperplastic follicles, thus resembling adenomas. Although there is little evidence to suggest that the functional nodules have neoplastic characteristics, the clinical presentation is similar to that of a normal thyroid with a single hyperfunctioning adenoma.

Clinical features: Patients with toxic multinodular goiter usually have less severe symptoms of hyperthyroidism than those with Graves disease and never develop exophthalmos. Since patients with a toxic goiter tend to be older, cardiac complications, including atrial fibrillation and congestive heart failure, may dominate the clinical presentation. Serum T_4 and T_3 levels are frequently only minimally elevated, and the uptake of radiolabeled iodine may be within the normal range or only slightly increased. Radiolabeled iodine administration after a course of antithyroid therapy is the most common therapy for toxic multinodular goiter.

TOXIC ADENOMA

Toxic adenoma, defined as a solitary, hyperfunctioning, follicular neoplasm in an otherwise normal thyroid, is an infrequent cause of hyperthyroidism. Such tumors display autonomous function, are not dependent on TSH, and are not suppressed by the administration of thyroid hormone. Hyperfunction of the toxic adenoma eventually suppresses the remainder of the thyroid, which then atrophies. Under these circumstances, a ^{131}I scintiscan shows a solitary focus of iodine uptake ("hot nodule") in a background of minimal uptake.

Toxic adenoma of the thyroid is most common in the fourth and fifth decades of life. Most patients do not suffer symptoms of hyperthyroidism until the adenoma has grown to a diameter of about 3 cm. On occasion, spontaneous necrosis and hemorrhage within the adenoma relieves the hyperthyroidism, after which the remainder of the gland resumes its normal function. In such cases, the adenoma appears as a "cold" nodule in a scintigram and may simulate thyroid cancer.

Since the normal thyroid tissue is suppressed, toxic adenoma is effectively treated with radiolabeled iodine. Alternatively, large nodules

may be excised surgically, especially in young patients who are at risk for the development of thyroid cancer many years after radiolabeled iodine administration.

HYPERSECRETION OF TSH

Pituitary adenomas that secrete TSH are rare causes of hyperthyroidism. Increased hypothalamic secretion of TSH has also been implicated in some cases of hyperthyroidism. Resistance on the part of thyrotropes in the pituitary to suppression by thyroid hormone has been documented on rare occasions. A thyroid stimulator distinct from TSH may also be produced by trophoblastic tumors, and hyperthyroidism may actually be the first manifestation of a molar pregnancy.

IODINE-INDICED HYPERTHYROIDISM

In areas of endemic iodine deficiency, treatment of a goiter with iodine infrequently leads to hypersecretion of thyroid hormone, a situation termed jobbasedow. It is now clear that jobbasedow occurs only in goiters that contain nodules capable of autonomous function independent of TSH stimulation. Even in areas in which iodine supplies are adequate, excessive iodine intake (e.g., iodine-containing expectorants in the treatment of pulmonary disease) may induce hyperthyroidism.

THYROIDITIS

Thyroiditis is a term that encompasses a heterogeneous group of inflammatory disorders of the thyroid gland, including those that are caused by autoimmune mechanisms and infectious agents.

HASHIMOTO THYROIDITIS

Hashimoto thyroiditis, also termed lymphadenoid thyroiditis and lymphocytic thyroiditis, is an autoimmune disease characterized by the presence of circulating antibodies to thyroid antigens and features suggestive of cell-mediated immunity to thyroid tissue. The disease arises most commonly in the fourth and fifth decades and afflicts women more often than men. In regions where supplies of iodine are adequate, hashimoto thyroiditis is the most common cause of goitrous hypothyroiditis.

Pathogenesis: Hashimoto thyroiditis is one of a triad of autoimmune thyroid disorders, the other two being graves disease and primary hypothyroidism (primary thyroid atrophy). However, it is not clear how thyroid tissue is destroyed by immune mechanisms. Patients with Hashimoto thyroiditis exhibit high titers of circulating antimicrosomal antibodies, which have been shown to be cytotoxic to thyroid epithelial cells in

vitro. In addition, the intense infiltration of the thyroid parenchyma by lymphocytes and plasma cells suggests cell-mediated destruction of the gland. These mechanisms may operate in concert through antibody-dependent, cell-mediated cytotoxicity (ADCC). It is speculated that a defect in suppressor cell activity may allow the persistence of sensitized clones of antithyroid lymphocytes.

Genetic influences also seem to play a role in the pathogenesis of Hashimoto thyroiditis. A familial tendency for the disease has been documented, and both patients and their relatives have a higher incidence of other autoimmune diseases, including insulin-dependent diabetes mellitus, pernicious anemia, Addison disease, and myasthenia gravis. Hashimoto thyroiditis is associated with an increased frequency of the HLA-B8 haplotype. In addition, HLA-DR3 is more common in those who progress to thyroid atrophy and HLA-DR5 accompanies diffuse goiter. Interestingly, Hashimoto thyroiditis is particularly frequent in the context of Down syndrome.

Pathology: on gross examination, the gland in cases of Hashimoto thyroiditis is diffusely enlarged, firm, and slightly lobular, weighing 60 to 200 g. The cut surface is pale tan and fleshy and exhibits a vaguely nodular pattern. The inflammatory infiltrates are focally arranged in lymphoid follicles, often with germinal centers. The Askanazy cells are filled with mitohondria and frequently display cytologic atypia, which may be mistaken for cancer. Interstitial fibrosis is present to a varying extent and in 10% of the cases is particularly conspicuous (fibrous variant).

SUBACUTE THYROIDITIS (DEQUERVAIN, GRANULOMATOUS, OR GIANT CELL THYROIDITIS)

Subacute thyroiditis is an infrequent, self-limited viral infection of the thyroid characterized by granulomatous inflammation. The disease typically occurs after upper respiratory tract infections, including those caused by influenza virus, adenovirus, echovirus, and coxsackievirus. Mumps virus has also been incriminated in some cases. DeQuervain thyroiditis principally affects women between the ages of *30* and 50 years.

Pathology: The thyroid gland is enlarged to 40 to 60 g, and the cut surface is firm and pale. Initially, microscopic examination reveals an acute inflammatory reaction, often with microabscesses. This is followed by the appearance of a patchy infiltrate of lymphocytes, plasma cells, and macrophages throughout the thyroid. Destruction of follicles allows the release of colloid, which elicits a conspicuous granulomatous reaction. Numerous multinucleated giant cells of the foreign body type, often containing colloid, are present. Fibro-

sis of the thyroid may follow resolution of the inflammatory reaction, but the normal thyroid architecture is usually restored.

SILENT THYROIDITIS

Silent thyroiditis, also termed painless subacute thyroiditis or lymphocytic thyroiditis, is a transient illness characterized by painless enlargement of the thyroid, self-limited hyper thyroid ism, and, on biopsy, destruction of thyroid parenchyma with a lymphocytic infiltrate. Thus, it clinically resembles subacute thyroiditis but pathologically is more similar to Hashimoto thyroiditis. Importantly, silent thyroiditis is distinguished from the latter by the lack of antithyroid antibodies or other evidence of autoimmune thyroiditis. However, an association with HLA-DR3 has been reported. As in subacute thyroiditis, the hyperthyroid state is a reflection of the release of preformed thyroid hormone from the injured gland. Silent thyroiditis predominantly affects women, often in the postpartum period. Hyperthyroidism usually persists for 2 to 4 months. Treatment is symptomatic, and most patients become euthyroid.

RIEDEL THYROIDITIS

Reidel thyroiditis is a rare disease characterized by dense fibrosis of the thyroid. The term thyroiditis is something of a misnomer since the disease also involves extrathyroidal soft tissue of the neck and is often associated with progressive fibrosis in other locations, including the retroperitoneum, mediastinum, and orbit. Reidel thyroiditis is primarily a disease of middle age with a female-to-male ratio of 3:1. The etiology is unknown, but is does not appear to be related to other forms of thyroiditis.

Pathology: on gross examination, part or all of the thyroid is stony hard and is described as ―woody‖. In most instances, the process is asymmetric and often affects only one lobe. Characteristically, fibrosis extends beyond the borders of the gland, and the surgeon may have extreme difficulty in identifying a tissue plane. The follicles are normal in the unaffected portions of the glands. Fibrous tissue also surrounds and infiltrates other tissues, including skeletal muscle, nerves, fat, and blood vessels. In some cases, the parathyroids are also embedded in the fibrosis.

TUMORS OF THE THYROID

FOLLICULAR ADENOMA

Thyroid adenomas are by definition benign neoplasms. they typically present as solitary ―cold‖ nodules, that is, tumors that do not take up radiolabeled iodine. Follicular adenoma is an encapsulated neoplasm in which the cells are either arranged in follicles resembling normal thyroid tissue or mimic stages in the embryonic development of the gland. It deserves em-

phasis that up to 90% of palpable, solitary follicular lesions are actually the dominant nodule in a multinodular goiter and that follicular adenomas are correspondingly infrequent. Follicular adenoma is most common in the fourth and fifth decades, with a female-to-male of 7:1.

Pathology: on gross examination, follicular adenoma is a solitary, circumscribed nodule, 1 to 3cm in diameter, which protrudes from the surface of the thyroid. The cut surface of the tumor is soft and paler than the surrounding parenchyma. Hemorrhage, fibrosis, and cystic change are common. Histologically, a number of distinctive patterns are observed.

- Embryonal adenoma is distinguished by a trabecular pattern in which poorly formed follicles contain little or no colloid.
- Fetal adenoma features cells that are similar to those of embryonal adenoma but tend to be arranged in microfollicles containing little colloid.
- Simple adenoma exhibits mature follicles with a normal amount of colloid.
- Colloid adenoma is similar to simple adenoma except that the follicles are larger and contain more abundant colloid.
- Hiirthle cell adenoma is a solid tumor characterized by oxyphil cells, small follicles, and scanty colloid.
- Atypical adenoma is a follicular tumor that displays mitoses, excessive cellularity, nuclear atypism, or equivocal capsular invasion but in which a diagnosis of carcinoma cannot be established with certainty.

THYROID CARCINOMA

The topic of thyroid neoplasia has aroused the interest of clinicians and pathologists out of proportion to the incidence of thyroid cancer. This attention can be attributed to the frequency of nontoxic thyroid nodules and the difficulty of distinguishing clinically between non-neoplastic lesions, benign tumors, and thyroid cancer. Whereas thyroid nodules are found in as many as 1% to 10% of the population, malignant tumors of the thyroid account for about 1 % of all cancers and only 0.4% of cancer-related deaths. It is therefore clear that only a very small proportion of clinically evident thyroid nodules are malignant. Nevertheless, thyroid cancer is the most common malignant endocrine tumor.

The large majority of cases of carcinoma of the thyroid occur between the third and seventh decades. The prognosis is related to the morphologic features of the tumor, ranging from a virtually benign clinical course to a rapidly fatal disease. The latter outcome is fortunately uncommon.

Before the advent of fine-needle aspiration, the definitive diagnosis of a thyroid nodule required open biopsy, often with the resection of a significant portion of the gland and consequent morbidity. Today, fine-needle biop-

sy of thyroid nodules is a safe and rapid procedure that provides a diagnosis in the majority of cases. As a result, the incidence of cancer in resected thyroid nodules has increased from 3% to over 70%.

PAPILLARY CARCINOMA

Papillary carcinoma is the most common thyroid cancer, comprising more than three fourths of all cases in the United States. The tumor is most frequent between the ages of 20 and 50 years, with a female-to-male ratio of 3:1. However, papillary carcinoma may arise at any age, even in children. The reported incidence of this tumor has varied from 35% to 90% of all thyroid cancers because some pathologists consider the most mature variant to be a papillary adenoma and others classify papillary tumors with follicular elements as follicular carcinoma. In this context we consider all neoplasms with papillary elements to be papillary cancers. Such a classification is of more than academic interest, since the biologic behavior of papillary cancers is different from that of other malignant tumors of the thyroid.

Pathogenesis: Although the etiology of papillary carcinoma of the thyroid remains to be established, a number of associations have been identified.

- Iodine excess: Papillary thyroid cancer has been produced in animals by administering excess iodine. In endemic goiter regions, the addition of iodine to the diet has increased the proportion of papillary carcinoma compared with follicular cancer.
- Radiation: External radiation to the neck of children and adults increases the incidence of later papillary carcinoma of the thyroid. Survivors of the atomic bomb Explosions in Japan experienced more papillary cancers than would otherwise be expected. On the other hand, treatment with radiolabeled iodine has not been shown to increase the risk of this tumor.
- Genetic factors: a concordance for papillary carcinoma of the thyroid has been described in monozygotic twins, and an association between this tumor and HLA-DR7 has been reported.

Pathology: Papillary carcinomas of the thyroid vary from microscopic lesions to tumors large than the normal gland. Serial sections of ostensibly normal thyroids obtained at autopsy have revealed a high proportion of papillary cancers that measure less than 1 mm across, but lymph node metastases in such cases are distinctly uncommon. On gross examination, most papillary carcinomas are pale and firm or hand and gritty lesions, with less than 10% being truly encapsulated. A few tumors display cystic changes. Microscopic examination reveals branching papillae that are composed of a central fibrovascular core and a single or stratified lining of cuboidal to columnar cells. In most instances, irregularly shaped or tubular neoplastic follicles are present within the tumor, but the proportions of the papillary and follicular elements

are highly variable. Nuclear atypism is an important diagnostic feature and includes clear (―ground-glass‖ or ―orphan Annie‖) nuclei, eosinophilic pseudoinclusions (which represent invaginations of the cytoplasm into the nucleus), and nuclear grooves. Many papillary cancers show dense fibrosis,and calcospherites (psammoma bodies) are present in half the cases. The latter feature is virtually diagnostic of papillary carcinoma, being rare in other conditions. The stroma may be infiltrated by lymphocytes and Largenhans cells. In over three fourth of the cases of papillary cancer, careful sectioning of the resected thyroid reveals multiple microscopic foci of tumor, but it is not clear whether this represents a multifocal origin of the tumor or lymphatic spread from a solitary primary. Vascular invasion is distinctly uncommon. Papillary thyroid carcinoma typically invades lymphatics and spreads to the regional cervical lymph nodes. The lymph node metastases vary from microscopic foci in otherwise normal lymph nodes to large masses that dwarf the primary lesion. direct extension of papillary carcinoma into the soft tissues of the neck occurs in one fourth of the cases. Although hematogenous metastases are less common than in other varieties of thyroid cancer, they occasionally occur, most commonly to the lungs.

In general, the prognosis of papillary carcinoma is excellent, and life expectancy for these patients differs little from that of the general population. The prognosis in individual cases is influenced by age, sex, and the size and differentiation of the tumor. The prognosis is more serious in patients older than 50 years of age, whereas in children the outlook is good even when lung metastases are detected. Papillary cancer tends to be more aggressive in men than in women. As a rule, the larger the size of the primary tumor, the more aggressive it is, and direct extension into the adjacent soft tissues points to a poorer prognosis. The proportion of papillary and follicular elements contributes little to the prognosis, but less-differentiated papillary carcinomas tend to be more aggressive. The presence of metastases to cervical nodes at the time or surgery does not change the prognosis, and less than 10% of these patients succumb to the tumor. In fatal cases of papillary cancer, death is caused principally by metastases to the lungs or brain or by obstruction to the trachea or esophagus.

FOLLICULAR CARCINOMA

Follicular carcinoma of the thyroid is defined as a malignant neoplasm that is purely follicular and does not contain any papillary or other elements. This tumor represents about 15% of all thyroid cancers. Most patients are older than 40 years of age, and the female-to-male ratio is 3:1. The risk factors for follicular carcinoma are not as clear as those for papillary cancer, because many studies have classified tumors with both features as follicular.

The incidence of follicular carcinoma seems to be increased in endemic goiter areas among persons who do not receive iodine supplements. The effect of radiation with respect to this tumor is controversial.

Pathology: Follicular carcinomas are subdivided into minimally invasive and widely invasive variants.

Minimally invasive follicular carcinoma is seen grossly as a well-defined, encapsulated tumor, which on cut section is soft and pale tan to pink and bulges from the confines of its capsule. Microscopically, most lesions resemble follicular adenoma, although they tend more to a microfollicular or trabecular pattern. Occasionally, hemorrhagic necrosis is present in the center of the tumor. Mitoses are commonly encountered, a feature that distinguishes follicular cancer from a benign adenoma. The principal distinction from adenoma is in the interface of the capsule and the normal parenchyma. Carcinoma is diagnosed when the tumor extends into or through the capsule and invades small veins external to the capsule. Interestingly, intravascular masses of follicular carcinoma are often covered by endothelium in a manner similar to that of an ordinary thrombus.

Widely invasive follicular carcinoma presents few diagnostic difficulties, since it is not encapsulated, exhibits widespread infiltration of blood vessels, and often extends into the surrounding soft tissues.

Follicular carcinoma differs from papillary cancer in being solitary and rarely occult. Metastases are blood borne rather than lymphatic and are directed principally to the bones of the shoulder and pelvic girdles, sternum, and skull. Whereas metastases in widely invasive follicular carcinoma are common, less than *5%* of the minimally invasive variants metastasize. The metastases may be so well differentiated that they are hardly recognizable as neoplastic tissue and at one time were referred to as ―benign metastasizing struma‖.

Minimally invasive follicular tumors have a 10-year survival rate of 85%, compared with a rate of only 45% for the widely invasive form.

MEDULLARY CARCINOMA

Medullary carcinoma of the thyroid is a tumor derived from the parafollicular or C cells of the thyroid, ehich are distinguished by their secretion of the calcium-lowering hormone calcitonin. This tumor presents no more yhan 5% of all thyroid cancers, although the proportion in referral centers is higher. The disease occurs in sporadic and familial forms, the latter accounting for 20% of the cases. Patients with the familial form of medullary carcinoma are often afflicted with multiple endocrine neoplasia (MEN) type 2, which includes pheochromocytoma of the adrenal medulla and parathyroid hyperplasia or adenoma. The mean age of patients with medullary carcinoma is 50 years, but familial cases appear earlier (mean age, 20 years). There is

slight female predominance (1.5:1); in familial cases the inheritance is autosomal dominant and the sex distribution is equal.

Pathology: on gross examination, medullary carcinomas tend to arise in the superior portion of the thyroid, the regions that are richest in C cells. Although they are not encapsulated, they are usually circumscribed. The cut surface is firm and grayish white. The histologic appearance is highly variable. Characteristically, the tumor is solid and composed of polygonal, granular cells, which are separated by a distinctly vascular stroma. A conspicuous feature is the presence of stromal amyloid, representing the deposition of procalcitonin. The nests of tumor cells are embedded in a hyalinized collagenous framework. Focal calcification is often present and may be sufficiently extensive to be detected radiologically. The histologic variability of medullary carcinoma is evidenced by different architectural patterns, including trabecular, tubular, follicular, carcinoid-like, or pseudopapillary arrangements. The neoplastic cells may exhibit peripheral nuclei (plasmacytoid pattern) or may be spindle shaped, anaplastic, or oxyphilic. In addition, the stroma may feature hemorrhage or bone formation and amyloid may be absent. By electron microscopy, the neoplastic C cells show dense-core secretory granules, which stain immunohistochemically for a variety of endocrine markers, including calcitonin, synaptophysin, chromogranin, and neuronspecific enolase. Almost all of these tumors are positive for carcinoembryonic antigen (CEA). Many cases are also positive for ACTH, serotonin, substance P, glucagons, insulin, and human chorionic gonadotropin (hCG). Medullary carcinoma extends by direct invasion into soft tissues and metastasizes to the regional lymph nodes and to lung, liver, and bones. In some instances, metastatic disease is responsible for the initial presentation. The metastatic deposits resemble the primary tumor and also tend to contain amyloid. The precursor lesion of the familial variety of medullary carcinoma is C cell hyperplasia. Thus, patients with MEN types 2A and 2B who are at risk for the development of medullary carcinoma of the thyroid are monitoredby periodic measurements of serum calcitonin, CEA, and sometimes chromogranin. When levels of these substances are elevated, the patient is subjected to total thyroidectomy.

ANAPLASTIC (UNDIFFERENTIATED) CARCINOMA

Anaplastic carcinoma is a highly aggressive, undifferentiated thyroid cancer, which is usually rapidly fatal. This type of thyroid cancer principally afflicts women (female:male ratio of 4:1) over the age of 60 years. The tumor comprises 10% of thyroid cancer and is more common in endemic goiter areas. In fact, overall at least half of the patients have a history of long-standing goiter. In addition, many cases of anaplastic carcinoma occur in patients with a history of a lower-grade thyroid cancer. Thus, it seems likely that anaplastic thyroid carcinoma often represent the transformation of a benign or low-grade thyroid neoplasm

into a poorly differentiated and highly aggressive cancer. There is evidence that the risk of such an event is enhanced by external radiation.

Pathology: Anaplastic carcinoma of the thyroid presents as large masses in the gland, which are poorly circumscribed and frequently extend into the soft tissues of the neck. The cut surface is hard and grayish white. The histologic appearance is highly variable. The most common pattern is a sarcoma-like proliferation of bizarre spindle and giant cells, with polyploid nuclei, many mitoses, necrosis, and stromal fibrosis. Other specimens reveal distinct epithelial differentiation. The tumor tends to invade veins and arteries, often occluding the vessels and producing foci of infarction within the tumor.

The prognosis is dismal and widespread metastases are frequent. Less than 10% of patients survive for 5 years.

THYROID LYMPHOMA

Lymphoma originating in the thyroid is distinctly uncommon, accounting for 2% of all thyroid cancers. The large majority (95%) are B cell tumors. Most if not all cases arise in the setting of chronic thyroiditis, and in regions where this disorder is frequent, up to 10% of malignant tumors of the thyroid are lymphomas. Similar to chronic thyroiditis, thyroid lymphoma is more common in women than in men (4:1), but the mean age at presentation (seventh decade) is older.

Thyroid lymphomas present as large, soft, tannish masses in the thyroid, usually extending beyond the confines of the gland. Microscopically, they present the spectrum of lymphomas seen at other sites, the most common subtype being the diffuse large cell pattern. A few tumors exhibit plasmacytoid differentiation, whereas others resemble immunoblastic lymphoma.

The prognosis of thyroid lymphoma depends on the stage at the time of diagnosis. If restricted to the thyroid gland, the prognosis is excellent, and three fourths of the patients now survive for 10 years. The outlook for patients with disseminated disease is poorer and is similar to that of other lymphomas.

PARATHYROID GLANDS

The parathyroid glands are small endocrine glands which secrete the parathormone. There are usually four (sometimes up to eight) parathyroid glands, which are usually located close to the thyroid gland.

Parathormone (PTH), the parathyroid hormone, is important in calcium balance, acting at two sites:

1. The bone surface, where it stimulates the resorption of bone by osteoclasts and release of calcium.
2. The renal tubules, where it stimulates the resorption of calcium from the urine, minimizing phosphate resorption.

Parathyroid adenoma is usually a solitary tumour that affects only one of the parathyroid gland; the other parathyroids often showing atrophy. The tumour is usually small and very rarely palpable in the neck. The main presenting symptoms develop due to excessive secretion of parathyroid hormone (primary hyperparathyroidism) with the symptoms and signs of hypercalcemia.

Malignant parathyroid tumours, with invasion and metastatic spread, are very rare, although some parathyroid adenoma may show considerable pleomorphism and nuclear and cytoplasmic atypia.

Primary parathyroid adenoma is only one of the possible causes of hypercaleemia. Rarely, primary hyperparathyroidism is the result of diffuse hyperplasia of the parathyroids rather than a solitary tumour.

Diffuse hyperplasia of all parathyroid glands is usually a compensatory response to persistently low serum calcium levels. The most common cause of compensatory parathyroid hyperplasia is in renal failure, in which excessive urinary loss of calcium leads to a persistent serum hypocalcemia.

The parathyroid glands may be removed inadvertently or deliberately during surgery on the thyroid gland. If not surgically excised, they may be severely damaged by operative trauma or by interference with their blood supply. Much less commonly, the parathyroid glands may be affected by an autoimmune process (autoimmune parathyroid disease) associated with the presence of an autoantibody; this usually occurs in patients who have another autoimmune endocrine disease, e.g. Hashimoto's disease or Addison's disease. Reduced PTH secretion leads to a reduction in the serum calcium, with a corresponding increase in serum phosphate levels. Hypoparathyroidism is only one of the causes of hypocalcemia.

PANCREAS

DIABETES MELLITUS (DM)

DIABETES MELLITUS, commonly referred to as diabetes, is a disease which results from absolute or relative insufficiency of insulin and is characterized by severe carbohydrate metabolism disturbances with hyperglycemia and glucosuria, and other metabolic disturbances too.

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.

Classification of diabetes mellitus and mixed categories of tollerance to glucose disturbances (WHO)

A. Clinical class

I. Diabetes mellitus.

II. Disturbed tolerance to glucose :

- in patient with normal weight,

- in patient with obesity,
- disturbed tolerance to glucose, resulting from other states and syndromes.

III. Gestational diabetes.

B. Classes of risk.

Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".

Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes".

Gestational diabetes (Diabetus mellitus of pregnant female) is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

Table 6. Carachteristics of Type 1 DM and Type 1 DM

Risk factors	**Type 1**	**Type 2**
Age	Until 30	After 40
Virus infection	High antibody titres to a number of viruses	Antibodies to virus are absent
Genetic factors	Association with definite HLA-D antigens	Association with histocompatibility antigens is absent
Autoimmunization	Presence of antibodies to beta-cells	None
Obesity	None	Marked

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM.

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.

Pathology: The pancreas is diminished with lipomatosis and sclerosis (liposclerosis). Degeneration and hyalinosis are observed in the islets, some of them are hypertrophic. The liver is enlarged, glycogen is absent, fat degeneration is observed.

Diabetic macro- and microanglopathy is seen in the vessels. Macroangiopathy is represented by arterial atheroscierosis. Microangiopathy is characterized by plasmatic saturation, hyalinosis, sclerosis with lipohyalin appearance. There is marked proliferation of endothelium and perithelium accompanied by lymphohistiocyte infiltration. The signs of vasculitis can be seen. There is generalized microangiopathy in the kidneys, retina, skeletal muscles, digestive tract mucosa, pancreas, brain, nerves.

In the kidneys, diabetic glomerulonephritis and glomerulosclerosis develop. Microscopically proliferation of mesangial cells in response to mesangium clogging with «ballast» metabolic products and immune complexes are observed. Mesangium hyalinosis and glomerulosclerosis develop. Diabetic glomerulosclerosis may be diffuse and nodular as well as mixed type. Its clinical manifestations are Kimmelstiel-Wilson syndrome (proteinuria, edema, arterial hypertension).

In the lungs, lipogranulomas consisting of macrophages and gigantic cell of foreign bodies are present in the walls of the arteries.

In the spleen, liver, lymphatic glands: infiltration of histiomacrophagal system and skin with cell lipids (xantomatosis) develop.

Complications: All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20) but may be the first symptom in those who have otherwise not received a diagnosis before that time.

The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease and about 75% of deaths in diabetics are due to coronary artery disease. Other "macrovascular" diseases are stroke, and peripheral artery disease.

The primary complications of diabetes due to damage in small blood vessels (microangiopathy) include damage to the eyes, kidneys, and nerves. Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness. Diabetes also increases the risk of having glaucoma, cataracts, and other eye problems. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplantation.

Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes. The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to

the skin. Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle atrophy and weakness.

So, common complications of DM are:

1) diabetic coma,

2) those connected with angiopathy (gangrene of extremities, myocardial infarction, blindness),

3) diabetic nephropathy (acute and chronic renal failure),

4) infectious sepsis.

Though gestational diabetes may be transient, untreated it can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and skeletal muscle malformations. Increased levels of insulin in a fetus's blood may inhibit fetal surfactant production and cause respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

The death of patients with DM can be caused by coma, diabetic glomerulopathy with uremia, gangrene, myocardium infarction, stroke, complications of infectious nature.

PATHOLOGY OF REPRODUCTIVE SYSTEM

MALE REPRODUCTIVE SYSTEM

TESTIS

CONGENITAL ANOMALIES

CRYPTORCHIDISM

Cryptorchidism or undescended testis is a condition in which the testicle is arrested at some point in its descent. Its incidence is about 0.2% in adult male population. In 70% of cases, the undescended testis lies in the inguinal ring, in 25% in the abdomen and, in the remaining 5%, it may be present at other sites along its descent from intra-abdominal location to the scrotal sac.

Etiology. The exact etiology is not known in majority of cases. However, a few apparent causes associated with Cryptorchidism are as under:

1. Mechanical factors e.g. short spermatic cord, narrow inguinal canal, adhesions to the peritoneum.
2. Genetic factors e.g. trisomy 13, maldevelopment of scrotum or cremaster muscles.
3. Hormonal factors e.g. deficient androgenic secretions.

Pathologic changes. Cryptorchidism is unilateral in majority of cases but in 25% of patients, it is bilateral.

Grossly, the cryptorchid testis is small in size, firm and fibrotic.

Histologically, contrary to previous beliefs, the changes of atrophy begin to appear by about 2 years of age. These changes are as under: 1. Seminiferous tubules: There is progressive loss of germ cell elements so that the tubules may be lined by only spermatogonia and spermatids but foci of spermatogenesis are discernible in 10% of cases. The tubular basement membrane is thickened. Advanced cases show hyalinised tubules with a few Sertoli cells only, surrounded by prominent basement membrane. 2. Interstitial stroma: There is usually increase in the interstitial fibrovascular stroma and conspicuous presence of Leydig cells, seen singly or in small clusters.

As such, cryptorchidism is completely asymptomatic and is discovered only on physical examination. However, if surgical correction by orchiopexy is not undertaken by about 2 years of age, or certainly in the prepubertal period, significant adverse clinical outcome may result as under:

1. Sterility-infertility. Bilateral cryptorchidism is associated with sterility while unilateral disease may result in infertility.
2. Inguinal hernia. A concomitant inguinal hernia is frequently present along with cryptorchidism.
3. Malignancy. Cryptorchid testis is at 35-times increased risk of developing testicular malignancy, most commonly seminoma and embryonal carcinoma, than a normally descended testis. The risk of malignancy is greater in intra-abdominal testis than in testis in the inguinal canal.

The morphologic pattern of testicular atrophy described above for cryptorchidism can result from various other causes of male infertility. These causes can be divided into 3 groups: pre-testicular, testicular and post-testicular.

A. Pre-testicular causes:

1. *Hypopituitarism.* Pre-pubertal or post-pubertal hypopituitarism such as from tumour, trauma, infarction, cyst and genetic deficiency of FSH and LH secretion.

2. *Oestrogen excess.* Endogenous excess such as from hepatic cirrhosis, adrenal tumour, Sertoli and Leydig cell tumour; or exogenous excess such as in the treatment of carcinoma of the prostate.

3. *Glucocorticoid excess.* Endogenous excess may occur in Cushing's syndrome while exogenous excess may occur in the treatment of ulcerative colitis, bronchial asthma, rheumatoid arthritis etc.

Other endocrine disorders. Hypothyroidism and diabetes mellitus are associated with hypospermatogenesis.

B. Testicular causes:

1. Agonadism i.e. total absence of the testes.
2. Cryptorchidism or undescended testis described above.
3. Maturation arrest i.e. failure of spermatogenesis beyond one of the immature stages.
4. Hypospermatogenesis i.e. presence of all the maturation stages of spermatogenesis but in decreased number.
5. Sertoli cell-only syndrome. Congenital or acquired absence of all germ cells so that the seminiferous tubules are lined by Sertoli cells only.
6. Klinefelter's syndrome. An XXY intersexuality characterised by primary hypogonadism, azoospermia, gynaecomastia, eunuchoid built and subnormal intelligence.
7. Mumps orchitis occurring as a complication of parotitis.
8. Irradiation damage resulting in permanent germ cell destruction.

C. **Post-testicular causes:**

1. Congenital block e.g. absence or atresia of vas deferens.
2. Acquired block e.g. due to gonorrhoea and surgical intervention.
3. Impaired sperm motility in the presence of normal sperm counts e.g. immotile cilia syndrome.

INFLAMMATIONS

Inflammation of the testis is termed as orchitis and of epididymis as epididymitis; the latter being more common. A combination epididymo-orchitis may also occur. A few important types are described below.

NON-SPECIFIC EPIDIDYMITIS AND ORCHITIS

Nonspecific epididymitis and orchitis, or their combination, may be acute or chronic. The common routes of spread of infection are via the vas deferens, or via lymphatic and haematogenous routes. Most frequently, the infection is caused by urethritis, cystitis, prostatitis and seminal vesiculitis. Other causes are mumps, smallpox, dengue fever, influenza, pneumonia and filariasis. The common infecting organisms in sexually-active men under 35 years of age are Neisseria gonorrhoeae and Chlamydia trachomatis, whereas in older individuals the common organisms are urinary tract pathogens like Escherichia coli and Pseudomonas.

Pathologic changes. Grossly, in acute stage the testicle is firm, tense, swollen and congested. There may be multiple abscesses, especially in gonorrheal infection. In chronic cases, there is usually variable degree of atrophy and fibrosis. Histologically, acute orchitis and epididymitis are characterised by congestion, oedema and diffuse infiltration by neutrophils, lymphocytes, plasma cells and macrophages or formation of neutrophilic abscesses. Acute inflammation may resolve, or may progress to chronic form. In chronic epididymoorchitis, there is focal or diffuse chronic inflammation, disappearance of seminiferous tubules, fibrous scarring and destruction of interstitial Leydig cells. Such cases usually result in permanent sterility.

GRANULOMATOUS (AUTOIMMUNE) ORCHITIS

Non-tuberculous granulomatous orchitis is a peculiar type of unilateral, painless testicular enlargement in middle-aged men that may resemble a testicular tumour clinically. The exact etiology and pathogenesis of the condition are not known though an autoimmune basis is suspected.

Pathologic changes. Grossly, the affected testis is enlarged with thickened tunica. Cut section of the testicle is greyish-white to tan-brown. Histologically, there are circumscribed non-caseating granulomas lying within the seminiferous tubules. These granulomas are composed of epithelioid cells, lymphocytes, plasma cells, some neutrophils and multinucleate giant cells. The origin of the epithelioid cells is from Sertoli cells lining the tubules. The tubules show peritubular fibrosis which merges into the interstitial tissue that is infiltrated by lymphocytes and plasma cells.

TUBERCULOUS EPIDIDYMO-ORCHITIS

Tuberculosis invariably begins in the epididymis and spreads to involve the testis. Tuberculous epididymo-orchitis is generally secondary tuberculosis from elsewhere in the body. It may occur either by direct spread from genitourinary tuberculosis such as tuberculous seminal vesiculitis, prostatitis and renal tuberculosis, or may reach by haematogenous spread of in-

fection such as from tuberculosis of the lungs. Primary genital tuberculosis may occur rarely.

Pathologic changes. Macroscopically, discrete, yellowish, caseous necrotic areas are seen. Microscopically, numerous tubercles which may coalesce to form large caseous mass are seen. Characteristics of typical tubercles such as epithelioid cells, peripheral mantle of lymphocytes, occasional multinucleate giant cells and central areas of caseation necrosis are seen. Numerous acid-fast bacilli can be demonstrated by Ziehl-Neelsen staining. The lesions produce extensive destruction of the epididymis and may form chronic discharging sinuses on the scrotal skin. In late stage, the lesions heal by fibrous scarring and may undergo calcification.

SPERMATIC GRANULOMA

Spermatic granuloma is the term used for development of inflammatory lesions due to invasion of spermatozoa into the stroma. Spermatic granuloma may develop due to trauma, inflammation and loss of ligature following vasectomy.

Pathologic changes. Grossly, the sperm granuloma is a small nodule, 3 mm to 3 cm in diameter, firm, white to yellowish-brown. Histologically, it consists of a granuloma composed of histiocytes, epithelioid cells, lymphocytes and some neutrophils. Characteristically, the centre of spermatic granuloma contains spermatozoa and necrotic debris. The late lesions have fibroblastic proliferation at the periphery and hyalinisation.

ELEPHANTIASIS

Elephantiasis is enormous thickening of the scrotal skin resembling the elephant's hide and results in enlargement of the scrotum. The condition results from filariasis in which the adult worm lives in the lymphatics, while the larvae travel in the blood. The most important variety of filaria is Wuchereria bancrofti. The condition is common in all tropical countries. The vector is generally the Culex mosquito. The patients may remain asymptomatic or may manifest with fever, local pain, swelling, rash, tender lymphadenopathy and blood eosinophilia. An asthma-like respiratory complaint may develop in some cases.

Pathologic changes. Grossly, the affected leg and scrotum are enormously thickened with enlargement of regional lymph nodes. The affected area of skin may show dilated dermal lymphatics and varicosities.

Histologically, the changes begin with lymphatic obstruction by the adult worms. The worm in alive, dead or calcified form may be found in the dilated lymphatics or in the lymph nodes. Dead or calcified worm in lymphatics is usually followed by lymphangitis with intense infiltration by eosin-

ophils. Sometimes, granulomatous reaction may be evident. In advanced cases, chronic lymphoedema with tough subcutaneous fibrosis and epidermal hyperkeratosis develops which is termed elephantiasis.

MISCELLANEOUS LESIONS

TORSION OF TESTIS

Torsion of the testicle may occur either in a fully-descended testis or in an undescended testis. The latter is more common and more severe. It results from sudden cessation of venous drainage and arterial supply to the testis, usually following sudden muscular effort or physical trauma. Torsion is common in boys and young men.

Pathologic changes. The pathologic changes vary depending upon the duration and severity of vascular occlusion. There may be coagulative necrosis of the testis and epididymis, or there may be haemorrhagic infarction. The inflammatory reaction is generally not so pronounced.

VARICOCELE

Varicocele is the dilatation, elongation and tortuosity of the veins of the pampiniform plexus in the spermatic cord. It is of 2 types: primary (idiopathic) and secondary.

- Primary or idiopathic form is more frequent and is common in young unmarried men. It is nearly always on the left side as the loaded rectum presses the left vein. Besides, the left spermatic vein enters the renal vein at right angles while the right spermatic vein enters the vena cava obliquely.
- Secondary form occurs due to pressure on the spermatic vein by enlarged liver, spleen or kidney. It is commoner in middle-aged people.

HYDROCELE

A hydrocele is abnormal collection of serous fluid in the tunica vaginalis. It may be acute or chronic, congenital or acquired. The usual causes are trauma, systemic oedema such as in cardiac failure and renal disease, and as a complication of gonorrhoea, syphilis and tuberculosis.

The hydrocele fluid is generally clear and straw-coloured but may be slightly turbid or haemorrhagic. The hydrocele sac may have single loculus or may have multiple loculi. The wall of the hydrocele sac is composed of fibrous tissue infiltrated with lymphocytes and plasma cells.

HAEMATOCELE

Haematocele is haemorrhage into the sac of the tunica vaginalis. It may result from direct trauma, from injury to a vein by the needle, or from haemorrhagic diseases. In recent haematocele, the blood coagulates and the wall is

coated with ragged deposits of fibrin. In longstanding cases, the tunica vaginalis is thickened with dense fibrous tissue and occasionally may get partly calcified.

TESTICULAR TUMOURS

Testicular tumours are the cause of about 1% of all cancer deaths. They are more frequent in white male population but are less common in Africans and Asians. They have trimodal age distribution – a peak during infancy, another during late adolescence and early adulthood, and a third peak after 60 years of age.

Classification. The most widely accepted classification is the histogenetic classification proposed by the World Health Organisation. Based on this, all testicular tumours are divided into: germ cell tumours, sex-cord stromal tumours and mixed forms. Vast majority of the testicular tumours (95%) arise from germ cells or their precursors in the seminiferous tubules, while less than 5% originate from sex cord-stromal components of the testis.

Etiologic factors. The cause of testicular germ cell tumours is unknown, but a few factors have been implicated. These are as under:

1. *Cryptorchidism.* The probability of a germ cell tumour developing in an undescended testis is 35 times greater than in a normally-descended testis. About 10% of testicular germ cell tumours are associated with cryptorchidism. The high incidence is attributed to higher temperature to which the undescended testis in the groin or abdomen is exposed. Intraabdominal testis is at greater risk than the inguinal testis. There is increased incidence of tumour in the contralateral normally-descended testis. There are no data to confirm or deny whether surgical repositioning or orchiopexy of a cryptorchid testis alters the incidence of testicular tumour. However, surgical correction is still helpful since it is easier to detect the tumour in scrotal testis than in an abdominal or inguinal testis.

2. *Other developmental disorders.* Dysgenetic gonads associated with endocrine abnormalities such as androgen insensitivity syndrome have higher incidence of development of germ cell tumours.

3. *Genetic factors.* Genetic factors play a role in the development of germ cell tumours supported by the observation of high incidence in other family members, twins and in white male populations while blacks in Africa have a very low incidence. However, no definite pattern of inheritance has been recognised.

4. *Other factors.* A few less common factors include the following:

i) Orchitis. A history of mumps or other forms of orchitis may be given by the patient with germ cell tumour.

ii) Trauma. Many patients give a history of trauma prior to the development of the tumour but it is not certain how trauma initiates the neoplastic process.

iii) Carcinogens. A number of carcinogens such as use of certain drugs (e.g. LSD, hormonal therapy for sterility, copper, zinc etc), exposure to radiation and endocrine abnormalities may play a role in the development of testicular tumours.

Histogenesis. Pathogenesis of testicular tumours remains controversial except that vast majority of these tumours originate from germ cells. Based on current concepts on histogenesis of testicular tumours, following agreements and disagreements have emerged:

1. Developmental disorders: Disorders such as cryptorchidism, gonadal dysgenesis and androgen insensitivity syndrome are high risk factors for development of testicular germ cell tumours. These observations point to developmental defect in gonadogenesis. In more than 90% of testicular germ cell tumours irrespective of histologic type (as also ovarian germ cell tumours), anisochromosome of short arm of chromosome 12, abbreviated as i (12p), is found suggesting a common molecular pathogenesis of all germ cell tumours.

2. CIS: A preinvasive stage of carcinoma in situ (CIS) termed intratubular germ cell neoplasia generally precedes the development of most of the invasive testicular germ cell tumours in adults. CIS originates from spermatogenic elements. Areas of CIS are found in seminiferous tubules adjacent to most seminomas, embryonal carcinomas and other mixed germ cell tumours. However, CIS is not found in seminiferous tubules adjoining yolksac carcinoma of childhood, benign teratoma in children and adolescents, and spermatocytic seminoma indicating different pathogenetic mechanisms.

3. ―Three hit‖ process: Germ cells in seminiferous tubules undergo activation ('first hit') before undergoing malignant transformation confined to seminiferous tubules (CIS) ('second hit') and eventually into invasive stage by some epigenetic phenomena ('third hit'). Though this sequential tumorigenesis explains the development of seminomatous tumours, it is yet not clear whether non-seminomatous germ cell tumours develop directly or through intermediate stage.

Clinical features and diagnosis. The usual presenting clinical symptoms of testicular tumours are gradual gonadal enlargement and a dragging sensation in the testis. Metastatic involvement may produce secondary symptoms such as pain, lymphadenopathy, haemoptysis and urinary obstruction.

Spread. Since testicular germ cell tumours originate from potipotent germ cells, it is not unusual to find metastases of histologic types different from the primary growth. Testicular tumours may spread by both lymphatic and haematogenous routes:

- Lymphatic spread occurs to retroperitoneal paraaortic lymph nodes, mediastinal lymph nodes and supraclavicular lymph nodes.
- Haematogenous spread primarily occurs to the lungs, liver, brain and bones.

Tumour markers. Germ cell tumours of the testis secrete polypeptide hormones and certain enzymes which can be detected in the blood. Two tumour markers widely used in the diagnosis, staging and monitoring the follow-up of patients with testicular tumours are: human chorionic gonadotropin (HCG) and alphafoetoprotein (AFP). In addition, carcinoembryonic antigen (CEA), human placental lactogen (HPL), placental alkaline phosphatase, testosterone, oestrogen and luteinising hormone may also be elevated.

- HCG is synthesised by placental syncytiotrophoblast such as in various non-seminomatous germ cell tumours of the testis (e.g. in choriocarcinoma, yolk sactumour and embryonal carcinoma). However, ectopic HCG production may occur in a variety of non-testicular non-germ cell tumours as well.
- AFP is normally synthesised by the foetal liver cells, yolk sac and foetal gut. Its levels are elevated in testicular tumours associated with yolk sac components. However, elevated serum AFP levels are also found in liver cell carcinoma.

Prognosis for selecting post-orchiectomy treatment (radiation, surgery, chemotherapy or all the three) and for monitoring prognosis, 3 clinical stages are defined:

Stage I: tumour confined to the testis.

Stage II: distant spread confined to retroperitoneal lymph nodes below the diaphragm.

Stage III: distant metastases above the diaphragm.

Seminomas tend to remain localised to the testis (stage I) while non-seminomatous germ cell tumours more often present with advanced clinical disease (stage II and III). Seminomas are extremely radiosensitive while non-seminomatous germ cell tumours are radio-resistant. In general, seminomas have a better prognosis with 90% cure rate while the non-seminomatous tumours behave in a more aggressive manner and have poor prognosis.

GERMCELLTUMOURS

Germ cell tumours comprise approximately 95% of all testicular tumours and are more frequent before the age of 45 years. Testicular germ cell tumours are almost always malignant. Nearly half of them contain more than one histologic type. Germ cell tumours are also found in the ovary, retroperitoneum and mediastinum.

INTRATUBULAR GERM CELL NEOPLASIA

The term intratubular germ cell neoplasia (ITGCN) is used to describe the preinvasive stage of germ cell tumours, notably intratubular seminoma

and intratubular embryonal carcinoma. Others have used carcinoma in situ (CIS) stage of germ cell tumours as synonymous term.

Histologically, the malignant atypical tumour cells are restricted to the seminiferous tubules without evident invasion into the interstitium.

SEMINOMA

Seminoma is the commonest malignant tumour of the testis and corresponds to dysgerminoma in the female. It constitutes about 45% of all germ cell tumours, and in another 15% comprises the major component of mixed germ cell tumour. The tumour has a peak incidence in the 4th decade of life and is rare before puberty. Undescended testis harbours seminoma more frequently as compared to other germ cell tumours. Only about 10% pure seminomas are associated with elevated AFP or HCG levels in serum.

Pathologic changes. Grossly, the involved testis is enlarged up to 10 times its normal size but tends to maintain its normal contour since the tumour rarely invades the tunica. The larger tumour replaces the entire testis, whereas the smaller tumour appears as circumscribed mass in the testis. Cut section of the affected testis shows homogeneous, grey-white lobulated appearance. Necrosis and haemorrhage in the tumour are rare. Microscopically, the tumour has the following characteristics;

1. *Tumour cells.* The seminoma cells generally lie in cords, sheets or columns forming lobules. Typically, in a classic seminoma, the tumour cells are fairlyuniform in size with clear cytoplasm and well-defined cell borders. The cytoplasm contains variable amount of glycogen that stains positively with PAS reaction. The nuclei are centrally located, large, hyperchromatic and usually contain 1-2 prominent nucleoli. Tumour giant cells may be present. Mitotic figures are infrequent. However, about 10% of seminomas have increased mitotic activity and have aggressive behaviour and are referred to as anaplastic seminomas.

2. *Stroma.* The stroma of seminoma is delicate fibrous tissue which divides the tumour into lobules. The stroma shows a characteristic lymphocytic infiltration, indicative of immunologic response of the host to the tumour. About 20% of the tumours show granulomatous reaction in the stroma.

The prognosis of seminoma is better than other germ cell tumours. The tumour is highly radiosensitive.

SPERMATOCYTIC SEMINOMA

Spermatocytic seminoma is both clinically and morphologically a distinctive tumour from classic seminoma and is, therefore, classified separately in the WHO classification. It is an uncommon tumour having an incidence of about 5% of all germ cell tumours. Spermatocytic seminoma usually occurs in older patients, generally in 6th decade of life. The tumour is bilateral in 10% of patients.

Pathologic changes. Grossly, Spermatocytic seminoma is homogeneous, larger, softer and more yellowish and gelatinous than the classic seminoma. Histologically, the distinctive features are as under:

1. *Tumour cells.* The tumour cells vary considerably in size from lymphocyte-like to huge mononucleate or multinucleate giant cells. Majority of the tumour cells are, however, of intermediate size. The cells have eosinophilic cytoplasm devoid of glycogen. The nuclei of intermediate and large cells have filamentous or spireme pattern. Mitoses are often frequent.

2. *Stroma.* The stroma lacks lymphocytic and granulomatous reaction seen in classic seminoma.

The prognosis of spermatocytic seminoma is excellent since the tumour is slow-growing and rarely metastasises. The tumour is believed to be radiosensitive.

EMBRYONAL CARCINOMA

Pure embryonal carcinoma constitutes 30% of germ cell tumours but areas of embryonal carcinoma are present in 40% of germ cell tumours. These tumours are more common in 2nd to 3rd decades of life. About 90% cases are associated with elevation of AFP or HCG or both. They are more aggressive than the seminomas.

Pathologic changes. Grossly, embryonal carcinoma is usually a small tumour in the testis. It distorts the contour of the testis as it frequently invades the tunica and the epididymis. The cut surface of the tumour is grey-white, soft with areas of haemorrhages and necrosis. Microscopically, the following features are seen:

1. The tumour cells are arranged in a variety of patterns – glandular, tubular, papillary and solid.

2. The tumour cells are highly anaplastic carcinoma tous cells having large size, indistinct cell borders, amphophilic cytoplasm and prominent hyperchromatic nuclei showing considerable variation in nuclear size. Mitotic figures and tumour giant cells are frequently present. Haemorrhage and necrosis are common.

• 3. The stroma is not as distinct as in seminoma and may contain variable amount of primitive mesenchyme.

Embryonal carcinoma is more aggressive and less radiosensitive than seminoma. Chemotherapy is considered more effective in treating this tumour.

YOLK SAC TUMOUR

(Synonyms: Endodermal Sinus Tumour, Orchioblastoma, Infantile Embryonal Carcinoma) is the most common testicular tumour of infants and young children up to the age of 4 years. In adults, however, yolk sac tumour in pure form is rare but may be present as the major component in 40% of germ cell tumours. AFP levels are elevated in 100% cases of yolk sac tumours.

Pathologic changes. Grossly, the tumour is generally soft, yellow-white, mucoid with areas of necrosis and haemorrhages.

Microscopically, yolk sac rumour has the following features:

1. The rumour cells form a variety of patterns - loose reticular network, papillary, tubular and solid arrangement.
2. The tumour cells are flattened to cuboid epithelial cells with clear vacuolated cytoplasm.
3. The rumour cells may form distinctive perivascular structures resembling the yolk sac or endodermal sinuses of the rat placenta called Schiller-Duval bodies.

There may be presence of both intracellular and extracellular PAS-positive hyaline globules, many of which contain AFP.

POLYEMBRYOMA

Polyembryoma is defined as a tumour composed predominantly of embryoid bodies. Embryoid bodies are structures containing a disc and cavities surrounded by loose mesenchyme simulating an embryo of about 2 weeks gestation. Polyembryoma is extremely rare but embryoid bodies may be present with embryonal carcinoma and teratoma.

CHORIOCARCINOMA

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

However, pure form is extremely rare and occurs more often in combination with other germ cell tumours. The patients are generally in their 2nd decade of life. The primary tumour is usually small and the patient may manifest initially with symptoms of metastasis. The serum and urinary levels of HCG are greatly elevated in 100% cases.

Pathologic changes. Grossly, the tumour is usually small and may appear as a soft, haemorrhagic and necrotic mass.

Microscopically, the characteristic feature is the identification of intimately related syncytiotrophoblast and cytotrophoblast without formation of definite placental-type villi.

- Syncytiotrophoblastic cells are large with many irregular and bizarre nuclei and abundant eosinophilic vacuolated cytoplasm which stains positively for HCG. These cells often surround masses of cytotrophoblastic cells.
- Cytotrophoblastic cells are polyhedral cells which are more regular and have clear or eosinophilic cytoplasm with hyperchromatic nuclei.

TERATOMA

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

constitute about 40% of testicular tumours in infants, whereas in adults they comprise 5% of all germ cell tumours. However, teratomas are found in combination with other germ cell tumours (most commonly with embryonal carcinoma) in about 45% of mixed germ cell tumours. About half the teratomas have elevated HCG or AFP levels or both.

Pathologic changes. Testicular teratomas are classified into 3 types:

1. Mature (differentiated) teratoma
2. Immature teratoma
3. Teratoma with malignant transformation. Grossly, most teratomas are large, grey-white masses enlarging the involved testis. Cut surface shows characteristic variegated appearance – grey-whitesolid areas, cystic and honey-combed areas, and foci of cartilage and bone. Dermoid tumours commonly seen in the ovaries are rare in testicular teratomas.

Microscopically, the three categories of teratomas show different appearances:

1. Mature (differentiated) teratoma. Mature teratoma is composed of disorderly mixture of a variety of well-differentiated structures such as cartilage, smooth muscle, intestinal and respiratory epithelium, mucous glands, cysts lined by squamous and transitional epithelium, neural tissue, fat and bone. This type of mature or differentiated teratoma is the most common, seen more frequently in infants and children and has favourable prognosis. But similar mature and benign-appearing rumour in adults is invariably associated with small hidden foci of immature elements so that their clinical course in adults is unpredictable. It is believed that all testicular teratomas in the adults are malignant.

As mentioned above, dermoid cysts similar to those of the ovary are rare in the testis.

2. Immature teratoma. Immature teratoma is composed of incompletely differentiated and primitive or embryonic tissues along with some mature elements. Primitive or embryonic tissue commonly present are poorly-formed cartilage, mesenchyme, neural tissues, abortive eye, intestinal and respiratory tissue elements etc. Mitoses are usually frequent.

3. Teratoma with malignant transformation. This is an extremely rare form of teratoma in which one or more of the tissue elements show malignant transformation. Such malignant change resembles morphologically with typical malignancies in other organs and tissues and commonly includes rhabdomyosarcoma, squamous cell carcinoma and adenocarcinoma.

MIXED GERM CELL TUMOURS

About 60% of germ cell rumours have more than one of the above histologic types (except spermatocytic seminoma) and are called mixed germ cell tumours. The clinical behaviour of these tumours is worsened by inclu-

sion of more aggressive tumour component in a less malignant tumour. Interestingly, metastases of the mixed germ cell tumours may not exactly reproduce the histologic types present in the primary tumour.

The most common combinations of mixed germ cell tumours are:

1. Teratoma, embryonal carcinoma, yolk sac tumour and syncytiotrophoblast;
2. Embryonal carcinoma and teratoma (teratocarcinoma); and
3. Seminoma and embryonal carcinoma.

SEX CORD-STROMALTUMOURS

Tumours arising from specialised gonadal stroma are classified on the basis of histogenesis. The primitive mesenchyme which forms the specialised stroma of gonads in either sex gives rise to theca, granulosa and lutein cells in the female, and Sertoli and interstitial Leydig cells in the male. Since the cell of origin of primitive mesenchyme is identical, Sertoli and interstitial Leydig cell tumours may occur in the ovaries (in addition to theca cell, granulosa cell and lutein cell tumours). Likewise, the latter three tumours may occur in the testis (in addition to Sertoli cell and Leydig cell tumours). All these tumours secrete various hormones. The biologic behaviour of these tumours generally cannot be determined on histological grounds alone.

LEYDIG (INTERSTITIAL) CELL TUMOUR

Leydig cell tumours are quite uncommon. They may occur at any age but are more frequent in the age group of 20 to 50 years. Characteristically, these cells secrete androgen, or both androgen and oestrogen, and rarely corticosteroids. Bilateral tumours may occur typically in congenital adrenogenital syndrome.

Pathologic changes. Grossly, the tumour appears as a small, well-demarcated and lobulated nodule. Cut surface is homogeneously yellowish or brown.

Histologically, the tumour is composed of sheets and cords of normal-looking Leydig cells. These cells contain abundant eosinophilic cytoplasm and Reinke's crystals and a small central nucleus.

Most of Leydig cell tumours are benign. Only about 10% may invade and metastasise.

SERTOLI CELL TUMOURS (ANDROBLASTOMA)

Sertoli cell tumours correspond to arrhenoblastoma of the ovary. They may occur at all ages but are more frequent in infants and children. These tumours may elaborate oestrogen or androgen and may account for gynaecomastia in an adult, or precocious sexual development in a child.

Pathologic changes. Grossly, the tumour is fairly large, firm, round, and well circumscribed. Cut surface of the tumour is yellowish or yellow-

grey. Microscopically, Sertoli cell tumour is composed of benign Sertoli cells arranged in well-defined tubules.

Majority of Sertoli cell tumours are benign but about 10% may metastasise to regional lymph nodes.

GRANULOSA CELL TUMOUR

This is an extremely rare tumour in the testis and resembles morphologically with its ovarian counterpart.

MIXED GERM CELL-SEX CORD STROMAL TUMOURS

An example of combination of both germ cells and sex cord stromal components is gonadoblastoma.

GONADOBLASTOMA

Dysgenetic gonads and undescended testis are predisposed to develop such combined proliferations of germ cells and sex cord-stromal elements. The patients are commonly intersexuals, particularly phenotypic females. Most of the gonadoblastomas secrete androgen so as to produce virilisation in female phenotype. A few, however, secrete oestrogen.

Pathologic changes. Grossly, the tumour is of variable size, yellowish-white and soft. Microscopically, gonadoblastoma is composed of 2 principal cell types – large germ cells resembling seminoma cells, and small cells resembling immature Sertoli, Leydig and granulosa cells. Call-Exner bodies of a granulosa cell tumour may be present.

Prognosis largely depends upon the malignant potential of the type of germ cell components included.

OTHER TUMOURS

MALIGNANT LYMPHOMA

Malignant lymphomas comprises 5% of testicular malignancies and is the most common testicular tumour in the elderly. Bilaterality is seen in half the cases. Most common are large cell non-Hodgkin's lymphoma of B cell type.

RARE TUMOURS

In addition to the testicular tumours described above, some other uncommon tumours in this location include: plasmacytoma, leukaemic infiltration, carcinoid tumour, haemangioma, primary sarcomas and metastatic tumours.

PENIS

CONGENITAL ANOMALIES

Some of the clinically significant congenital anomalies of the penis are phimosis, hypospadias and epispadias.

PHIMOSIS is a condition in which the prepuce is too small to permit its normal retraction behind the glans. It may be congenital or acquired. Congenital

phimosis is a developmental anomaly whereas acquired phimosis may result from inflammation, trauma or oedema leading to narrowing of preputial opening. In either case, phimosis interferes with cleanliness and predisposes to the development of secondary infection, preputial calculi and squamous cell carcinoma.

PARAPHIMOSIS is a condition in which the phimotic prepuce is forcibly retracted resulting in constriction over the glans penis and subsequent swelling.

HYPOSPADIA is a developmental defect of the urethra in which the urethral meatus fails to reach the end of the penis, but instead, opens on the ventral surface of the penis. Similar developmental defect with resultant urethral opening on the dorsal surface of the penis is termed epispadias. Hypospadias and epispadias may cause urethral constriction with consequent infection and may also interfere with normal ejaculation and insemination. Both these urethral anomalies are more frequently associated with cryptorchidism.

INFLAMMATIONS

Glans and prepuce are frequently involved in inflammation in a number of specific and non-specific conditions. The specific inflammations include various sexually-transmitted diseases such as hard chancre in syphilis, chancroid caused by Haemophilus ducreyi, gonorrhoea caused by gonococci, herpes progenitalis, granuloma inguinale (donovanosis), and lymphopathia venereum caused by Chlamydia trachomatis. Non-specific inflammations are designated as balanoposthitis.

BALANOPOSTHITIS is the term used for nonspecific inflammation of the inner surface of the prepuce (balanitis) and adjacent surface of the glans (posthitis). It is caused by a variety of microorganisms such as staphylococci, streptococci, coliform bacilli and gonococci. Balanoposthitis usually results from lack of cleanliness resulting in accumulation of secretions and smegma. It is a common accompaniment of phimosis. The type of inflammation may be acute or chronic, sometimes with ulceration on the mucosal surface of the glans.

BALANITIS XEROTICA OBLITERANS is a white atrophic lesion on the glans penis and the prepuce and is a counterpart of the lichen sclerosus et atrophicus in the vulva.

TUMOURS

Benign and malignant tumours as well as certain premalignant lesions may occur on the penis. These are discussed below:

BENIGN TUMOURS

CONDYLOMA ACUMINATUM

Condyloma acuminatum or venereal wart is a benign tumour caused by human papilloma virus (HPV) types 6 and 11. The tumour may occur singly,

or there may be conglomerated papillomas. A more extensive, solitary, exophytic and cauliflower-like warty mass is termed giant condyloma or Buschke-Lowenstein tumour or verrucous carcinoma.

Pathologic changes. The condyloma is commonly located on the coronal sulcus on the penis or the perineal area.

Grossly, the tumour consists of solitary or multiple, warty, cauliflower-shaped lesions of variable size with exophytic growth pattern. Histologically, the lesions are essentially like common warts (verruca vulgaris). The features include formation of papillary villi composed of connective tissue stroma and covered by squamous epithelium which shows hyperkeratosis, parakeratosis, and hyperplasia of prickle cell layer. Many of the prickle cells show clear vacuolisation of the cytoplasm (koilocytosis) indicative of HPV infection.

Giant condyloma shows upward as well as downward growth of the tumour but is otherwise histologically identical to condyloma acuminatum. Though histologically benign, clinically the giant condyloma is associated with recurrences and behaves as intermediate between truly benign condyloma acuminatum and squamous cell carcinoma.

PREMALIGNANT LESIONS (CARCINOMA IN SITU)

In the region of external male genitalia, three lesions display cytological changes of malignancy confined to epithelial layers only without evidence of invasion. These conditions are: Bowen's disease, erythroplasia of Queyrat and bowenoid papulosis.

BOWEN'S DISEASE

Bowen's disease is located on the shaft of the penis and the scrotum besides the sun-exposed areas of the skin.

Grossly, it appears as a solitary, circumscribed plaque lesion with ulceration.

Histologically, the changes are superficial to the dermo-epidermal border. The epithelial cells of the epidermis show hyperplasia, hyperkeratosis, parakeratosis and scattered bizarre dyskeratotic cells.

A fair proportion of cases of Bowen's disease are associated with internal visceral cancers.

ERYTHROPLASIA OF QUEyRAT

It appears on the penile mucosa.

Grossly, the lesions are pink, shiny and velvety soft. Histologically, the thickened and acanthotic epidermis shows variable degree of dysplasia.

Unlike Bowen's disease, there is no relationship between erythroplasia of Queyrat and internal malignancy.

BOWENOID PAPULOSIS

It appears on the penile shaft and adjacent genital skin.

Grossly, they are solitary or multiple, shiny, red-brown papular lesions.

Histologically, there is orderly maturation of epithelial cells in hyperplastic epidermis with scattered hyperchromatic nuclei and dysplastic cells.

MALIGNANT TUMOURS SQUAMOUS CELL CARCINOMA

The incidence of penile carcinoma shows wide variation in different populations. In the United States, the overall incidence of penile cancer is less than 2% of all cancers but it is 3-4 times more common in blacks than in whites. In China, its incidence is about 18%. Carcinoma of the penis is quite rare in Jews and Muslims who have a ritual of circumcision early in life. In India, cancer of the penis is rare in Muslims who practice circumcision as a rite in infancy, whereas Hindus who do not normally circumcise have higher incidence. Circumcision provides protection against penile cancer due to prevention of accumulation of smegma which is believed to be carcinogenic. The greatest incidence of penile cancer is between 45 and 60 years.

Pathologic changes. Grossly, the tumour is located, in decreasing frequency, on frenum, prepuce, glans and coronal sulcus. The tumour may be cauliflower-like and papillary, or flat and ulcerating.

Histologically, squamous cell carcinoma of both fungating and ulcerating type is generally well differentiated to moderately-differentiated type which resembles in morphology to similar cancer elsewhere in the body.

The tumour metastasises via lymphatics to regional lymph nodes. Visceral metastases by haematogenous route are uncommon and occur in advanced cases only.

PROSTATE

Prostate is involved in 3 important pathologic processes: prostatitis, nodular hyperplasia and carcinoma.

PROSTATITIS

Inflammation of the prostate i.e. prostatitis, may be acute, chronic and granulomatous types.

ACUTE PROSTATITIS

Acute focal or diffuse suppurative inflammation of the prostate is not uncommon. It occurs most commonly due to ascent of bacteria from the urethra, less often by descent from the upper urinary tract or bladder, and occasionally by lymphogenous or haematogenous spread from a distant focus of infection. The infection may occur spontaneously or may be a complication of urethral manipulation such as by catheterisation, cystoscopy, urethral dilatation and surgical procedures on the prostate. The common pathogens are those which cause UTI, most frequently E. coli, and others such as Klebsiel-

la, Proteus, Pseudomonas, Enterobacter, gonococci, staphylococci and streptococci. The diagnosis is made by culture of urine specimen.

Pathologic changes. Grossly, the prostate is enlarged, swollen and tense. Cut section shows multiple abscesses and foci of necrosis. Histologically, the prostatic acini are dilated and filled with neutrophilic exudate. There may be diffuse acute inflammatory infiltrate. Oedema, hyperaemia and foci of necrosis frequently accompany acute inflammatory involvement.

CHRONIC PROSTATITIS

Chronic Prostatitis is more common and foci of chronic inflammation are frequently present in the prostate of men above 40 years of age. Chronic prostatitis is usually asymptomatic but may cause allergic reactions, iritis, neuritis or arthritis.

Chronic prostatitis is of 2 types – bacterial and abacterial.

• Chronic bacterial prostatitis is caused in much the same way and by the same organisms as the acute prostatitis. It is generally a consequence of recurrent UTI. Diagnosis is made by detection of more than 10-12 leucocytes per high power field in expressed prostatic secretions, and by positive culture of urine specimen and prostatic secretions. This condition is more difficult to treat since antibiotics penetrate the prostate poorly.

• Chronic abacterial prostatitis is more common these days. There is no history of recurrent UTI and culture of urine and prostatic secretions is always negative, though leucocytosis is demonstrable in prostatic secretions. The pathogens implicated are Chlamydia trachomatis and Ureaplasma urealyticum.

Pathologic changes. Pathologic changes in both bacterial and abacterial prostatitis are similar. Grossly, the prostate may be enlarged, fibrosed and shrunken.

Histologically, the diagnosis of chronic prostatitis is made by foci of lymphocytes, plasma cells, macro-phages and neutrophils within the prostatic substance. Corpora amylacea, prostatic calculi and foci of squamous metaplasia in the prostatic acini may accompany inflammatory changes. Seminal vesicles are invariably involved.

GRANULOMATOUS PROSTATITIS

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

Pathologic changes. Grossly, the gland is firm to hard, giving the clinical impression of prostatic carcinoma on rectal examination. Histologically, the inflammatory reaction consists of macrophages, lymphocytes, plasma

cells and some multinucleate giant cells. The condition may be confused with tuberculous prostatitis.

NODULAR HYPERPLASIA

Non-neoplasric tumour-like enlargement of the prostate, commonly termed benign nodular hyperplasia (BNH) or benign enlargement of prostate (BEP), is a very common condition in men and considered by some as normal ageing process.

Etiology. The cause of BEP has not been fully established. However, a few etiologic factors such as endocrinologic, racial, inflammation and arteriosclerosis have been implicated but endocrine basis for hyperplasia has been more fully investigated and considered a strong possibility in its genesis. It has been found that both sexes elaborate androgen and oestrogen, though the level of androgen is high in males and that of oestrogen is high in females. With advancing age, there is decline in the level of androgen and a corresponding rise of oestrogen in the males. The periurethral inner prostate which is primarily involved in BEP is responsive to the rising level of oestrogen, whereas the outer prostate which is mainly involved in the carcinoma is responsive to androgen. A plausible hypothesis suggested is that there is synergistic stimulation of the prostate by both hormones – the oestrogen acting to sensitise the prostatic tissue to the growth promoting effect of dihydroxytestosterone derived from plasma testosterone.

Pathologic changes. Grossly, the enlarged prostate is nodular, smooth and firm and weighs 2-4 times its normal weight i.e. may weigh up to 40-80 gm. The appearance on cut section varies depending upon whether the hyperplasia is predominantly of the glandular or fibromuscular tissue. In primarily glandular BEP the tissue is yellow-pink, soft, honeycombed, and milky fluid exudes, whereas in mainly fibromuscular BEP the cut surface is firm, homogeneous and does not exude milky fluid. The hyperplastic nodule forms a mass mainly in the inner periurethral prostatic gland so that the surrounding prostatic tissue fonns a false capsule which enables the surgeon to enucleate the nodular masses. The left-over peripheral prostatic tissue may sometimes undergo recurrent nodbaiar enlargement or may develop carcinoma later. Histologically, in every case, there is hyperplasia of aii there tissue elements in varying proportions – glandular, fibrous and muscular:

• *Glandular hyperplasia* predominates in most cases and is identified by exaggerated intra-acinar papillary infoldings with delicate fibrovascular cores. The lining epithelium is two-layered: the inner tall columnar mucus-secreting with poorly-defined borders, and the outer cuboidal to flattened epithelium with basal nuclei.

• *Fibromuscular hyperplasia* when present as dominant component appears as aggregates of spindle cells forming an appearance akin to fibromyoma of the uterus.

In addition to glandular and/or fibromuscular hyperplasia, other histologic features frequently found include foci of lymphocytic aggregates, small areas of infarction, corpora amylacea and foci of squamous metaplasia.

Clinically, the symptomatic cases develop symptoms due to complications such as urethral obstruction and secondary effects on the bladder (e.g. hypertrophy, cystitis), ureter (e.g. hydroureter) and kidneys (e.g. hydronephrosis). The presenting features include frequency, nocturia, difficulty in micturition, pain, haematuria and sometimes, the patients present with acute retention of urine requiring immediate catheterisation.

CARCINOMA OF PROSTATE

Cancer of the prostate is the second most common form of cancer in males, followed in frequency by lung cancer. It is a disease of men above the age of 50 years and its prevalence increases with increasing age so that more than 50% of men 80 years old have asymptomatic (latent) carcinoma of the prostate. Many a times, carcinoma of the prostate is small and detected as microscopic foci in a prostate removed for BEP or found incidentally at autopsy. Thus, it is common to classify carcinoma of the prostate into the following 4 types:

1. Latent carcinoma. This is found unexpectedly as a small focus of carcinoma in the prostate during autopsy studies in men dying of other causes. Its incidence in autopsies has been variously reported as 25-35%.

2. Incidental carcinoma. About 15-20% of prostatectomies done for BEP reveal incidental carcinoma of the prostate.

3. Occult carcinoma. This is the type in which the patient has no symptoms of prostatic carcinoma but shows evidence of metastases on clinical examination and investigations.

4. Clinical carcinoma. Clinical prostatic carcinoma is the type detected by rectal examination and other investigations and confirmed by pathologic examination of biopsy of the prostate.

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

1. *Endocrinologic factors.* Androgens are considered essential for development and maintenance of prostatic epithelium. But how androgens are responsible for causing malignant transformation is not yet clear. However, the etiologic role of androgens is supported by the following indirect evidences:

i) Orchiectomy causes arrest of metastatic prostatic cancer disease (testis being the main source of testosterone).

ii) Administration of oestrogen causes regression of prostatic carcinoma.

iii) Cancer of the prostate is extremely rare in eunuchs and in patients with Klinefelter's syndrome.

iv) Cancer of the prostate begins at the stage of life when androgen levels are high. However, the cancer may remain latent with decline in androgen level with advancing age.

2. *Racial and geographic influences.* There are some racial and geographic differences in the incidence of prostatic cancer. It is uncommon in Japanese and Chinese, while the prevalence is high in Americans. American blacks have a markedly higher incidence as compared to whites.

3. *Environmental influences.* It is possible that some common, as yet unidentified, environmental factors and carcinogens may play a role in the evolution of prostatic cancer.

4. *Nodular hyperplasia.* Though nodular prostatic hyperplasia has been suggested by some as precursor for development of prostatic cancer, it is considered unlikely. Most prostatic cancers develop in the periphery of the gland while BEP occurs in the periurethral part of the gland. Any concomitant occurrence of the two diseases may be considered as aging process. Approximately 15-20% of nodular hyperplastic prostates harbour carcinoma.

5. *Genetic factors.* The possibility of genetic basis of prostatic cancer has been suggested by the observations of familial clustering and in first degree relatives. Recently prostatic cancer susceptibility gene has been identified in familial cases.

Histogenesis. Histogenesis of prostatic adenocarcinoma has been documented recently as arising from premalignant stage of prostatic intraepithelial neoplasia (PIN), PIN refers to multiple foci of cytologically atypical luminal cells overlying diminished number of basal cells in prostatic ducts and is a forerunner of invasive prostatic carcinoma. Based on cytologic atypia, PIN may be low grade to high grade. PIN of high grades progresses to prostatic adenocarcinoma.

Pathologic changes. *Grossly*, the prostate may be enlarged, normal in size or smaller than normal. In 95% of cases, prostatic carcinoma is located in the peripheral zone, especially in the posterior lobe. The malignant prostate is firm and fibrous. Cut section is homogeneous and contains irregular yellowish areas.

Microscopically, 4 histologic types are described— adenocarcinoma, transitional cell carcinoma, squamous cell carcinoma and undifferentiated carcinoma. However, adenocarcinoma is the most common type found in 96% of cases and is the one generally referred to as carcinoma of the prostate. The other three histologic types are rare and resemble in morphology with similar malignant tumours elsewhere in the body.

The histologic characteristics of adenocarcinoma of the prostate are as under:

1. *Architectural disturbance:* In contrast to convoluted appearance of the glands seen in normal and hyperplastic prostate, there is loss of intra-acinar papillary convolutions. The groups of acini are either closely packed in back-to-back arrangement without intervening stroma or are haphazardly distributed.

2. *Stroma:* Normally, fibromuscular sling surrounds the acini, whereas malignant acini have little or no stroma between them. The tumour cells may penetrate and replace the fibromuscular stroma.

3. *Gland pattern:* Most frequently, the glands in well-differentiated prostatic adenocarcinoma are small or medium-sized, lined by a single layer of cuboidal or low columnar cells. Moderately-differentiated rumours have cribriform or fenestrated glandular appearance. Poorly-differentiated tumours have little or no glandular arrangement but instead show solid or trabecular pattern.

4. *Tumour cells:* In many cases, the individual tumour cells in prostatic carcinoma do not show usual morphologic features of malignancy. The tumour cells may be clear, dark and eosinophilic cells. Clear cells have foamy cytoplasm, dark cells have homogeneous basophilic cytoplasm, and eosinophilic cells have granular cytoplasm. The cells may show varying degree of anaplasia and nuclear arypia but is generally slight.

5. *Invasion:* One of the important diagnostic features of malignancy in prostate is the early and frequent occurrence of invasion of intra-prostatk perineumi spaces. Lymphatic and vascular invasion may be present but are difficult to detect.

Spread. The tumour spreads within the gland by direct extension, and to distant sites by metastases.

Direct spread. Direct extension of the tumour occurs into the prostatic capsule and beyond. In late stage, the tumour may extend into the bladder neck, seminal vesicles, trigone and ureteral openings.

Metastases. Distant spread occurs by both lymphatic and haematogenous routes. The rich lymphatic network surrounding the prostate is the main mode of spread to the sacral, iliac and paraaortic lymph nodes. The earliest metastasis occur to the obturator lymph node. Haematogenous spread leads most often to osteoblastic osseous metastases, especially to pelvis, and lumbar spine; other sites are lungs, kidneys, breast and brain. The route of blood-borne metastases may be retrograde spread by prostatic venous plexus or via systemic circulation.

Clinical features. By the time symptoms appear, the carcinoma of prostate is usually palpable on rectal examination. In such symptomatic cases, clinical features are:

urinary obstruction with dysuria, frequency, retention of urine, haematuria, and in 10% of cases pain in the back due to skeletal metastases. Per-rectal examination shows a hard and nodular gland fixed to the surrounding tissues.

Clinical classification of carcinoma prostate takes into account the following:

- The tumour found incidentally or a clinically unsuspected cancer in prostate removed for benign disorder (Stage A).
- The rumour palpable by rectal digital examination but confined to the prostate (Stage B).
- The tumour has extended locally beyond the prostate into the surrounding tissues (Stage C).
- The rumour is associated with distant metastases (Stage D).

Such clinical staging has good correlation with histologic grading and, thus, has a prognostic significance. Gleason's microscopic grading system is based on the degree of glandular differentiation and the growth pattern of the tumour in relation to the stroma. These features are assessed by low-power examination of the prostatic tissue and is widely followed and preferred to other grading system. More recently TNM staging system has been proposed which is considered international standard for prostate cancer staging.

The diagnosis of prostatic carcinoma is made by cytologic, biochemical, radiologic, ultrasonographic and pathologic methods. Two tumour markers employed commonly for diagnosis and monitoring the prognosis of prostatic carcinoma are as under:

• Prostatic acid phosphatase (PAP) is secreted by prostatic epithelium. Elevation of serum level of PAP is found in cases of prostatic cancer which have extended beyond the capsule or have metastasised. A reading of 3-5 KA units (normal 1-3 KA units) is highly suspicious but above 5 KA units is diagnostic of prostatic carcinoma. PAP can also be demonstrated in the normal prostatic tissues.

• Prostate-specific antigen (PSA) can be detected by immunohistochemical method in the malignant prostatic epithelium as well as in the serum. PSA assay is also useful in deciding whether the metastasis originated from the prostate or not. PSA assay is also helpful in distinguishing high grade prostatic cancer from urothelial carcinoma, colonic carcinoma, lymphoma and prostatitis. PSA level is generally higher in low-grade tumours than in high-grade tumours.

FEMAIL REPRODUCTIVE SYSTEM

UTERINE CERVICAL ECTOPY

Uterine cervical ectopy is the occurrence of single-layered secreting columnar epithelium (which usually covers the cervical canal, i.e. the endocervix), beyond the external cervical orifice. Thus, the multilayered squamous epithelium typically found in the vagina and exocervix are replaced.

This condition has many designations in medical terminology: ectropion, erythroplakia, macula rubra and erosion (pseudoerosion).

Not all factors involved in the pathogenesis of cervical ectopy are known but there is an association with the action of estrogen. Ectopy is rare beyond the menopause and frequent at reproductive ages. It has higher prevalence during pregnancy and also among users of estrogen-based contraceptives.

The natural history of ectopy is well established. After its development, a process of metaplasia occurs in the columnar epithelium, known as squamous metaplasia.

There is a relationship between squamous metaplasia and induction of squamous cell carcinoma of the cervix. Cells undergoing metaplasia are more susceptible to carcinogens. Precancerous lesions often develop at the squamous-columnar junction, i.e. the area of transition between glandular and stratified epithelium, which is the location where metaplasia is most intense.

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

It also known as cervical dysplasia and cervical interstitial neoplasia, is the potentially premalignant transformation and abnormal growth (dysplasia) of squamous cells on the surface of the cervix.

The major cause of CIN is chronic infection of the cervix with the sexually transmitted human papillomavirus (HPV), especially the high-risk HPV types 16 or 18.

Depending on several factors and the location of the infection, CIN can start in any of the three stage, and can either progress, or regress.

CIN is classified in grades:

CIN 1 (Grade I) - The least risky type, represents only mild dysplasia, or abnormal cell growth. It is confined to the basal 1/3 of the epithelium. This usually corresponds to infection with HPV, and may be cleared by immune response, though it can take several years to clear.

CIN 2 (Grade II) - Moderate dysplasia confined to the basal 2/3 of the epithelium

CIN 3 (Grade III) - Severe dysplasia that spans more than 2/3 of the epithelium, and may involve the full thickness. This lesion may sometimes also be referred to as cervical carcinoma in situ.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia involves the proliferation of endometrial glands that results in a greater than normal gland-to-stroma ratio. This results in varying degrees of architectural complexity and cytologic atypia.

Like other hyperplastic disorders, endometrial hyperplasia initially represents a physiological response of endometrial tissue to the growth-promoting actions of estrogen. However, the gland-forming cells of a hyperplastic endometrium may also undergo changes over time which predispose them to cancerous transformation.

The classification below is the most commonly used system and is used by the World Health Organization (WHO) and the International Society of Gynecologic Pathologists since 1994. This system characterizes the glandular architectural pattern as simple or complex and describes the presence or absence of nuclear atypia.

- ✓ Simple hyperplasia - increased number of glands but regular glandular architecture,
- ✓ Complex hyperplasia - crowded irregular glands,
- ✓ Simple hyperplasia with atypia - simple hyperplasia with presence of cytologic atypia (prominent nucleoli and nuclear pleomorphism),
- ✓ Complex hyperplasia with atypia - complex hyperplasia with cytologic atypia.

Endometrial hyperplasia results from continuous estrogen stimulation that is unopposed by progesterone. This can be due to endogenous estrogen or exogenous estrogenic sources. Endogenous estrogen may be caused by chronic anovulation associated with polycystic ovary syndrome. Obesity also contributes to unopposed estrogen exposure due to chronic high levels of estradiol that result from aromatization of androgens in adipose tissue and conversion of androstenedione to estrone. Endometrial hyperplasia and cancer can also result from estradiol-secreting ovarian tumors such as granulosa cell tumors.

The most common clinical presentation of patients with endometrial hyperplasia is abnormal uterine bleeding, whether in the form of menorrhagia, metrorrhagia, or postmenopausal bleeding. It can be associated with uterine hemorrhage, requiring emergent medical or surgical interventions, loss of fertility, and blood transfusion therapy.

UTERINE CANCER

Uterine cancer is defined as any invasive neoplasm of the uterine corpus. Invasive neoplasms of the female pelvic organs account for almost 15% of all cancers in women. The most common of these malignancies is uterine cancer. Endometrial adenocarcinoma is the most common gynecologic malignancy. However, it has a favorable prognosis because the majority of patients present at an early stage, resulting in only 4% of cancer deaths in wom-

en. Uterine sarcomas comprise <9% of cancers of uterine corpus, however is associated with more aggressive behavior and a poorer prognosis.

Endometrioid adenocarcinoma can be due to excess estrogen from various sources, either exogenous or endogenous. Endogenous estrogen sources include obesity and polycystic ovary syndrome (PCOS) with anovulatory cycles, or estrogen-secreting tumors such as granulose cell tumors. Increasing body mass index has been associated with increasing risk of endometrial cancer.

Endometrial cancers are divided into 2 classes, each with differing pathophysiology and prognosis. More than 80% of endometrial carcinomas are type I and are due to unopposed estrogen stimulation, resulting in a low-grade histology. It is often found in association with atypical endometrial hyperplasia, which is thought to be a precursor lesion. Type II endometrial cancers are thought to be estrogen independent, occurring in older women, with high-grade histologies such as uterine papillary serous or clear cell.

Endometrial cancer may originate in a small area (e.g., within an endometrial polyp) or in a diffuse multifocal pattern. Early tumor growth is characterized by an exophytic and spreading pattern. This growth is characterized by friability and spontaneous bleeding, even at early stages. Later tumor growth is characterized by myometrial invasion and growth toward the cervix. Four routes of spread occur beyond the uterus:

- Direct/local spread accounts for most local extension beyond the uterus.
- Lymphatic spread accounts for spread to pelvic, para-aortic, and, rarely, inguinal lymph nodes.
- Hematologic spread is responsible for metastases to the lungs, liver, bone, and brain (rare).
- Peritoneal/transtubal spread results in intraperitoneal implants, particularly with uterine papillary serous carcinoma, similar to the pattern observed in ovarian cancer.

Endometrioid adenocarcinoma of the endometrium, the most common histology, is usually preceded by adenomatous hyperplasia with atypia. If left untreated, simple and complex endometrial hyperplasia with atypia progress to adenocarcinoma in 8% and 29% of cases, respectively. Without atypia, simple and complex hyperplasia progress to cancer in only 1% and 3% of cases, respectively.

Endometrial adenocarcinoma is histologically characterized by cribriform glands (or glandular crowding) with little, if any, stromal tissue between the glands. Nuclear atypia, variation in gland size, and increased mitoses are common in adenocarcinoma. Well-differentiated tumors may be confused with complex hyperplasia with atypia histologically. Likewise, poorly differ-

entiated tumors might be confused with sarcomas histologically. All papillary serous and clear cell histologies are considered grade 3. The differentiation of endometrial cancers is one of the most important prognostic factors. The degree of histologic differentiation of adenocarcinoma of the endometrium as defined by the International Federation of Gynecology and Obstetrics (FIGO) is as follows:

- FIGO grade 1 - 5% or less of solid/nonglandular areas
- FIGO grade 2 - 6-50% of solid/nonglandular areas
- FIGO grade 3 - More than 50% of solid/nonglandular areas

Histological variants. The most common histologic subtype of endometrial cancer is endometrioid adenocarcinoma, accounting for about 75-80% of endometrial cancers. Less common histologies include adenosquamous and mucinous.

Carcinosarcoma are typically comprised of a high grade epithelial carcinoma and stromal sarcoma. The sarcomatous portion of the tumor may exhibit an endometrial stromal sarcoma pattern, if differentiated. This tumor is characterized by early extrauterine spread and lymph node metastases.

Endometrial Stromal Sarcomas (ESS) are a type of uterine cancer arising from the uterine mesenchymal tissue. ESS can be divided into 2 categories: low-grade ESS (LGESS) and high-grade (HGESS) or undifferentiated ESS.

BENIGN BREAST LESIONS

Fibrocystic breasts or fibrocystic breast disease or fibrocystic breast condition commonly referred to as "FBC" is a condition of breast tissue affecting an estimated 30-60% of women and at least 50% of women of childbearing age. It is characterized by noncancerous breast lumps which can sometimes cause discomfort, often periodically related to hormonal influences from the menstrual cycle.

In ICD-10 the condition is called *diffuse cystic mastopathy*, or, if there is epithelial proliferation, *fibrosclerosis of breast*. Other names for this condition include *chronic cystic mastitis*, *fibrocystic mastopathy* and *mammary dysplasia*.

The changes in fibrocystic breast disease are characterised by the appearance of fibrous tissue and a lumpy, cobblestone texture in the breasts. These lumps are smooth with defined edges, and are usually free-moving in regard to adjacent structures. The bumps can sometimes be obscured by irregularities in the breast that are associated with the condition. The lumps are most often found in the upper, outer sections of the breast (nearest to the armpit), but can be found throughout the breast.

Women with fibrocystic changes may experience a persistent or intermittent breast aching or breast tenderness related to periodic swelling. Breasts and nipples may be tender or itchy.

Symptoms follow a periodic trend tied closely to the menstrual cycle.

The exact mechanism of the condition is not fully understood, though it is known to be tied to hormone levels, as the condition usually subsides after menopause and is also related to the menstrual cycle. Post-menopausal women placed on hormone replacement therapy (HRT) have also reported symptoms of FBC indicating hormones may play a role.

Fibrocystic breast changes is a cumulative process, caused partly by the normal hormonal variation during a woman's monthly cycle. The most important of these hormones are estrogen, progesterone and prolactin.

These hormones directly affect the breast tissues by causing cells to grow and multiply. Many other hormones such as TSH, insulin, growth hormone and growth factors such as TGF-beta exert direct and indirect effects amplifying or regulating cell growth. Years of such fluctuations eventually produce small cysts and/or areas of dense or fibrotic tissue. Multiple small cysts and an increasing level of breast pain commonly develop when a woman hits her 30s. Larger cysts usually do not occur until after the age of 35.

Several variants of fibrocystic breast changes may be distinguished and these may have different causes and genetic predispostions. Adenosis involves abnormal count and density of lobular units, while other lesions appear to stem mainly from ductal epithelial origins. Histologically, a wide range of lesions are seen within fibrocystic changes, including epithelial metaplasia, hyperplasia of benign or usual type, adenosis, cyst formation, inflammatory changes, and fibrosis.

Sclerosing adenosis is a variant of breast proliferation. This is an important entity to recognize, as clinically it is characterized by an irregular hard mass that is fixed to the adjacent structures, and by imaging, it also shows significant architectural distortion, rendering this indistinguishable from carcinoma. Histologically, there is proliferation of epithelial and myoepithelial cells in the small ducts and ductules, and these are present within a densely fibrotic stroma. Other variants include blunt duct adenosis (columnar cell changes), microglandular adenosis, apocrine adenosis, and nodular adenosis.

There are usually no adverse side effects to this condition. In almost all cases it subsides after menopause. Breast cancer risk is elevated for defined fraction of lesions. Except for patients with a strong family history of breast cancer, where the risk is two-fold, *nonproliferative lesions* have no increased risk. *Prolif-*

erative lesions also have approximately a 2-fold risk. In particular, atypical hyperplasia is associated with an increased risk of developing breast cancer.

Fibroadenomas are probably the most common benign breast tumor, presenting as solitary painless, mobile, and well-defined nodules. Multiple lesions are less frequent. Use of the immunosuppressant cyclosporine in transplant patients has resulted in an increased risk of fibroadenoma development. Macroscopically, fibroadenoma is ovoid, rubbery, and well circumscribed; the cut surface is grayish and may be lobulated. Microscopically, it shows a mixed epithelial and stromal proliferation, giving rise to the pericanalicular and intracanalicular patterns, with the former formed by stromal proliferation around the ducts and the latter formed by compression of the ductal elements by the proliferating stromal component into slit-like spaces. These patterns have little prognostic significance. Occasionally stromal giant cells, myxoid changes, dystrophic calcifications, and other mesenchymal metaplasia have been described. Complex fibroadenomas are those that show cysts larger than 3 mm, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes, and this group of fibroadenomas shows slightly higher (1.6×) cancer risk compared to the usual fibroadenomas.

Gynecomastia is a benign enlargement of the male breast (usually bilateral but sometimes unilateral) resulting from a proliferation of the glandular component of the breast. It is defined clinically by the presence of a rubbery or firm mass extending concentrically from the nipples. Gynecomastia should be differentiated from pseudogynecomastia (lipomastia), which is characterized by fat deposition without glandular proliferation.

Gynecomastia can be physiologic or pathologic. Physiologic gynecomastia is seen in newborn infants, pubescent adolescents, and elderly individuals.

Pathologic gynecomastia can be caused by an increase in the production and/or action of estrogen, by a decrease in the production and/or action of testosterone accompanied by increased aromatization and high estrogen, or by drug use.

Certain health problems in men such as liver disease, kidney failure or low testosterone can cause breast growth in men. Medications such as methadone, HIV medication, cancer chemotherapy, hormone treatment for prostate cancer, heartburn and ulcer medications, calcium channel blockers, antifungal medications such as ketoconazole, antibiotics such as metronidazole, tricyclic antidepressants such as amitriptyline, herbals such as lavender, tea tree oil, and dong quai are also known to cause gynecomastia. However, gynecomastia can also be idiopathic.

Histologic findings. Characteristic findings include proliferation of ductules and stroma (consisting of connective-tissue elements such as fibroblasts, collagen, and myofibroblasts) and occasional acini. Gynecomastia of short duration consists of a prominent ductular component with loose stroma. Long-standing gynecomastia consists of dense stroma with few ductules.

BREAST CANCER

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women. In less-developed countries, it is the leading cause of cancer death in women; in developed countries, however, it has been surpassed by lung cancer as a cause of cancer death in women.

The current understanding of breast cancer etiopathogenesis is that invasive cancers arise through a series of molecular alterations at the cell level. These alterations result in breast epithelial cells with immortal features and uncontrolled growth.

Genomic profiling has demonstrated the presence of discrete breast tumor subtypes with distinct natural histories and clinical behavior. The exact number of disease subtypes and molecular alterations from which these subtypes arise remains to be fully elucidated, but these generally align with the presence or absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).

Risk factors can be divided into two categories:

- *modifiable* risk factors (things that people can change themselves, such as consumption of alcoholic beverages), and
- *fixed* risk factors (things that cannot be changed, such as age and biological sex).

The primary risk factors for breast cancer are female sex and older age. Other potential risk factors include: genetics, lack of childbearing or lack of breastfeeding, higher levels of certain hormones, certain dietary patterns, and obesity. Recent studies have indicated that exposure to light pollution is a risk factor for the development of breast cancer.

The various types of breast cancers are listed below by percentage of cases:

- Infiltrating ductal carcinoma is the most commonly diagnosed breast tumor and has a tendency to metastasize via lymphatics; this lesion accounts for 75% of breast cancers;
- Over the past 25 years, the incidence of lobular carcinoma in situ (LCIS) has doubled, reaching a current level of 2.8 per 100,000 women; the peak incidence is in women aged 40-50 years;

- Infiltrating lobular carcinoma accounts for fewer than 15% of invasive breast cancers;
- Medullary carcinoma accounts for about 5% of cases and generally occurs in younger women;
- Mucinous (colloid) carcinoma is seen in fewer than 5% of invasive breast cancer cases;
- Tubular carcinoma of the breast accounts for 1-2% of all breast cancers;
- Papillary carcinoma is usually seen in women older than 60 years and accounts for approximately 1-2% of all breast cancers;
- Metaplastic breast cancer accounts for fewer than 1% of breast cancer cases, tends to occur in older women (average age of onset in the sixth decade), and has a higher incidence in blacks;
- Mammary Paget disease accounts for 1-4% of all breast cancers and has a peak incidence in the sixth decade of life (mean age, 57 years).

Histology. Breast cancers usually are epithelial tumors of ductal or lobular origin. The following features are all important in deciding on a course of treatment for any breast tumor: size, status of surgical margin, presence or absence of estrogen receptor (ER) and progesterone receptor (PR), nuclear and histologic grade, proliferation, vascular invasion, tumor necrosis, quantity of intraductal component, HER2 status

Breast cancer is usually classified primarily by its histological appearance. Most breast cancers are derived from the epithelium lining the ducts or lobules, and these cancers are classified as ductal or lobular carcinoma. *Carcinoma in situ* is growth of low grade cancerous or precancerous cells within a particular tissue compartment such as the mammary duct without invasion of the surrounding tissue. In contrast, *invasive carcinoma* does not confine itself to the initial tissue compartment.

Grade. Grading compares the appearance of the breast cancer cells to the appearance of normal breast tissue. Normal cells in an organ like the breast become differentiated, meaning that they take on specific shapes and forms that reflect their function as part of that organ. Cancerous cells lose that differentiation. In cancer, the cells that would normally line up in an orderly way to make up the milk ducts become disorganized. Cell division becomes uncontrolled. Cell nuclei become less uniform. Pathologists describe cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in normal breast cells. Poorly differentiated cancers (the ones whose tissue is least like normal breast tissue) have a worse prognosis.

Histologic grade is the best predictor of disease prognosis in carcinoma in situ, but it is dependent on the grading system used, such as the Van Nuys classification (high-grade, low-grade comedo, low-grade noncomedo). The

grading of invasive carcinoma is also important as a prognostic indicator, with higher grades indicating a worse prognosis.

Stage. Breast cancer staging using the TNM system is based on the size of the tumor (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits, and whether the tumor has metastasized (M) (i.e. spread to a more distant part of the body). Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis. The main stages are:

- ✓ Stage 0 is a pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).
- ✓ Stages 1–3 are within the breast or regional lymph nodes.
- ✓ Stage 4 is 'metastatic' cancer that has a less favorable prognosis since it has escaped into the blood stream.

Ductal carcinoma in situ. Increased use of screening mammography has resulted in a dramatic increase in the detection of ductal carcinoma in situ. About 90% of DCIS cases are identified on mammography as suspicious calcifications: linear, clustered, segmental, focal, or mixed distribution.

DCIS is broadly divided into 2 subtypes: comedo (i.e., cribriform, micropapillary, and solid) and noncomedo. The likelihood of progression or local recurrence, as well as the prognosis, varies in accordance with the DCIS subtype present.

Lobular carcinoma in situ arises from the terminal duct apparatus and shows a rather diffuse distribution throughout the breast, which explains its presentation as a nonpalpable mass in most cases. The peak incidence is in women aged 40-50 years.

Infiltrating ductal carcinoma is the most commonly diagnosed breast tumor (accounting for 75% of breast cancers) and has a tendency to metastasize via lymphatic vessels. This lesion has no specific histologic characteristics other than invasion through the basement membrane. DCIS is a frequently associated finding on pathologic examination.

Infiltrating lobular carcinoma has a much lower incidence than infiltrating ductal carcinoma, accounting for 15-20% of invasive breast cancers. Histologically, it is characterized by the "single-file" arrangement of small tumor cells. Like ductal carcinoma, infiltrating lobular carcinoma typically metastasizes to axillary lymph nodes first. However, it also has a tendency to be multifocal and have discontinuous areas of involvement.

Medullary carcinoma is relatively uncommon (5%) and generally occurs in younger women. Most patients present with a bulky palpable mass and axillary lymphadenopathy. Diagnosis of this type of breast cancer depends on the following histologic triad:

- Sheets of anaplastic tumor cells with scant stroma
- Moderate or marked stromal lymphoid infiltrate

- Histologic circumscription or a pushing border

DCIS may be observed in the surrounding normal tissues. Medullary carcinomas are typically high-grade lesions that are negative for ER, PR, and HER2 and that commonly demonstrate mutation of *TP53*.

Mucinous carcinoma (colloid carcinoma) is another rare histologic type, seen in fewer than 5% of invasive breast cancer cases. It usually presents during the seventh decade of life as a palpable mass or appears mammographically as a poorly defined tumor with rare calcifications.

Mucin production is the histologic hallmark. There are 2 main types of lesions, A and B, with AB lesions possessing features of both. Type A mucinous carcinoma represents the classic variety, with larger quantities of extracellular mucin, whereas type B is a distinct variant with endocrine differentiation.

DCIS is not a frequent occurrence in this setting, though it may be found. Most cases are ER- and PR-positive, but HER2 overexpression is rare. Additionally, these carcinomas predominantly express glycoproteins MUC2 and MUC6.

Tubular carcinoma of the breast is an uncommon histologic type, accounting for only 1-2% of all breast cancers. Characteristic features of this type include a single layer of epithelial cells with low-grade nuclei and apical cytoplasmic snoutings arranged in well-formed tubules and glands.

Tubular components make up more than 90% of pure tubular carcinomas and at least 75% of mixed tubular carcinomas. This type of breast cancer has a low incidence of lymph node involvement and a very high overall survival rate. Because of its favorable prognosis, patients are often treated with only breast-conserving surgery and local radiation therapy.

Papillary carcinoma of the breast encompasses a spectrum of histologic subtypes. There are 2 common types: cystic (noninvasive form) and micropapillary ductal carcinoma (invasive form). This form of breast cancer is usually seen in women older than 60 years and accounts for approximately 1-2% of all breast cancers. Papillary carcinomas are centrally located in the breast and can present as bloody nipple discharge. They are strongly ER- and PR-positive.

Cystic papillary carcinoma has a low mitotic activity, which results in a more indolent course and a good prognosis. However, invasive micropapillary ductal carcinoma has a more aggressive phenotype similar to that of infiltrating ductal carcinoma, even though about 70% of cases are ER-positive. Additionally, lymph node metastasis is seen frequently in this subtype.

Metaplastic breast cancer (MBC) accounts for fewer than 1% of breast cancer cases. It tends to occur in older women (average age of onset in the sixth decade) and has a higher incidence in blacks. It is characterized by a combination of adenocarcinoma plus mesenchymal and epithelial components.

A wide variety of histologic patterns includes the following:

- Spindle-cell carcinoma,
- Carcinosarcoma,
- Squamous cell carcinoma of ductal origin,
- Adenosquamous carcinoma,
- Carcinoma with pseudosarcomatous metaplasia,
- Matrix-producing carcinoma.

This diverse group of malignancies is identified as a single entity on the basis of a similarity in clinical behavior. Compared with infiltrating ductal carcinoma, MBC tumors are larger, faster-growing, commonly node-negative, and typically negative for ER, PR, and HER2.

Mammary Paget disease is relatively rare, accounting for 1-4% of all breast cancers. The peak incidence is seen in the sixth decade of life. This adenocarcinoma is localized within the epidermis of the nipple-areola complex and is composed of the histologic hallmark Paget cells within the basement membrane. Paget cells are large, pale epithelial cells with hyperchromatic, atypical nuclei, dispersed between the keratinocytes singly or as a cluster of cells.

Lesions are predominantly unilateral, developing insidiously as a scaly, fissured, oozing, or erythematous nipple-areola complex. Retraction or ulceration of the nipple is often noted, along with symptoms of itching, tingling, burning, or pain. In situ or invasive breast cancer is found in approximately 85% of patients with Paget disease.

OVARIAN CANCER

Malignant lesions of the ovaries include primary lesions arising from normal structures within the ovary and secondary lesions from cancers arising elsewhere in the body. Primary lesions include epithelial ovarian carcinoma (70% of all ovarian malignancies), germ-cell tumors, sex-cord stromal tumors, and other more rare types. Metastases to the ovaries are relatively frequent, with the most common being from the endometrium, breast, colon, stomach, and cervix.

The precise cause of ovarian cancer is unknown. However, several risk and contributing factors (including both reproductive and genetic factors) have been identified. Most of the risk for ovarian cancer is related to the amount of time spent in ovulation. Thus not having children is a risk factor for ovarian cancer, likely because ovulation is not suppressed via pregnancy. Both obesity and hormone replacement therapy also raise the risk.

Things that halt ovulation: breast feeding, oral contraceptive use with estrogen/progesterone combination meds, multiple pregnancies, and pregnancy at an early age, all decrease risk of ovarian cancer. These conditions decrease the overall time during one's lifetime spent ovulating. A positive family history of ovarian cancer is a risk factor for ovarian cancer. People with

hereditary nonpolyposis colon cancer (Lynch Syndrome), and those with BRCA-1 and BRCA-2 genetic abnormalities are at increased risk.

Epithelial tumors represent the most common histology (90%) of ovarian tumors. Other histologies include the following: sex-cord stromal tumors, germ cell tumors, primary peritoneal carcinoma, metastatic tumors of the ovary.

EPITHELIAL OVARIAN CANCER

Epithelial ovarian cancer is thought to arise from epithelium covering the fimbria of the fallopian tubes, or the ovaries, both of which are derived from the coelomic epithelium in fetal development. This coelomic epithelium is also involved in formation of the müllerian ducts, from which the fallopian tubes, uterus, cervix, and upper vagina develop.

Four main histologic subtypes, which are similar to carcinoma, arise in the epithelial lining of the cervix, uterus, and fallopian tube, as follows:

- Serous (from fallopian tube),
- Endometrioid (endometrium),
- Mucinous (cervix),
- Clear cell (mesonephros).

Some variation is observed in the patterns of spread and disease distribution within the various histologic subtypes.

Epithelial tumors are found as partially cystic lesions with solid components. The surface may be smooth or covered in papillary projections, and the cysts contain fluid ranging from straw-colored to opaque brown or hemorrhagic.

Serous carcinoma

Most people with epithelial ovarian carcinoma, about two-thirds, have a serous carcinoma, though this proportion is estimated as high as 80%. Low-grade serous carcinoma is less aggressive than high-grade serous carcinomas, though it does not typically respond well to chemotherapy or hormonal treatments. Serous carcinomas are thought to begin in the Fallopian tube. Histologically, serous adenocarcinomas have psammoma bodies. Low-grade serous adenocarcinomas resemble Fallopian tube epithelium, whereas high-grade serous adenocarcinomas show anaplasia and nuclear atypia.

50% of the time, serous carcinomas are bilateral, and in 85% of cases, they have spread beyond the ovary at the time of diagnosis. Most have a diameter over 15 cm.

Endometrioid adenocarcinomas make up approximately 15-20% of epithelial ovarian cancers. Because they are typically low-grade, endometrioid adenocarcinomas have a good prognosis. These tumors frequently co-occur with endometriosis or endometrial cancer.

Mucinous tumors include mucinous adenocarcinoma and mucinous cystadenocarcinoma. Mucinous adenocarcinomas make up 5-10% of epithelial ovarian cancers. Histologically, they are similar to intestinal or cervical

adenocarcinomas, and are often actually metastases of appendiceal or colon cancers. Advanced mucinous adenocarcinomas have a poor prognosis, generally worse than serous tumors, and are often resistant to platinum chemotherapy, though they are rare.

Clear-cell carcinoma

Clear-cell ovarian carcinomas do not typically respond well to chemotherapy and may be related to endometriosis. They represent approximately 5% of all endometrial cancers. Japanese women develop clear-cell ovarian cancer more frequently than other groups of women.

Clear-cell adenocarcinomas are histopathologically similar to other clear cell carcinomas, with clear cells and hobnail cells. They represent approximately 5-10% of epithelial ovarian cancers and are associated with endometriosis in the pelvic cavity. They are typically early-stage and therefore curable by surgery, but advanced clear-cell adenocarcinomas (approximately 20%) have a poor prognosis and are often resistant to platinum chemotherapy.

Small-cell carcinoma

Small-cell ovarian carcinoma is rare and aggressive, with two main subtypes: hypercalcemic and pulmonary. It is typically fatal within 2 years of diagnosis. Hypercalcemic small cell ovarian carcinoma overwhelmingly affects those in their 20s, causes high blood calcium levels, and affects one ovary. Pulmonary small cell ovarian cancer usually affects both ovaries of older women and looks like oat-cell carcinoma of the lung.

***Malignant mixed müllerian tumor (carcinosarcoma*)**

Mixed müllerian tumors make up less than 1% of ovarian cancer. They have epithelial and mesenchymal cells visible and tend to have a poor prognosis.

Undifferentiated epithelial

Undifferentiated cancers - those where the cell type cannot be determined - make up about 10% of epithelial ovarian cancers and have a comparatively poor prognosis. When examined under the microscope, these tumors have very abnormal cells that are arranged in clumps or sheets. Usually there are recognizable clumps of serous cells inside the tumor.

Epithelial ovarian cancer most often spreads initially within the peritoneal cavity. Metastatic disease often is found on the peritoneal surfaces, particularly on the undersurface of the diaphragms, the paracolic gutters, the bladder, and the cul-de-sac. Other common sites are as follows: surface of the liver; mesentery and serosa of the large and small bowel; omentum; uterus; para-aortic and pelvic lymph nodes.

Outside the peritoneal cavity, epithelial ovarian cancer may spread to the pleural cavity, lungs, and groin lymph nodes. The presence of pleural effusion does not necessarily indicate disease in the chest, and malignancy can be diagnosed only cytologically. Mucinous tumors tend to form large dominant masses, while papillary serous tumors have a more diffuse distribution and are more

commonly bilateral. Endometrioid and clear-cell variants more commonly exhibit local invasion, retroperitoneal disease, and hepatic metastases.

TUMORS OF LOW MALIGNANT POTENTIAL

Tumors of low malignant potential (LMP), or borderline tumors, are a distinct variety of epithelial ovarian cancer that behave in a much less aggressive fashion and have a very favorable prognosis. These tumors cause great anxiety to patients, and the concept of LMP sometimes is difficult to explain. They comprise approximately 20% of malignant ovarian tumors. The mean age of diagnosis is younger than for invasive epithelial ovarian cancer, at approximately 48 years, and no large peak of incidence is observed.

LMP tumors can cause a range of symptoms similar to epithelial ovarian cancer, including increasing abdominal girth, an abdominal mass, abdominal pain, abnormal uterine bleeding, urinary symptoms, and gastrointestinal symptoms. They may be asymptomatic and found on routine physical examination or ultrasound scan.

MALIGNANT GERM CELL TUMORS

Malignant germ cell tumors (GCTs), which include dysgerminoma, endodermal sinus tumor, malignant teratoma, embryonal carcinoma, and choriocarcinoma, are thought to derive from primitive germ cells in the embryonic gonad. GCT of the ovary is much rarer than GCT of the testis in males, and much of the development of the management approach has been based on experience with male GCT.

Common characteristics of these tumors include rapid growth, a predilection for lymphatic spread, frequent mixtures of tumor types, and a predominantly unilateral pattern of ovarian involvement (except for dysgerminoma). GCT is much more common in young women but occasionally occurs in infants and older women.

Many GCTs produce tumor markers that can be measured in the blood and then used to monitor response to treatment and for follow-up care. Endodermal sinus tumors secrete alpha-fetoprotein and choriocarcinoma, and dysgerminomas occasionally secrete beta human chorionic gonadotropin (bHCG). Dysgerminoma may secrete lactate dehydrogenase and placental alkaline phosphatase.

No factors have been established related to etiology, apart from an increased incidence associated with dysgenetic gonads.

Although these tumors may be asymptomatic and present as a palpable mass, many patients present with abdominal pain. The mass may lead to acute pain due to torsion, rupture, or hemorrhage, or, patients may have abdominal distension, vaginal bleeding, or fever.

Most are stage I and confined to the ovary at the time of diagnosis.

Dysgerminoma. This is the most common malignant GCT and represents 3-5% of all ovarian malignancies. Ninety percent occur in people younger than 30 years, and 75% occur in the second and third decades, with a median age of 22 years.

Dysgerminomas are bilateral in 10-35% of cases. Five percent occur in phenotypic females with abnormal gonads. They may have a 46XY karyotype with pure gonadal dysgenesis or androgen insensitivity syndrome, or, they may have a 45X, 46XY karyotype with mixed gonadal dysgenesis. Dysgerminomas may be large and usually are solid, with a smooth external surface and a fleshy pink-tan color inside. The majority are confined to the ovary at diagnosis, but approximately 25% of otherwise stage I dysgerminomas have lymph node metastasis.

Cystic teratoma. Teratomas are germ cell tumors commonly composed of multiple cell types derived from one or more of the 3 germ layers. Inconsistent nomenclature often confuses discussions of various subtypes of teratomas. The word is derived from the Greek *teras,* meaning monster, which Virchow coined in the first edition of his book on tumors published in 1863. Teratomas range from benign, well-differentiated (mature) cystic lesions to those that are solid and malignant (immature). Additionally, teratomas may be monodermal and highly specialized. Rarely, within some mature teratomas certain elements (most commonly squamous components) undergo malignant transformation.

In 1831, Leblanc coined the term dermoid cyst in the veterinary literature when he removed a lesion that resembled skin at the base of a horse's skull, which he called a ―kyste dermoid.‖ Both dermoid and teratoma, terms now more than a century old, remain in general use and often are used interchangeably with various preferences among subspecialties. The earliest implications were that dermoids comprised elements similar to skin and its appendages, whereas teratomas had no such limits. Dermoids now are recognized as often being trigeminal and containing practically any type of tissue.

For those who continue to make a distinction, dermoids are tumors that maintain rather orderly arrangements, with well-differentiated ectodermal and mesodermal tissues surrounding endodermal components. Teratomas, specifically solid teratomas, are essentially devoid of organization; thus, the presence of some degree of organization, a high degree of cellular differentiation, and cystic structure differentiates dermoids from teratomas.

Immature teratoma.

This is the second most common GCT. It occurs mostly in females aged 10-20 years but may occur after menopause. The tumor spreads most commonly to peritoneal surfaces.

OTHER GERM CELL TUMORS

Endodermal sinus tumor occurs at a mean age of 18 years, and one third occur before puberty. Embryonal carcinoma and choriocarcinoma are extremely rare.

SEX-CORD STROMAL TUMORS

These include tumors arising from the sex cords; granulosa cells; Sertoli cells; and the specialized stroma of the genital ridge, theca, and Leydig cells. They comprise fewer than 5% of all ovarian tumors.

Although granulosa cell tumors are malignant and Sertoli-Leydig cell tumors less so, they behave in a much less malignant fashion than epithelial ovarian cancers. Benign tumors in the group include thecoma and fibroma. Granulosa cell tumors and pure Sertoli cell tumors commonly secrete estrogen, while Leydig cell tumors and combined Sertoli-Leydig tumors often secrete androgens.

Granulosa cell tumor

This is the most common malignant sex-cord stromal tumor. Ninety percent of granulosa cell tumors are stage I at the time of diagnosis. This tumor account for approximately 2% of all ovarian tumors and can be divided into adult (95%) and juvenile (5%) types based on histologic findings. Juvenile granulosa cell tumor is a variant of granulosa cell tumor that is rarely malignant. It most often presents in young girls with isosexual precocious puberty. The tumor is usually unilateral and confined to the ovary and can be managed with surgery alone.

Granulosa cell tumor can occur at any age, with a mean age of the early 50s. Because of the secretion of estrogen, the presenting features depend on the patient's age. Prepubertal girls typically present with precocious sexual development, women of reproductive age have heavy or irregular periods, and postmenopausal women may have postmenopausal bleeding. At all ages, the tumor may present with acute abdominal pain due to rupture or hemorrhage.

The tumors vary in size and may be solid or partially cystic. The cut surface may be gray-white or yellow, depending on lipid content. Necrosis and hemorrhage often are present, with cystic compartments filled with fluid or clotted blood. The microscopic features are granulosa cells in a wide variety of patterns, and characteristic Call-Exner bodies may be present.

Sertoli-Leydig cell tumor

These tumors are rare. They are a form of low-grade malignancy that typically produces androgens and rarely estrogens.

Metastatic tumors of the ovary arise from direct extension and spread within the bloodstream or lymphatic system or within the peritoneal cavity. Sites of origin include the endometrium; cervix; and nongynecologic sites

such as breast, colon, and stomach. The classic Krukenberg tumor refers to bilateral enlargement of the ovaries from metastases from a signet-ring carcinoma of the stomach.

Staging. Ovarian cancer is typically staged by means of the system formulated and updated by the International Federation of Obstetrics and Gynecology (FIGO), as listed below.

Ovarian cancer typically spreads to the peritoneal surfaces and omentum. Spread can occur by local extension, lymphatic invasion, intraperitoneal implantation, hematogenous dissemination, or transdiaphragmatic passage. Intraperitoneal dissemination is the most common and recognized characteristic of ovarian cancer. Malignant cells can implant anywhere in the peritoneal cavity but are more likely to implant in sites of stasis along the peritoneal fluid circulation.

PATHOLOGY OF PREGNANCY, FETUS AND INFANTS

GESTATIONAL AND PLACENTAL DISORDERS

GESTOSIS

It is a pregnancy specific illness which manifests itself the definition of this disease has changed with increased blood pressure and/or egg-white excretions in the urine and/or water inclusions (edemas).

Two forms of the gestosis are distinguished into dependence of the time of their occurrence:

- Early gestosis: in the first pregnancy third,
- Late gestation disorder: in the last pregnancy third.

No gestoses appear in the second pregnancy third for common. One talks about the so-called tolerance stage. Most gestoses are late gestation disorders.

The exact causes of the gestosis are unknown. Several pathological events apparently overlap. Being suspected: Lacking adaptation of the body to the pregnancy - particularly the womb, insufficient blood fluid increase, disturbances in the biochemical metabolism, acute nutrient deficiency.

Risk groups. Gestoses appear in large numbers: women who are charged by high blood pressure illnesses familially, multiple pregnancies, very young or old first giving birth, existing vessel illnesses of the mother (by chronic kidney diseases, high blood pressure, diabetes, nicotine abuse), overweight pregnant women and women fed badly (protein deficiency).

HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum (HG) is a complication of pregnancy that is characterized by severe nausea and vomiting such that weight loss and dehydration occur. Signs and symptoms may include vomiting several times a day and feeling faint. It is more severe than morning sickness. Often symptoms get better after the 20th week of pregnancy but may last the entire pregnancy.

The exact cause of hyperemesis gravidarum is not known. Risk factors include the first pregnancy, multiple pregnancy, obesity, prior or family history of hyperemesis gravidarum, trophoblastic disorder, and a history of an eating disorder. The diagnosis is usually made based on the signs and symptoms. It has been technically defined as more than three episodes of vomiting per day such that weight loss of 5% or three kilograms has occurred and ketones are present in the urine. Other potential causes of the symptoms should be excluded including urinary tract infection and high thyroid levels.

Complications:

Pregnant woman. If HG is inadequately treated, anemia, hyponatremia, Wernicke's encephalopathy, kidney failure, central pontine mye-

linolysis, coagulopathy, atrophy, Mallory-Weiss tears, hypoglycemia, jaundice, malnutrition, pneumomediastinum, rhabdomyolysis, deconditioning, deep vein thrombosis, pulmonary embolism, splenic avulsion, or vasospasms of cerebral arteries are possible consequences.

Infant. The effects of HG on the fetus are mainly due to electrolyte imbalances caused by HG in the mother. Infants of women with severe hyperemesis who gain less than 7 kg (15.4 lb) during pregnancy tend to be of lower birth weight, small for gestational age, and born before 37 weeks gestation. In contrast, infants of women with hyperemesis who have a pregnancy weight gain of more than 7 kg appear similar to infants from uncomplicated pregnancies.

HYPERTENSIVE STATES OF PREGNANCY

GESTATIONAL HYPERTENSION

Gestational hypertension is usually defined as having a blood pressure higher than 140/90 measured on two separate occasions, more than 6 hours apart, without the presence of protein in the urine and diagnosed after 20 weeks of gestation.

PRE-ECLAMPSIA

Pre-eclampsia is gestational hypertension plus proteinuria (>300 mg of protein in a 24-hour urine sample). Severe preeclampsia involves a blood pressure greater than 160/110, with additional medical signs and symptoms. HELLP syndrome is a type of preeclampsia. It is a combination of three medical conditions: hemolytic anemia, elevated liver enzymes and low platelet count.

ECLAMPSIA

This is when tonic-clonic seizures appear in a pregnant woman with high blood pressure and proteinuria.

Pathogenesis. The exact mechanisms leading to development of preeclampsia are still being investigated; however, it is clear that the placenta plays a central role in the pathogenesis of the syndrome, since the symptoms disappear rapidly after delivery of the placenta. The critical abnormalities in preeclampsia are diffuse endothelial dysfunction, vasoconstriction (leading to hypertension), and increased vascular permeability (resulting in proteinuria and edema). Recent work has demonstrated that these effects are most likely mediated by placenta derived factor(s) released into the maternal circulation. Although the release of these factors and the clinical syndrome develop late in gestation, the pathogenesis of the disease appears to be closely tied to the earliest events of pregnancy and placentation. The principal pathophysiologic aberrations appear to be the following.

Abnormal placental vasculature. The initial event in the pathogenesis of preeclampsia is abnormal trophoblastic implantation and lack of development of physiologic alterations in the maternal vessels required for adequate perfusion of the placental bed. In normal pregnancy, fetal extravillous trophoblastic cells (trophoblastic cells not associated with chorionic villi) at the implantation site invade the maternal decidua and decidual vessels, destroy the vascular smooth muscle and replace the maternal endothelial cells with fetal trophoblastic cells (forming hybrid feto-maternal blood vessels). This process converts the decidual spiral arteries from small-caliber resistance vessels to large capacity uteroplacental vessels lacking a smooth muscle coat. In preeclampsia this remodeling fails to occur, leaving the placenta ill equipped to meet the increased circulatory demands of late gestation and setting the stage for the development of placental ischemia.

Endothelial dysfunction and imbalance of angiogenic and anti-angiogenic factors. Although not formally proven, it is postulated that in response to hypoxia, the ischemic placenta releases factors into the maternal circulation that cause an imbalance in circulating angiogenic and anti-angiogenic factors; this in turn leads to systemic maternal endothelial dysfunction and the clinical symptoms of the disease. In support of this, the blood levels of two placenta-derived anti-angiogenic factors, soluble Fms-like tyrosine kinase (sFltl) and endoglin, are several orders of magnitude higher in women with preeclampsia than in healthy controls. Placental hypoxia causes overproduction of sFlt1 from the villous trophoblast; sFltl is a truncated soluble form of VEGF receptor that acts as a decoy receptor, binding VEGF and placental growth factor in circulation and thereby neutralizing their pro-angiogenic activity. Similarly circulating endoglin, a soluble form of a TGF-β receptor, can bind TGF-β and inhibit signaling via cellular TGF-β receptors. Normally, in late gestation, levels of sFltl and soluble endoglin in the blood increase while placental growth factor and vascular endothelial growth factor decrease, leading to a reduction in angiogenic activity. In preeclampsia, high levels of sFlt1 and soluble endoglin bring about a decrease in angiogenesis much earlier than in normal pregnancy. The result is defective vascular development in the placenta.

Studies in animal models also implicate sFltl and soluble endoglin in the pathogenesis of endothelial dysfunction. When sFlt and endoglin are overexpressed together, rats develop nephrotic-range proteinuria, severe hypertension, and fetal growth restriction, the hallmarks of severe preeclampsia, as well as features of the HELLP syndrome, including elevated liver enzymes, decreased platelet counts, and hemolysis. Thus, it seems that sFlt1 and soluble endoglin are key mediators that link the placenta to the characteristic maternal endothelial dysfunction of preeclampsia. These effects of sFltl

and endoglin appear to be related to their inhibition of VEGF and TGF-β-mediated production of endothelial-dependent nitric oxide (NO) and prostacyclin (PGI2). The capillary endothelium of the kidney is extremely sensitive to locally produced VEGF, which may explain why proteinuria and renal dysfunction are early markers of preeclampsia.

Coagulation abnormalities. Preeclampsia is associated with a hypercoaguable state; thrombosis of arterioles and capillaries may occur throughout the body, particularly in the liver, kidneys, brain, and pituitary. This hypercoaguability is likely related to the reduced endothelial production of PGI2, a potent antithrombotic factor, and increased release of procoagulant factors. Production of PGI2 is stimulated by both VEGF and TGF-β, and women with preeclampsia have been shown to have decreased endothelial production of PGI2.

Morphology. The placenta reveals various microscopic changes, most of which reflect malperfusion, ischemia, and vascular injury. These include:

1) Placental infarcts small, peripheral ones that may occur in normal full-term placentasare larger and more numerous in preeclampsia. There is also an exaggeration of ischemic changes in the chorionic villi and trophoblast. This includes increased syncytial knots and the appearance of accelerated villous maturity.

2) There is increased frequency of retroplacental hematomas due to bleeding and instability of uteroplacental vessels.

3) The most characteristic finding is in the decidual vessels, reflecting abnormal implantation. This can be in the form of thrombosis, lack of normal physiologic conversion (described earlier), fibrinoid necrosis, or intraintimal lipid deposition (acute atherosis).

The liver lesions, when present, take the form of irregular, focal, subcapsular, and intraparenchymal hemorrhages. On histologic examination there are fibrin thrombi in the portal capillaries and foci of hemorrhagic necrosis.

The kidney lesions are variable. Glomerular lesions are diffuse, when assessed by electron microscopy. They consist of marked swelling of endothelial cells, the deposition of fibrinogen-derived amorphous dense deposits on the endothelial side of the basement membrane, and mesangial cell hyperplasia. Immunofluorescent studies show an abundance of fibrin in glomeruli. In the better defined cases, fibrin thrombi are present in the glomeruli and capillaries of the cortex. When the lesion is far advanced, it may produce complete destruction of the cortex in the pattern referred to as bilateral renal cortical necrosis. The brain may have gross or microscopic foci of hemorrhage along with small-vessel thromboses. Similar changes are often found in the heart and the anterior pituitary.

Preeclampsia most commonly starts after 34 weeks of gestation but begins earlier in women with hydatidiform mole or preexisting kidney disease, hypertension, or coagulopathies. The onset is typically insidious, characterized by hypertension and edema, with proteinuria following within several days. Headaches and visual disturbances are serious events and are indicative of severe preeclampsia, often requiring delivery. Eclampsia is heralded by central nervous system involvement, including convulsions and eventual coma. Management of preeclampsia differs depending upon the gestational age and severity of disease. For term pregnancies, delivery is the treatment of choice regardless of disease severity. In preterm pregnancies, where delivery may not be in the best interest of the fetus, patients with mild disease can be managed expectantly with close monitoring of the mother and fetus. However, eclampsia, severe preeclampsia with maternal end-organ dysfunction, fetal compromise, or the HELLP syndrome are indications for delivery regardless of gestational age. Antihypertensive therapy does not affect the disease course or improve outcomes. Proteinuria and hypertension usually disappear within 1 to 2 weeks after delivery except when they predate the pregnancy. Although it is typically believed that preeclampsia has no lasting sequelae, recent studies indicate that about 20% of women develop hypertension and microalbuminuria within 7 years of a pregnancy complicated by preeclampsia. There is also a two-fold increase in the long-term risk of vascular diseases of the heart and the brain.

HELLP syndrome is a life-threatening obstetric complication usually considered to be a variant or complication of pre-eclampsia. Both conditions usually occur during the later stages of pregnancy, or sometimes after childbirth. "HELLP" is an abbreviation of the three main features of the syndrome: Hemolysis; Elevated Liver enzymes; Low Platelet count.

HELLP usually begins during the third trimester; rare cases have been reported as early as 21 weeks gestation. Often, a woman who develops HELLP syndrome has already been followed up for pregnancy-induced hypertension (gestational hypertension), or is suspected to develop pre-eclampsia (high blood pressure and proteinuria). Up to 8% of all cases occur after delivery.

Arterial hypertension is a diagnostic requirement, but may be mild. Rupture of the liver capsule and a resultant hematoma may occur. If a woman has a seizure or coma, the condition has progressed into full-blown eclampsia.

Disseminated intravascular coagulation is also seen in about 20% of all women with HELLP syndrome, and in 84% when HELLP is complicated by acute renal failure. Pulmonary edema is found in 6% of all women with HELLP syndrome, and in 44% when HELLP is complicated by acute renal failure.

Histologic Findings. Hepatic endothelial disruption and subsequent platelet activation, aggregation, and consumption lead to distal ischemia and

hepatocyte death, which can be segmental or apparent diffusely throughout the liver. Since HELLP tends to involve smaller terminal arterioles, characteristic histiologic features are periportal or focal parenchymal necrosis with hyaline deposits of fibrinlike material in the sinusoids. If larger-vessel vasculopathy occurs, hepatic infarction or subcapsular hematomas may result.

SPONTANEOUS ABORTION

Spontaneous abortion, or ―miscarriage,‖ is defined as pregnancy loss before 20 weeks of gestation. Most of these occur before 12 weeks. Ten to fifteen percent of clinically recognized pregnancies terminate in spontaneous abortion. However, using sensitive chorionic gonadotropin assays, it has been identified that an additional 22% of early pregnancies in otherwise healthy women terminate spontaneously.

In the first trimester, embryonic causes of spontaneous abortion are the predominant etiology and account for 80-90% of miscarriages.

Genetic abnormalities within the embryo (i.e., chromosomal abnormalities) are the most common cause of spontaneous abortion and account for 50-65% of all miscarriages. Teratogenic and mutagenic factors may also play a role in spontaneous abortion, but quantification is difficult. Iatrogenic causes include Asherman syndrome.

Maternal causes of spontaneous miscarriage include the following: genetic - maternal age is directly related to the aneuploidy risk (>30% in people aged 40 years). Couples with recurrent miscarriages have a 2-3% incidence of a parental chromosomal anomaly (i.e., balanced translocation). Structural abnormalities of the reproductive tract include the following: congenital uterine defects (particularly uterine septum), fibroids, cervical incompetence

Acute maternal factors include the following: Corpus luteum deficiency; active infection (e.g., rubella virus, cytomegalovirus, Listeria infection, toxoplasmosis, malaria, brucellosis, human immunodeficiency virus (HIV), dengue fever, influenza, as well as vaginal infection with bacterial vaginosis)

Chronic maternal health factors include the following: polycystic ovary syndrome; poorly controlled diabetes mellitus; renal disease; systemic lupus erythematosus (SLE); untreated thyroid disease; severe hypertension; antiphospholipid syndrome; exogenous factors include the following: tobacco, alcohol, cocaine, caffeine (high doses).

Independent risk factors for a spontaneous miscarriage include the following: advanced age, extremes of age, feeling stressed, advanced paternal age.

STILLBIRTH

Stillbirth is often defined as fetal death after 20 weeks of gestation, but a fetus greater than any combination of 16, 20, 22, 24, or 28 weeks gestation-

al age and 350g, 400g, 500g, or 1000g birth weight may be considered stillborn depending on local law. Once the fetus has died, the mother may or may not have contractions and undergo childbirth or in some cases, a Caesarean section. Most stillbirths occur in full-term pregnancies.

The causes of a large percentage of human stillbirths remain unknown, even in cases where extensive testing and autopsy have been performed. Many stillbirths occur at full term to apparently healthy mothers, and a postmortem evaluation reveals a cause of death in only about 40% of autopsied cases.

In cases where the cause is known, some possibilities of the cause of death are: bacterial infection, birth defects, especially pulmonary hypoplasia, chromosomal aberrations, growth retardation, Induced Fetal Demise, intrahepatic cholestasis of pregnancy, maternal diabetes, high blood pressure, including preeclampsia, maternal consumption of recreational drugs (such as alcohol, nicotine, etc.) or pharmaceutical drugs contraindicated in pregnancy, postdate pregnancy, placental abruptions, physical trauma, radiation poisoning, Rh disease, celiac disease, female genital mutilation, umbilical cord accidents.

ECTOPIC PREGNANCY

Ectopic pregnancy is the term applied to implantation of the fetus in any site other than a normal intrauterine location. The most common site is within the fallopian tubes (~90%). Other sites include the ovary, the abdominal cavity, and the intrauterine portion of the fallopian tube (cornual pregnancy). Ectopic pregnancies occur about once in every 150 pregnancies.

There are a number of risk factors for ectopic pregnancies. However, in as many as one third to one half no risk factors can be identified. Risk factors include: pelvic inflammatory disease, infertility, use of an intrauterine device, tubal surgery, intrauterine surgery, smoking, previous ectopic pregnancy, endometriosis, and tubal ligation. A previous induced abortion does not appear to increase the risk.

Tubal pregnancy is when the egg is implanted in the Fallopian tubes. Hair-like cilia located on the internal surface of the Fallopian tubes carry the fertilized egg to the uterus. Fallopian cilia are sometimes seen in reduced numbers subsequent to an ectopic pregnancy, leading to a hypothesis that cilia damage in the Fallopian tubes is likely to lead to an ectopic pregnancy. Women who smoke have a higher chance of an ectopic pregnancy in the fallopian tubes. Smoking leads to risk factors of damaging and or killing cilia. As cilia degenerate the amount of time it takes for the fertilized egg to reach the uterus will increase. The fertilized egg, if it doesn't reach the uterus in time, will hatch from the non-adhesive zona pellucida and implant itself inside the fallopian tube, thus causing the pregnancy.

Women with pelvic inflammatory disease (PID) have a high occurrence of ectopic pregnancy. This results from the build-up of scar tissue in the Fallopian tubes, causing damage to cilia. If however both tubes were completely blocked, so that sperm and egg were physically unable to meet, then fertilization of the egg would naturally be impossible, and neither normal pregnancy nor ectopic pregnancy could occur. Intrauterine adhesions (IUA) present in Asherman's syndrome can cause ectopic cervical pregnancy or, if adhesions partially block access to the tubes via the ostia, ectopic tubal pregnancy. Asherman's syndrome usually occurs from intrauterine surgery. Endometrial/pelvic/genital tuberculosis, another cause of Asherman's syndrome, can also lead to ectopic pregnancy as infection may lead to tubal adhesions in addition to intrauterine adhesions.

Tubal ligation can predispose to ectopic pregnancy. Reversal of tubal sterilization (Tubal reversal) carries a risk for ectopic pregnancy. This is higher if more destructive methods of tubal ligation (tubal cautery, partial removal of the tubes) have been used than less destructive methods (tubal clipping). A history of a tubal pregnancy increases the risk of future occurrences to about 10%. This risk is not reduced by removing the affected tube, even if the other tube appears normal. The best method for diagnosing this is to do an early ultrasound.

Morphology. Tubal pregnancy is the most common cause of hematosalpinx (blood-filled fallopian tube) and should always be suspected when a tubal hematoma is present. Initially the embryonal sac, surrounded by placental tissue composed of immature chorionic villi, implants in the lumen of the fallopian tube. With time trophoblastic cells and chorionic villi start to invade the fallopian tube wall as they do in the uterus during normal pregnancy. However, proper decidualization is lacking in the fallopian tube, and growth of the gestational sac distends the fallopian tube causing thinning and rupture. Fallopian tube rupture frequently results in massive intraperitoneal hemorrhage. Less commonly the tubal pregnancy may undergo spontaneous regression and resorption of the entire conceptus. Still less commonly, the tubal pregnancy is extruded through the fimbriated end into the abdominal cavity (tubal abortion).

The clinical course of ectopic pregnancy is punctuated by the onset of severe abdominal pain, most commonly about 6 weeks after a previous normal menstrual period, when rupture of the tube leads to pelvic hemorrhage. Rupture of a tubal pregnancy constitutes a medical emergency. In such cases the patient may rapidly develop hemorrhagic shock with signs of an acute abdomen, and early diagnosis is critical. Chorionic gonadotropin assays, ultrasound studies, and laparoscopy may be helpful. Endometrial biopsy specimens may or may not disclose decidual changes, but excluding the extreme-

ly rare dual pregnancy do not exhibit chorionic villi or evidence of an implantation site.

The most common complication is rupture with internal bleeding which may lead to hypovolemic shock. Death from rupture is still the leading cause of death in the first trimester of the pregnancy.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease constitutes a spectrum of tumors and tumor-like conditions characterized by proliferation of placental tissue, either villous or trophoblastic. The lesions include hydatidiform mole (complete and partial), invasive mole, and malignant choriocarcinoma.

Hydatidiform mole is characterized histologically by cystic swelling of the chorionic villi, accompanied by variable trophoblastic proliferation. The most important reason for the correct recognition of moles is that they are associated with an increased risk of persistent trophoblastic disease (invasive mole) or choriocarcinoma. In the past, most patients presented in the fourth or fifth month of pregnancy with vaginal bleeding. Currently, hydatidiform moles are being diagnosed at earlier gestational ages (8.5 versus 17.0 weeks) due to routine ultrasound and close monitoring of early pregnancy. Molar pregnancy can develop at any age, but the risk is higher at the far ends of reproductive life: in teens and between the ages of 40 and 50 years. For poorly explained reasons, the incidence varies considerably in different regions of the world. Two types of benign, noninvasive moles complete and partial can be identified by cytogenetic and histologic studies.

Complete mole results from fertilization of an egg that has lost its chromosomes, and the genetic material is completely paternally derived. Ninety percent have a 46,XX diploid pattern, all derived from duplication of the genetic material of one sperm (a phenomenon called androgenesis). The remaining 10% are from the fertilization of an empty egg by two sperm (46,XX and 46,XY). Histologically, in complete mole all or most of the villi are enlarged and edematous, and there is diffuse trophoblast hyperplasia. Although fetal vessels and fetal parts are extremely rare in complete moles since the embryo dies very early in development, they do occur. Patients have 2.5% risk of subsequent choriocarcinoma.

Partial moles result from fertilization of an egg with two sperm. In these moles the karyotype is triploid (e.g., 69,XXY) or even occasionally tetraploid (92,XXXY). Fetal parts are more commonly present than in complete moles. In partial moles some of the villi are edematous, and other villi show only minor changes; the trophoblastic proliferation is focal and less marked. Although partial moles have an increased risk of persistent molar disease, they are not considered to have an increased risk for choriocarcinoma.

*Morphology***.** The classic gross appearance is of a delicate, friable mass of thin-walled, translucent, cystic, grapelike structures consisting of swollen edematous (hydropic) villi. Fetal parts are frequently seen in partial moles. On histologic examination complete moles show abnormalities that involve all or most of the villous tissue. The chorionic villi are enlarged, scalloped in shape with central cavitation (cisterns), and lack adequately developed vessels. The most impressive abnormality is, however, an extensive trophoblast proliferation that involves the entire circumference of the villi, in addition to ―extravillous‖ islands of trophoblast proliferation. The implantation site often displays atypia and an exuberant proliferation of implantation trophoblast. In contrast, partial moles demonstrate villous enlargement and architectural disturbances in only a proportion of villi. The trophoblastic proliferation is moderate but still may be circumferential.

Histologic distinction of complete mole from partial molar gestations is important. In equivocal cases immunostaining for p57, a cell cycle inhibitor, may aid the diagnosis. The p57KIP2 gene is maternally transcribed but paternally imprinted, and shows expression in maternal decidual tissue as well as cytotrophoblast and stromal cells of the villi, when maternal genetic material is present in the conceptus. In contrast, since both the X chromosomes in complete moles are derived from the father, there is no expression of p57 protein in the cytotrophoblast or stromal cells of the villi in complete moles.

Most women with partial and early complete moles present with spontaneous pregnancy loss or undergo curettage because of abnormalities in ultrasound showing diffuse villous enlargement. In complete moles quantitative analysis of human chorionic gonadotropin (HCG) shows levels of hormone greatly exceeding those produced during a normal pregnancy of similar gestational age. Serial hormone determination indicates a rapidly mounting level that climbs faster than for the usual normal single or even multiple pregnancy. The vast majority of moles are removed by thorough curettage. Monitoring serum concentrations of HCG is necessary to determine the early development of persistent trophoblastic disease, since up to 10% of moles develop into persistent or invasive moles. In addition, 2.5% of complete moles evolve into gestational choriocarcinoma. Therefore, serum HCG levels are usually followed until they fall to and remain at zero for 6 months to a year.

Invasive mole. This is defined as a mole that penetrates or even perforates the uterine wall. There is invasion of the myometrium by hydropic chorionic villi, accompanied by proliferation of both cytotrophoblast and syncytiotrophoblast. The tumor is locally destructive and may invade parametrial tissue and blood vessels. Hydropic villi may embolize to distant sites, such as lungs and brain, but do not grow in these organs as true metastases, and even without chemotherapy they eventually regress. The tumor is manifested clini-

cally by vaginal bleeding and irregular uterine enlargement. It is always associated with a persistently elevated serum HCG and varying degrees of luteinization of the ovaries. The tumor responds well to chemotherapy but may result in uterine rupture and necessitate hysterectomy.

Choriocarcinoma. Gestational choriocarcinoma is a malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy, which can even include extrauterine ectopic pregnancy. Choriocarcinoma is rapidly invasive and metastasizes widely.

Morphology. Choriocarcinoma is classically a soft, fleshy, yellow-white tumor with a marked tendency to form large pale areas of ischemic necrosis, foci of cystic softening, and extensive hemorrhage. Histologically, it does not produce chorionic villi and consists entirely of a mixed proliferation of syncytiotrophoblasts and cytotrophoblasts. Mitoses are abundant and sometimes abnormal. The tumor invades the underlying myometrium, frequently penetrates blood vessels and lymphatics, and in some cases extends out onto the uterine serosa and into adjacent structures. Due to rapid growth it is subject to hemorrhage, ischemic necrosis, and secondary inflammation. In fatal cases metastases are found in the lungs, brain, bone marrow, liver, and other organs. On occasion, metastatic choriocarcinoma is discovered without a detectable primary in the uterus (or ovary), presumably because the primary has undergone complete necrosis.

Uterine choriocarcinoma usually does not produce a large, bulky mass, but it manifests as irregular vaginal spotting of a bloody, brown fluid. This discharge may appear in the course of an apparently normal pregnancy, after a miscarriage, or after curettage. Sometimes the tumor does not appear until months after these events. Usually, by the time the tumor is discovered, radiographs of the chest and bones already disclose the presence of metastatic lesions. The titers of HCG are elevated to levels above those encountered in hydatidiform moles. Occasionally, tumors produce little hormone, and some tumors become so necrotic as to become functionally inactive. Widespread metastases are characteristic. Frequent sites of involvement are the lungs (50%) and vagina (30% to 40%), followed in descending order of frequency by the brain, liver, and kidney.

PUERPERAL INFECTIONS

Puerperal infections, also known as postpartum infections, puerperal fever or childbed fever, is any bacterial infection of the female reproductive tract following childbirth or miscarriage. In addition to trauma sustained during the birth process or cesarean procedure, physiologic changes during pregnancy contribute to the development of postpartum infections. The typical pain that many women feel in the immediate postpartum period also

makes it difficult to discern postpartum infection from postpartum pain. Signs and symptoms usually include a fever greater than 38.0°C (100.4°F), chills, lower abdominal pain, and possibly bad-smelling vaginal discharge. It usually occurs after the first 24 hours and within the first ten days following delivery.

After childbirth a woman's genital tract has a large bare surface, which is prone to infection. Infection may be limited to the cavity and wall of her uterus, or it may spread beyond to cause septicaemia (blood poisoning) or other illnesses, especially when her resistance has been lowered by a long labour or severe bleeding. Puerperal infection is most common on the raw surface of the interior of the uterus after separation of the placenta (afterbirth); but pathogenic organisms may also affect lacerations of any part of the genital tract. By whatever portal, they can invade the bloodstream and lymph system to cause septicemia, cellulitis (inflammation of connective tissue), and pelvic or generalized peritonitis (inflammation of the abdominal lining). The severity of the illness depends on the virulence of the infecting organism, the resistance of the invaded tissues, and the general health of the woman. Organisms commonly producing this infection are Streptococcus pyogenes; staphylococci (inhabitants of the skin and of pimples, carbuncles, and many other pustular eruptions); the anaerobic streptococci, which flourish in devitalized tissues such as may be present after long and injurious labour and unskilled instrumental delivery; Escherichia coli and Clostridium welchii (inhabitants of the lower bowel); and Clostridium tetani.

Local spread of colonized bacteria is the most common etiology for postpartum infection following vaginal delivery. Endometritis is the most common infection in the postpartum period. Other postpartum infections include (1) postsurgical wound infections, (2) perineal cellulitis, (3) mastitis, (4) respiratory complications from anesthesia, (5) retained products of conception, (6) urinary tract infections (UTIs), and (7) septic pelvic phlebitis. Wound infection is more common with cesarean delivery.

Complications include the following: scarring, infertility, sepsis, septic shock.

PRENATAL PATHOLOGY

Prenantal (antenatal) pathology includes pathologic processes of the human embryo, beginning with fertilization and ending with delivery. Prenatal period lasts 280 days, or 40 weeks. The whole development from fertilization to delivery is called kinetogenesis which is preceded by progenesis – period of male and female sex cells (gametes) ripening before the fertilization. Kinetogenesis period is divided into three periods – blastogenesis, lasts from fertilization to the 15th day of pregnancy, when the fertilized ovum division

takes place and it ends up with embryo- and trophoblast elimination; embryogenesis – from the 16th to the 75th day of pregnancy when the main organogenesis takes place amnion and chorion are formed; fetogenesis – lasts from the 76th to the 280th day of pregnancy when differentiation and ripening of the fetal tissue take place, placenta is formed, ends up with delivery. Fetogenesis period can be divided into early fetal (from the 76th to the 180th day), at the end of this period fetus becomes viable, and late fetal (from the 181st to the 280th day), when the fetus becomes mature. Pathology which occurs during the kinetogenesis period is called kinetopathy and it is correspondingly divided into blastosis, embryopathy, early and late fetopathy.

The reasons for **kinetopathy** according to the latest data: 20% deformities (main kinetogenesis period pathology) are connected with gene mutations, 10% – with chromosome aberration, 10% – with the exogenous factors influence, 60% – of ambiguous etiology. German measles, rubeola, chickenpox, mononucleosis, parotitis, hepatitis, influenza, poliomyelitis, pale treponema, toxoplasmosis, tuberculosis microbacterium belong to the exogenous factors.

Apart from infection agents kinetopathies can be caused by radiation energy, some pharmaceutical preparations (tolidomide, cytostatic drugs), hormones, vitamins, alcohol, drugs, hypoxia.

Gametopathies. During protogenesis pathology of gametes may occur – gametopathies. They are manifested through nuclear substance and sex cells cytoplasm pathology. Nucleus changes are characterized by hereditary apparatus of gamete pathology. Gene, chromosome and genomic mutations are distinguished that are the cause of congenital maldevelopment (deformity). Deformities are not viable and end up with spontaneous abortion. Gamete cytoplasm pathology as a rule results in sterility (infertility).

Blastopathies. They are the most frequently caused by chromosome aberrations accompanied with environmental influence (mother‘s endocrine diseases, hypoxia, intoxications, etc.). To blastopathy belong: blastocyte implantation disturbance (extrauterine pregnancy), twin deformities, solitary deformities, placenta and umbilical cord formation deformities. Twin deformities are connected with appearance of two or more independent growing centres during division. If centres of growth are in close location and have common intermediate zone, than two conjoined twins develop. If the conjoined twins are identical, symmetrically developed, they are called diplopagus (from Gr. diplos – double, pagus – to connect), if the twins are asymmetrically developed, it is heteropagus. The twin lesser in size is called teratic parasite. Sometimes such twin is found in the body of the bigger one – ―fetus in fetu‖. In 1995 in the medical press was announced that a 43-year-old man had suddenly died in Nizhni Novgorod, in his thorax a dead fetus was found, its weight was 6,1 kg and sizes 32×26×18 cm. The body of the fetus was of

ligneous density, yellow-red colour. Lungs and heart of the dead man were deformed, underdeveloped. The medical workers were surprised how this man had lived to the age of 43 with such deformation of thorax organs. A few years before it was reported that in China a fetus, extracted from the thorax of a 46-year-old man during the tumor ablation, began to grow. The doctors treated it as growth of the thorax tumor.

The degree of twins conjugation can be different – from minor conjoined superficial tissues to such degree when only heads and limbs are separated. To determine the localization of twins conjugation a word pagus was added to the anatomic name of the site of conjugation – craniopagus, thoracopagus, ischiopagus, etc.

Embryopathy is an embryonic period pathology from the 16th to the 75th day of pregnancy, during which the main organogenesis is completed. To the embryopathies belong mostly congenital maldevelopment – deformities. With the embryo‘s development the ability to react to different pathogenic influences with disturbance of morphogenesis is gradually developed. This ability is called dysontogenesis. It was found out that different teratogenic agents can cause the same deformity. Along with it the same teratogenic agent can cause different deformities of development influencing during different periods of embryogenesis. There is a certain period of time for each organ during which under the influence of a teratogenic agent hypoplasia of this organ occurs. This period of time is called teratogenic termination period (from Lat. teratos – deformity and terminus – boundary). So, it is a certain period of time during which anlage and formation of different organs is performed and the influence of teratogenic factors in this period causes the disturbance of this process which results in deformities. Morphogenesis of different organs is carried out during different periods of embryogenesis and during this time the organs are the most susceptible to the teratogenic agent effect. Teratogenic agents are the viruses – bacteria, toxins, alcohol, medicine, hormones, vitamins, penetrating radiation, etc.

Congenital maldevelopment is persistent morphologic changes of the organs which appeared as a result of the region‘s or organism‘s morphogenesis disturbance and they are beyond the measures of normal variations. To the congenital maldevelopment belong:

1) absence of any organ or region – agenesia, aplasia;

2) underdevelopment of an organ – hypoplasia;

3) excessive development – hyperplasia;

4) change in forms: conjugated organs, arthrodesia or stenosis of apertures or canals, nonclosure of embryonic fissures – persistence, eversion – ectropion;

5) change in organs‘ location – ectopia;

6) persistence of embryonic (provisional) organs, more frequently of branchial arches or their remnants.

Apart from the pathology of organs their can be congenital maldevelopment with disturbance in differentiation of some tissues of:

- skeletal muscles – congenital Oppenheim‘s myopathy;
- connective tissue – Marphan‘s disease;
- skin – ichthyosis congenita;
- bones of cartilage genesis – congenital chondrodysplasia.

Congenital maldevelopment can be simple – when one organ is involved, complicated – a few organs of one system and numerous – organs of few systems.

Congenital heart defect (CHD), also known as a congenital heart anomaly or congenital heart disease, is a problem in the structure of the heart that is present at birth. Signs and symptoms depend on the specific type of problem. Symptoms can vary from none to life-threatening. When present they may include rapid breathing, bluish skin, poor weight gain, and feeling tired. It does not cause chest pain. Most congenital heart problems do not occur with other diseases. Complications that can result from heart defects include heart failure.

The cause of a congenital heart defect is often unknown. Certain cases may be due to infections during pregnancy such as rubella, use of certain medications or drugs such as alcohol or tobacco, parents being closely related, or poor nutritional status or obesity in the mother. Having a parent with a congenital heart defect is also a risk factor. A number of genetic conditions are associated with heart defects including Down syndrome, Turner syndrome, and Marfan syndrome. Congenital heart defects are divided into two main groups: cyanotic heart defects and non-cyanotic heart defects, depending on whether the child has the potential to turn bluish in color. The problems may involve the interior walls of the heart, the heart valves, or the large blood vessels that lead to and from the heart.

A number of classification systems exist for congenital heart defects. In 2000 the International Congenital Heart Surgery Nomenclature was developed to provide a generic classification system.

Hypoplasia can affect the heart, typically resulting in the underdevelopment of the right ventricle or the left ventricle. This causes only one side of the heart to be capable of pumping blood to the body and lungs effectively. Hypoplasia of the heart is rare but is the most serious form of CHD. It is called hypoplastic left heart syndrome when it affects the left side of the heart and hypoplastic right heart syndrome when it affects the right side of the heart. In both conditions, the presence of a patent ductus arteriosus (and, when hypoplasia affects the right side of the heart, a patent foramen ovale) is

vital to the infant's ability to survive until emergency heart surgery can be performed, since without these pathways blood cannot circulate to the body (or lungs, depending on which side of the heart is defective). Hypoplasia of the heart is generally a cyanotic heart defect.

Obstruction defects occur when heart valves, arteries, or veins are abnormally narrow or blocked. Common defects include pulmonic stenosis, aortic stenosis, and coarctation of the aorta, with other types such as bicuspid aortic valve stenosis and subaortic stenosis being comparatively rare. Any narrowing or blockage can cause heart enlargement or hypertension.

Septal defects. The septum is a wall of tissue which separates the left heart from the right heart. Defects in the interatrial septum or the interventricular septum allow blood to flow from the right side of the heart to the left, reducing the heart's efficiency. Ventricular septal defects are collectively the most common type of CHD, although approximately 30% of adults have a type of atrial septal defect called probe patent foramen ovale.

Cyanotic defects. Cyanotic heart defects are called such because they result in cyanosis, a bluish-grey discoloration of the skin due to a lack of oxygen in the body. Such defects include persistent truncus arteriosus, total anomalous pulmonary venous connection, tetralogy of Fallot, transposition of the great vessels, and tricuspid atresia.

Neural tube defects (NTDs) are a group of conditions in which an opening in the spinal cord or brain remains from early in human development. In the 3rd week of pregnancy called gastrulation, specialized cells on the dorsal side of the embryo begin to change shape and form the neural tube. When the neural tube does not close completely, an NTD develops.

Specific types include: spina bifida which affects the spine, anencephaly which results in little to no brain, encephalocele which affects the skull, and iniencephaly which results in severe neck problems.

Facial abnormalities number as the most frequent congenital anomalies (1:1000 newborns) and are often encountered in combined forms, occurring with other anomalies. Probably environmental factors as well as genetic factors play a role.

Cheiloschisis is a disorder during the fusioning of the maxillary process with the prolabium (both globular processes of the medial nasolateral process). This disorder can occur unilaterally or bilaterally.

In **cheilognathoschisis,** besides the soft tissue fusion disorder of the upper lip the fusing of the lateral edges of the primary palate with the two anterior edges of the secondary palate is also disturbed. This disorder can also occur unilaterally or bilaterally.

Cheilognathopalatoschisis (cleft lip, jaw and palate). In addition to the two previously mentioned disorders there is also a fusion disorder of the left and right portions of the secondary palatine lamina.

Since it is not possible for such an infant to suck and thereby take in nourishment a surgical separation between the nasal and oral cavities must be undertaken as quickly as possible.

Facial cleft. The disorders that affect the whole face are much more seldom. In an oblique facial cleft a fissure runs from the lower lid edge to the lower edge of the nasal opening. This results from a deficient fusion of the epithelium of the lacrimonasal duct. It can occur unilaterally or bilaterally or even combined with a cleft lip-jaw-palate.

The middle cleft face can be understood mainly as a disorder of the bringing to the front of the nose and eyes. Thereby no flattening of the medial facial furrows occurs, e.g., between the two globular processes. It is supposed that this comes from an inhibition of tissue proliferation in this region.

The transversal cleft face can only arise via a disorder of cheek formation and a survival of the early, primitive oral fissure (macrostomia) that extends into the anlage region of the ears (between the 1st and 2nd pharyngeal arches).

Fetopathies are pathologies of the fetal period, from the 76th to the 280th day of pregnancy, during which the basic tissue differentiation of the organs is carried out. Two types of manifestations are typical: blood-circulation disorders, dystrophy and necroses, mutated immune reactions and compensatory and time-serving processes. Disturbances of tissue morphogenesis are typical of early fetopathies, reactive reactions – of the late ones. Fetus infection takes place in ascending way through genital organs and placenta and in a descending haematogenic way, mainly with either salpingitis or ovaritis. Morphologically infectional fetopathies manifest through generalization of the inflammatory process with numerous foci of reactive necroses, granuloma formation, hemorrhagic syndrome resulted from vasculitis, hemolytic jaundice, retention of foci of extramedullar hematosis, accidental involution (athrophy) of the retrosternal gland (thymus), general hypothrophy, prematurity. As a rule, such infants die during their first months of life. If they survive, persistent changes in the organs remain that cause disability.

Noninfectious fetopathies can be early or late. To the early ones belong: hypertrophic pylorostenosis, megacolon, megaurethra, agenesis, hypoplasia or hyperplasia of bile ductules, polycystic lung disease, polycystic renal disease, etc., to the late ones – hemolytic disease of the infants, fetal mucoviscidosis, endocardial fibroelastosis, diabetic and alcoholic fetopathy, etc.

PATHOLOGIES OF THE INFANTS

Perinatal period (period ―around delivery‖) lasts from the 154th day of the intrauterine life of fetus (22 weeks of pregnancy) to the first week of the extrauterine independent life. Infant is a neonate which has begun to breathe by itself. Stillborn is a fetus which doesn‘t breathe at the moment of birth and it could not be stimulated artificially although the heart beating can be observed during some time. Stillbirth and death of infants during the first seven days after delivery are called perinatal mortality. Perinatal period and corresponding pathology and mortality can be divided into antenatal (prenatal), intranatal (during the delivery), postnatal (postpartum) or neonatal.

Features of prematurity: gestation duration is less than 38 weeks, the weight of fetus is less than 2500 g, height – less than 45 cm, long, lanugo hair on the face, shoulders, back, soft auricles, underdeveloped nails, the boys‘ testicles are not dropped into the gates and the girls‘ pudendal fissure gapes because of the maldevelopment of vulvar lips, cranial bones are soft, foci of bones in the long cortical bones are absent.

Features of postmaturity: gestation duration is over 41 weeks, dryness, desquamation and partial maceration of skin, general hypothrophy, anemia, water, umbilical cord and membranes are imbued with meconium into bottle green because of hypoxia.

To the pathology of infants belong asphyxia, pneumopathies, birth trauma, hemorrhagic and hemolytic disease of infants.

BIRTH TRAUMA is a mechanic injury of tissues and organs of the fetus during delivery. The causes which determine it are divided into three groups. The first group is those laid in the condition of fetus itself: fragility of tissues at prematurity or postmaturity, congenital maldevelopments which are accompanied by venous hyperemia, hemorrhagic syndrome, fetopathies, hypoxia. The second group is determined by pathologies in the mother‘s maternal passages: rigidity of the maternal passages tissues, inclination of pelvis, contracted pelvis, tumors, olygoamnios, early pouring-out of the waters. The third group is those laid in the course of delivery – accelerated and prolonged labor.

Morphology of the birth traumas.

Cephalic tumor appears in the part of head that adjoins the pelvic outlet. It is determined by disorders of blood-circulation and lymphokinesis. The tissues of the latter become dropsy, swollen, can suppurate.

Cephalohematoma is a hemorrhage under the cranial bones, it is always restricted to the one bone site. External hematoma is the most frequently found. It resolves slowly, undergoes organization and petrification. If there is a purulence, meningitis can develop.

Hemorrhage into the meninges and brain. Epidural, subarachnoid and intracerebral hemorrhages are distinguished. Epidural hemorrhages (internal

cephalohematoma) are always massive. They can take place when there are traumas of cranial bones and dura mater of brain. Subdural hemorrhages most frequently occur along with laceration of tentorium of cerebellum, of crescent, they are as a rule massive and located on the surface of celebrum. Subarachnoid hemorrhages are mostly determined by rupture of small veins. Unlike asphyctic, traumatic subarachnoid hemorrhages are always massive.

Intracerbral hemorrhages are caused by rupture of terminal veins, can lead to development of hematomas. Intraventricular hemorrhages are most frequently observed among the premature infants.

Spinal cord trauma is a result of injury of the spine mostly on the level of the IV cervical vertebra and is accompanied by development of descending subdural hemorrhages.

Among the skeleton bones clavicle is most frequently injured (fracture of clavicle). Paralyses of arms and diaphragm of the infants are determined by trauma of root of cervical plexus and brachial plexus. Rapture and hemorrhage into the nodding muscle results in torticollis. Among the internals liver and adrenal glands are most frequently injured.

HEMOLYTIC DISEASE of the infants develops with blood incompatibility between the mother and the fetus (mother is Rh-negative and child is Rh-positive). From the mother‘s blood anti-Rh antibodies penetrate to the child‘s blood and attack red blood cells. It develops during the second and the following gestations because immunization of the network (antibody titer) grows with gestation. Three main types of disease are distinguished – edematous, anemic and jaundice diseases. Manifestation of their certain forms depends on the period and amount of penetration of the mother‘s antibodies into the blood of fetus.

When early massive penetration of the antibodies takes place, in some cases early fetopathy develops and antenatal death of the 5-7-month-old fetus, in the others – chronic fetopathy in the form of heavy edematous form of the hemolytic disease with maldevelopment of the tissue ripening. Pathologoanatomic changes with the intrauterine fetal death manifest through maceration and autolysis. Maceration (from the lat. maceratio – maceration) is softening of the tissues by the water. Along with it edema of face and peeling of the epidermic tissue in big layers. Autolysis (from the gr. autolis – by oneself, lisis – dissolution) is an autodigestion, disintegration of tissues of the organism which takes place under aseptic conditions and effect of their own enzymes. Organs and tissues disintefrate till the formation of the uniform mass of the murrey colour. If it is chronic edematous form, the skin of the infant is pale, half-transparent, glossy, partly macerated, with solitary petechial hemorrhages. Hypodermic cellulose, cerebral tissue and cerebral membranes are

sharply dropsical, in the body cavity is transsudate (hydrops factus universalis). Liver and spleen are greatly enlarged, retrosternal gland is atrophied. The heart is enlarged due to myocardium hyperplasia, lungs are diminished. With the help of the microscope foci of extramedullar hematosis with the dominance of erythroblasts (erythroblastosis) in the liver, spleen, lymph nodi, kidneys and petechial hemorrhages, dystrophic and necrobiotic changes in the internals.

During the later and moderate penetration of the mother‘s antibodies into the blood of fetus anemic form of the hemolytic disease of the infants develops, it is more frequent observed with the premature infants. Paleness, slight pitting edemas are observed. There is no icteritiousness. The internals are anemic. Liver and spleen are slightly enlarged, they contain microscopic displays of marked erythroblastosis.

Icteritous form seldom develops itrauterinally, because placenta is able to remove bilirubin from the organism of fetus. During the massive penetration of the antibodies at delivery time a heavy postnatal icterous form of the hemolytic disease of the infants develops (icterus neonatorum gravis). Jaundice appears at the end of the first or on the second day after delivery and grows quickly. Penetration of the indirect toxic bilirubin into the brain causes the damage of ganglionic cells till their very necrosis – bilirubinic encephalopathy.

The changes develop mostly in the subcortical sections – hypostones, nuclei of the bottom of the diamond-shaped fossa, inferior olives, pale nucleus and nuclei of the cerebellum. Hypostones, nuclei of the bottom of the diamond-shaped fossa, inferior olives, pale nucleus and nuclei of the cerebellum are intensively coloured yellow – nuclear icterus. Erythroblastosis, hemosiderosis, biliarystases and thrombi, sometimes even gallstones; in the kidneys – bilirubinic infarctions are observed in the liver. Spleen is enlarged, dense. Microscopically hemosiderosis and erythroblastosis are found in it.

The children who overcame hemolytic disease can have considerable defects in the development of the central nervous system (CNS) that results in mental deficiency.

INFECTIOUS DISEASES

Infectious diseases - the diseases which are caused by infectious agents – viruses, bacteria, fungi and others.

Gate of infection is the site through which infectious agent penetrates the organism. In exogenous infections it may be intestine, skin, lungs. Endogenous infections develop when normal microflora microorganisms receives/get properties by which they leads to disease.

Common features of infectious diseases are:

1) Infection spreads by lymph, blood, intracanalicularly and also along nerves;

2) Each disease has its own causative agent;

3) Each causative agent has proper gate to entry;

4) There is development of focus of primary damage and inflammation of lymphatic vessels and nodes – lymphangitis, lymphadenitis.

5) There is development of specific local changes in each infectious disease;

6) Infectious diseases correspond to general changes in organism (skin rash, lymphadenitis, splenomegaly), inflammatory processes in vessels (vasculitis) and dystrophy of internal organs;

7) Infectious diseases have incubation period – from moment of penetration to appearance of primary symptoms; prodromal period of beginning of disease appearance; and period of basic disease appearance.

8) Outcomes of infectious diseases:

A. Death,
B. Recovery,
C. Chronic course,
D. Carriage,
E. Development of complications.

Classification of Infectious Diseases

A. Under the biological sign:

1. Antroponosis – which affect only human,
2. Antropozoonosis – which affect both human and animals,
3. Zoonosis – which affect only animals.

B. Under the etiology:

1. Bacterial,
2. Viral,
3. Ricketsiosis,
4. Fungal,
5. Protozoa,
6. Parasitic.

C. Under the route of transmission:

1. Fecal-oral – through intestine,
2. Air-droplet – through respiratory tract,
3. Blood transmissible – trough the blood,
4. Contact infectious disease – through skin,
5. Infectious through different ways.

D. Under predominant damaged system:

1. Respiratory infections,
2. Infections of digestive tract,
3. Infections of nervous system,
4. Infections of cardiovascular system,
5. Blood infectious,
6. Urinary tract infections,

DISEASES CAUSED BY VIRUSES

Viral diseases are the most common cause of human illness. However, many of the viral infections remain asymptomatic while others produce viral disease. Another peculiar feature of viral infection is that a single etiologic agent may produce different diseases in the same host depending upon host immune response and age at infection (e.g. varicella-zoster virus is causative for chickenpox as well as herpes zoster). Viruses are essentially intracellular parasites. Depending upon their nucleic acid genomic composition, they may be single-stranded or double-stranded, RNA or DNA viruses.

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis (IM) or glandular fever is a benign, self-limiting lymphoproliferative disease caused by Epstein-Barr virus (EBV), one of the herpes viruses. Infection may occur from childhood to old age but the classical acute infection is more common in teenagers and young adults. The infection is transmitted by person-to-person contact such as by kissing with transfer of virally-contaminated saliva. Groups of cases occur particularly in young people living together in boarding schools, colleges, camps and military institutions. Primary infection in childhood is generally asymptomatic, while 50% of adults develop clinical manifestations. The condition is so common that by the age of 40, most people have been infected and developed antibodies. It may be mentioned here that EBV is oncogenic as well and is strongly implicated in the African (endemic) Burkitt's lymphoma and nasopharyngeal carcinoma.

Pathogenesis. EBV, the etiologic agent for IM, is a B lymphotropic herpesvirus. The disease is characterized by fever, generalized lymphadenopathy, hepatosplenomegaly, sore throat, and appearance in blood of atypi-

cal 'mononucleosis cells'. The pathogenesis of these pathologic changes is outlined below:

1. In a susceptible sero-negative host who lacks antibodies, the virus in the contaminated saliva invades and replicates within epithelial cells of the salivary gland and then enters B cells in the lymphoid tissues which possess receptors for EBV. The infection spreads throughout the body via the blood stream or by infected B cells.

2. Viraemia and death of infected B cells causes an acute febrile illness and appearance of specific humoral antibodies which peak about 2 weeks after the infection and persist throughout life. The appearance of antibodies marks the disappearance of virus from the blood.

3. Though the viral agent has disappeared from the blood, the EBV-infected B cells continue to be present in the circulation as latent infection. EBV-infected B cells undergo polyclonal activation and proliferation. These cells perform two important roles which are the characteristic diagnostic features of IM:

i) They secrete antibodies — initially IgM but later IgG appear. IgM antibody is the heterophile anti-sheep antibody used for diagnosis of Dvl while IgG antibody persists for life and provides immunity against reinfection.

ii) They activate T lymphocytes of two types — CD8+ T lymphocytes and suppressor T cells. CD8+ T cells bring about killing of B cells while the suppressor T cells are pathognomonic atypical lymphocytes seen in blood in IM.

4. The proliferation of these cells is responsible for generalized lymphadenopathy and hepatosplenomegaly.

5. The sore throat in IM may be caused by either necrosis of B cells or due to viral replication within the salivary epithelial cells in early stage.

Clinicomorphological features. The incubation period is thought to be about 30 to 40 days. The disease incapacitates individuals for varying periods of time; some affected people are physically fit for normal activities within two or three weeks, while others remain ill for as long as two months, while children have shorter incubation period. A prodromal period of 3-5 days is followed by frank clinical features lasting for 1-3 weeks, and complete recovery after 2 months. The usual clinical features are as under:

1. During prodromal period (first 3-5 days), the symptoms are mild such as malaise, myalgia, headache and fatigue.

2. Frank clinical features (next 7-21 days) commonly are fever, sore throat and bilateral cervical lymphadenopathy. Less commonly, splenomegaly (50% patients), hepatomegaly (10% cases), transient erythematous maculopapular eruption on the trunk and extremities, and neurologic manifestations are found. Pneumonia and cardiac involvement are infrequent.

Complications. A common, but usually not serious, complication of IM is a mild inflammation of the liver, or hepatitis. The enlargement of the spleen that occurs with IM makes traumatic rupture of the spleen a possible complication. Swelling of the throat and tonsils can also lead to airway obstruction when severe. Infection in the area of the tonsil can rarely be a serious abscess referred to as a peritonsillar abscess. Another rare complication is swelling of the throat to an extent that breathing is obstructed.

The rare severe complications include destruction of red blood cells (hemolytic anemia) and inflammation of the sac surrounding the heart (pericarditis), the heart muscle itself (myocarditis), and the brain (encephalitis). IM tends to be more aggressive in patients with abnormal immune systems, such as people with AIDS or those who are taking medications that suppress immune function.

The diagnosis of IM is made by characteristic haematologic and serologic findings.

INFLUENZA

Influenza (known as "flu") is one of the most common infectious diseases. It is a highly contagious airborne disease that occurs in seasonal epidemics and manifests as an acute febrile illness with variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death. Influenza causes significant loss of workdays, human suffering, and mortality.

Although the seasonal strains of influenza virus that circulate in the annual influenza cycle constitute a substantial public health concern, far more lethal influenza strains than these have emerged periodically. These deadly strains produced 3 global pandemics in the last century, the worst of which occurred in 1918. Called the Spanish flu, this pandemic killed an estimated 20-50 million persons.

Besides humans, influenza also infects a variety of animal species. Some of these influenza strains are species-specific, but new strains may spread from other animals to humans. The term avian influenza, in this context, refers to zoonotic human infection with an influenza strain that primarily affects birds. Swine influenza refers to infections from strains derived from pigs. The 2009 influenza pandemic was a recombinant influenza involving a mix of swine, avian, and human gene segments (H1N1 Influenza (Swine Flu)).

Influenza viruses are encapsulated, negative-sense, single-stranded RNA viruses of the family Orthomyxoviridae. The core nucleoproteins are used to distinguish the 3 types of influenza viruses: A, B, and C. Influenza A viruses cause most human and all avian influenza infections. The RNA core consists of 8 gene segments surrounded by a coat of 10 (influenza A) or 11

(influenza B) proteins. Immunologically, the most significant surface proteins include hemagglutinin (H) and neuraminidase (N).

Hemagglutinin and neuraminidase are critical for virulence, and they are major targets for the neutralizing antibodies of acquired immunity to influenza. Hemagglutinin binds to respiratory epithelial cells, allowing cellular infection. Neuraminidase cleaves the bond that holds newly replicated virions to the cell surface, permitting the infection to spread.

Influenza viruses spread from human to human via aerosols created when an infected individual coughs or sneezes. Infection occurs after an immunologically susceptible person inhales the aerosol. If not neutralized by secretory antibodies, the virus invades airway and respiratory tract cells.

Once the virus is within host cells, cellular dysfunction and degeneration occur, along with viral replication and release of viral progeny. As in other viral infections, systemic symptoms result from release of inflammatory mediators.

Incubation period is 2-4 days. Virus penetrates the bronchial and alveolar epithelium and leads to their necrosis and erosion. Then virus enters into blood and shows paralytic actions on vessels (causes congestion and stasis); and damages defense systems of organism that leads to development of secondary infection.

Forms of influenza:

1. *Simple form* – there is acute catarrhal inflammation of nasal epithelium, laryngeal and bronchial mucosa. Recovery occurs in 5-6 days.

2. *Moderate form* – there is an inflammation in upper and lower respiratory tract. Bronchioles and lung parenchyma are also affected. Hemorrhagic inflammation and necrosis zones appear in trachea and bronchi due to obstruction of the bronchial lumen by desquamated epithelium. Acute emphysema and atelectasis of lungs may develop. Signs of pneumonia are accompanied with appearance of viral particles in bronchial and alveolar epithelium. Recovery occurs in 3-4 weeks.

3. *Severe form* – it may be of two variants:

i) with general intoxication – there are serous-hemorrhagic inflammation in trachea and bronchi, foci of pneumonia in lungs with possibility of hemorrhagic lung edema. Patients may develop hemorrhagic syndrome with the hemorrhages into brain, serous and mucous membranes, skin, that may causes death;

ii) with pulmonary complications – develops due to association with secondary infection and is characterized by development of fibrinous-

hemorrhagic inflammation in the trachea, bronchopneumonia, formation of abscesses, hemorrhages and pleuritis.

Dystrophic changes are observed in the internal organs. There are impairment in circulation and inflammatory processes; thrombi in vessels may arise.

In children Influenza causes more severe changes and affects the nervous system, respiratory system with pulmonary complications (edema of tracheal mucous membrane, asphyxia).

PARAINFLUENZA

It is caused by parainfluenza virus. Source and route of transmission is the same as in influenza.

Human parainfluenza viruses (hPIVs) are a group of four distinct serotypes of enveloped single-stranded RNA viruses belonging to the paramyxovirus family. These viruses are closely associated with both human and veterinary disease.

Clinical manifestation are like in influenza, but not so severe. There is damage of upper respiratory tract. Sometimes in children croup develops (it results from the spasm of laryngeal muscles and edema of the mucous membrane, that may cause an asphyxia). Mucous membrane usualy demonstrates moderate inflammatory infiltration and congestion. The most common complications are secondary bacterial infections, airway obstruction because of croup and bronchiolitis, bronchopneumonia, otitis. They are more dangerous for children.

RESPIRATORY SYNCYTIAL VIRUS INFECTION

Respiratory syncytial virus (RSV) is a virus that causes respiratory tract infection. It is a major cause of lower respiratory tract infections and hospital visits during infancy and childhood.

RSV is a negative-sense, single-stranded RNA virus of the family Paramyxoviridae, which includes common respiratory viruses such as those causing measles and mumps. Its name comes from the fact that F proteins on the surface of the virus cause the cell membranes on nearby cells to merge, forming syncytia.

In temperate climates there is an annual epidemic during the winter months. In tropical climates, infection is most common during the rainy season.

The incubation time (from infection until symptoms arrive) is 4–5 days. For adults, RSV produces mainly mild symptoms, often indistinguishable from common colds and minor illnesses. The Centers for Disease Control consider RSV to be the "most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of

age in the United States". For some children, RSV can cause bronchiolitis, leading to severe respiratory illness requiring hospitalization and, rarely, causing death. This is more likely to occur in patients that are immunocompromised or infants born prematurely. Other RSV symptoms common among infants include listlessness, poor or diminished appetite, and a possible fever.

However, it can cause serious problems in young babies, including pneumonia and severe breathing problems. There is damage of upper respiratory tract and lungs with the development of laryngotracheitis, bronchitis, bronchopneumonia.

Microscopicaly there is proliferation of epithelium in the form of nipples. That can lead to impairment in bronchial lumen and development of acute emphysema and atelectasis.

Recurrent wheezing and asthma are more common among individuals who suffered severe RSV infection during the first few months of life than among controls; whether RSV infection sets up a process that leads to recurrent wheezing or whether those already predisposed to asthma are more likely to become severely ill with RSV has yet to be determined.

Death can occur from pneumonia and other pulmonary complications.

ADENOVIRUS INFECTION

It most commonly causes illness of the respiratory system; however, depending on the infecting serotype, they may also cause various other illnesses and presentations.

Causative agent is DNA-containing viruses. Adenoviruses are a group of viruses that can infect the membranes (tissue linings) of the respiratory tract, conjunctiva, lymphoid tissue of pharynx, intestine and lymph nodes.

Adenoviral infections affect babies and small children much more often than adults. Adenovirus is highly contagious, so multiple cases are common in close-contact settings like childcare centers, schools, hospitals, and summer camps.

The illness often appears flu-like and can include symptoms of acute rhinolaryngotracheobronchitis, pharyngitis, rhinitis, cough, and swollen lymph nodes (cervical and submandibular). Sometimes the respiratory infection leads to acute otitis media, an infection of the middle ear. Symptoms of conjunctivitis include red eyes, discharge, tearing, and the feeling that there's something in the eye.

Severe form is characterized by the intestine, liver, kidney, pancreas and brain damage. Because of secondary infection association pus is formed.

Complications include otitis, pneumonia, lymphadenitis, tonsillitis. Patients with compromised immune systems are especially susceptible to severe complications of adenovirus infection.

SMALL POX

It was an infectious disease caused by either of two virus variants, Variola major and Variola minor. The disease is also known by the Latin names Variola or Variola vera, derived from varius ("spotted") or varus ("pimple").

Infection with smallpox is focused in small blood vessels of the skin and in the mouth and throat before disseminating. In the skin it results in a characteristic maculopapular rash and, later, raised fluid-filled blisters.

Classification. There were two clinical forms of smallpox. *Variola major* was the severe and most common form, with a more extensive rash and higher fever and had an overall mortality rate of 30–35 percent.

V. minor caused a milder form of disease (also known as alastrim, cottonpox, milkpox, whitepox, and Cuban itch) which killed about 1 percent of its victims. It was a less common presentation, and a much less severe disease, with historical death rates of 1 percent or less.

Subclinical (asymptomatic) infections with variola virus were noted but were not common. In addition, a form called variola sine eruptione (smallpox without rash) was seen generally in vaccinated persons. This form was marked by a fever that occurred after the usual incubation period and could be confirmed only by antibody studies or, rarely, by virus isolation.

Epidemiology. The most frequent mode of transmission is person to person. The virus spreads through direct deposit of infective droplets onto the nasal, oral, or pharyngeal mucosal membranes or the alveoli of the lungs. These droplets are acquired through face-to-face contact with the infectious person. Virus particles can remain on such items as clothing, bedding, and surfaces for up to one week. Virus enters the blood after penetrating of the respiratory mucous membrane and spreads to the skin, intestines, lungs, kidneys, and brain.

Pathogenesis. The incubation period between contraction and the first obvious symptoms of the disease is around 12 days. Once inhaled, variola major virus invades the oropharyngeal (mouth and throat) or the respiratory mucosa, migrates to regional lymph nodes, and begins to multiply. In the initial growth phase the virus seems to move from cell to cell, but around the 12th day, lysis of many infected cells occurs and the virus is found in the bloodstream in large numbers (this is called viremia), and a second wave of multiplication occurs in the spleen, bone marrow, and lymph nodes. The initial or prodromal symptoms are similar to other viral diseases such as influenza and the common cold: fever of at least 38.3 °C (101 F), muscle pain, malaise, headache and prostration. As the digestive tract is commonly involved, nausea and vomiting and backache often occur. The prodrome, or preeruptive stage, usually lasts 2–4 days. By days 12–15 the first visible lesions—small reddish spots called enanthem—appear on mucous membranes of the mouth, tongue, palate, and throat, and temperature falls to near normal.

These lesions rapidly enlarge and rupture, releasing large amounts of virus into the saliva.

Clinical picture. The eruptive stage is characterized by maculopapular rash that progresses to papules, then vesicles, and then pustules and scab lesions.

A rash develops on the skin 24 to 48 hours after lesions on the mucous membranes appear. Typically the macules first appear on the forehead, then rapidly spread to the whole face, proximal portions of extremities, the trunk, and lastly to distal portions of extremities. The process takes no more than 24 to 36 hours, after which no new lesions appear.

According to the main skin symptoms there are 3 forms of small pox:

1. *Papulopustular form* is characterized by appearance of papulopastules on the face, neck, scalp, chest and back. Balloon dystrophy develops in epidermal cells which contain viral particles. These cells attach to each other and form vesicles which are separated by epithelial bridges. These papules then convert into vesicles and into pustules. Necrosis develops in the centre of pustule. On the 3rd week healing of pustule occurs and scars are formed at pustular places.

2. *Hemorrhagic form* is a association of hemorrhage, edema and skin rach. Vesicles rupture with the formation of bleeding erosion – black chickenpox and it ends with death of patient. The hemorrhagic variety of variola has a much higher death rate (95%) than classic smallpox and leads to death more quickly. Infected people often die before the pustules form. This variety is recognizable by certain types of bleeding sores in mucous tissues.

3. *Varioloid form* is the simple form seen in vaccinated persons.

Differentiated diagnosis. The most common disease that may be confused with smallpox is varicella, or chickenpox. In contrast to them, smallpox lesions appear on days 12 to 14, and the infection manifests with high fevers, malaise, and prostration with accompanying headache and backache. Smallpox lesions begin as a maculopapular rash, progress into vesicular lesions, and finally develop into pustules.

Historically, smallpox has an overall fatality rate of about 30 percent; however, the malignant and hemorrhagic forms are usually fatal. Death may occur due to toxicosis or secondary infections.

Smallpox pustular lesions persist for 8 to 9 days, the lesions then crust, and scabs form and separate, producing the characteristic pitted scarring 14 days after they appear.

CHICKENPOX

It is caused by the varicella-zoster virus (VZV), a DNA virus belonging to the Herpesviridae family. Similar to smallpox, chickenpox is transmitted through respiratory secretions or contact with skin lesions.

Chickenpox manifests with an abrupt onset of a pruritic rash, low-grade fever, and malaise. As chickenpox virus reaches the skin, it causes the characteristic rash, which appears in crops of lesions throughout the course of the infection.

Chickenpox lesions appear predominately on the central and proximal upper extremities; fever and symptoms resolve in three to five days. Chickenpox and smallpox are most often confused during the first two to three days of the rash. However, the lesions and clinical course of the two diseases aid in the ability to distinguish one from another. For example, all smallpox lesions develop at the same pace on all parts of the body (concentrated on the face and limbs and may appear on the palms or soles) and appear identical. Chickenpox lesions, which look like small red papules, appear in crops, are denser on the trunk, and are rarely found on the palms or soles.

In chickenpox organs are damaged with the appearance of vesicles and pustules in mucous membrane of trachea and bronchi, oral cavity, oesophagus, intestine. Sometimes necrotic pneumonia and orchitis develop. There is damage of conjunctiva with loss of vision and damage of middle ear with hearing loss. Chickenpox that affects a healthy child is usually a self-limited disease.

Increased morbidity occurs in adult and immunocompromised populations.

POLIOMYELITIS

It is an acute infectious disease caused by the poliovirus (RNA – containing enterovirus). In about 0.5% of cases there is muscle weakness resulting in an inability to move. Because of this it is often called polio or infantile paralysis.

Poliomyelitis is highly contagious via the fecal-oral (intestinal source) and the oral-oral (oropharyngeal source) routes. It is seasonal in temperate climates, with peak transmission occurring in summer and autumn. These seasonal differences are far less pronounced in tropical areas. The time between first exposure and first symptoms, known as the incubation period, is usually 6 to 20 days, with a maximum range of three to 35 days. Virus particles are excreted in the feces for several weeks following initial infection.

This group of RNA viruses colonize the gastrointestinal tract — specifically the oropharynx and the intestine.

Few numbers of viruses enter the blood and go to other sites where the virus multiplies more extensively. Another round of viremia (presence of virus in the blood) leads to invasion of the central nervous system (spinal cord and brain). In around 1% of infections, poliovirus spreads along certain nerve fiber pathways, preferentially replicating in and destroying motor neurons

within the spinal cord, brain stem, or motor cortex. This leads to the development of paralytic poliomyelitis, the various forms of which (spinal, bulbar, and bulbospinal) vary only with the amount of neuronal damage and inflammation that occurs, and the region of the CNS affected.

The destruction of neuronal cells produces lesions within the spinal ganglia; these may also occur in the reticular formation, vestibular nuclei, cerebellar vermis, and deep cerebellar nuclei. Inflammation associated with nerve cell destruction often alters the color and appearance of the gray matter in the spinal column, causing it to appear reddish and swollen. Other destructive changes associated with paralytic disease occur in the forebrain region, specifically the hypothalamus and thalamus. The molecular mechanisms, by which poliovirus causes paralytic disease, are poorly understood.

There are three clinic stages: acute, recovery and residual-paralysis stage.

Acute stage. Poliovirus infections can be divided into minor and major forms.

Minor illnesses. The minor associated illnesses occur 1–3 days before the onset of paralysis, with gastrointestinal complaints such as nausea and vomiting, abdominal cramps and pain, and diarrhea. There are also systemic manifestations, such as sore throat, fever, malaise, and headache. This stage lasts usually for 2–3 weeks but may extend for up to 2 months; the presence of any tenderness in the muscles is evidence that the acute stage is not over.

Major illnesses. The major associated illnesses include all forms CNS disease caused by poliovirus, including aseptic meningitis (or nonparalytic polio), polio encephalitis, bulbar polio, and paralytic poliomyelitis, alone or in combination.

The clinical findings associated with an attack of polio are as follows:

- ✓ Fever, neck stiffness (nuchal rigidity), and a pleocytosis in the CSF,
- ✓ Profound asymmetrical muscle weakness,

The initial phase is typically followed by some recovery of muscle strength, but permanent weakness results from necrosis of anterior horn cells,

- ✓ Rarely, a transverse myelitis with paraparesis, urinary retention, sensory symptoms and signs, autonomic dysfunction (including hyperhidrosis or hypohidrosis), and decreased limb temperature may occur.

Recovery stage. In this stage, also known as the convalescent stage, the acute symptoms and muscle tenderness disappear and the paralyzed muscles begin to recover. This stage lasts for up to 2 years after the onset of the disease. During this entire period, there is gradual recovery of the muscles; the recovery is rapid in the first 6 months but is slower during the subsequent months.

Residual-paralysis stage. The period beyond 2 years after the onset of the disease is called the residual-paralysis stage. No recovery of muscle power occurs in this stage. Deformities are liable to occur due to imbalance of muscle power and poor posture. There is also disuse atrophy of muscles and shortening of the leg due to interference with growth. In neglected cases, gross fixed deformities of the hip, knee, and foot occur with severe wasting of muscles.

Death may occur due to damage of respiratory center and paralysis of respiratory muscles.

In April 2012, the World Health Assembly declared the completion of polio eradication a programmatic emergency for global public health. But in 2015, polio was believed to remain endemic in only two countries: Pakistan, and Afghanistan, although it continued to cause epidemics in other nearby countries due to hidden or reestablished transmission.

MUMPS (EPIDEMIC PAROTITIS)

Mumps is an acute, self-limited, systemic viral illness characterized by the swelling of one or more of the salivary glands, typically the parotid glands.

Today, most reported mumps cases occur in school-aged children (age 5-14). The illness is caused by the RNA virus, Rubulavirus. Rubulavirus is within the genus *Paramyxovirus* and is a member of the family Paramyxoviridae. This virus contains a single-stranded, negative-sense RNA surrounded by a glycoprotein envelope. Of 2 glycoproteins on the surface of the RNA viral envelope, one mediates neuraminidase and hemagglutination activity, whereas the other is responsible for fusion to the lipid membrane of the host cell.

Mumps occurs worldwide. Humans are the only known natural hosts. This *Paramyxovirus* is highly infectious to nonimmune individuals and is the only cause of epidemic parotitis. Although mumps cases occur at any time of year, an increase in case number is noted during late winter and early spring.

Humans are the sole reservoir for the mumps virus. The transmission mode is person to person via respiratory droplets and saliva, direct contact, or fomites. The presence of maternal antibodies typically protects infants younger than 1 year from the disease. Infections can be a symptomatic in 20-30% of persons. Of those with symptomatic infection, adults tend to be more severely affected when compared to children. Lifelong immunity usually follows clinical or subclinical mumps infection, although second infections have been documented.

Mumps has an incubation period of 16-18 days. After this period, prodromal symptoms (such as low-grade fever, malaise, myalgias, headache, and anorexia) occur; these symptoms can last 3-5 days.

After the prodromal period (about 48 h), one or both parotid glands begin to enlarge which occurs in 30 to 40% of all patients and in 95% of those who are symptomatic. Parotitis is caused by the direct viral infection of the ductal epithelium and presents with localized gland inflammation. Ordinarily, the parotid glands are not palpable; but in patients with mumps, parotid swelling increases rapidly over several days. Edema over the parotid gland presents with non-discrete borders, pain with pressure, and obscures the angle of the mandible. Parotid swelling can last for 10 days.

A patient is considered infectious from about 3 days before the onset of and up to 4 days after the start of active parotitis.

Cell necrosis and inflammation with mononuclear cell infiltration is the tissue response. Salivary glands show edema and desquamation of necrotic epithelial cells lining the ducts. Focal hemorrhage and destruction of germinal epithelium may occur, leading to duct plugging.

Permanent complications of mumps infection: aseptic meningitis/encephalitis, sensorineural hearing loss/deafness, pancreatitis, orchitis, oophoritis. Other rare complications include myocarditis, thyroiditis, mastitis, viral pneumonia nephritis, arthritis, and thrombocytopenia purpura. Death due to mumps is rare.

Mumps infection in pregnant women increases the risk of embryonic loss, spontaneous fetal loss, and fetal death, especially during the first trimester of pregnancy (reported to be as high as 27%).

MEASLES

Measles is best known for causing a fever and rash in childhood, but measles can affect other parts of the body and sometimes occurs in adults.

There are two types of measles, each caused by a different virus.

1. The rubeola virus causes "red measles," also known as "hard measles" or just "measles." Although most people recover without problems, rubeola can lead to pneumonia or inflammation of the brain (encephalitis).
2. The rubella virus causes "German measles," also known as "three-day measles." This is usually a milder disease than red measles. However, this virus can cause significant birth defects if an infected pregnant woman passes the virus to her unborn child.

Both the rubeola and rubella viruses are spread through the respiratory route. In fact, the rubeola virus is one of the most contagious viruses known to man. As a result, it can spread rapidly in a susceptible population. Infected

people carry the virus in their respiratory tract before they get sick, so they can spread the disease without being aware of it.

Source of infection – sick person.

Route of transmission: air-droplet. Viruses penetrate the mucous membrane of upper respiratory tract and conjunctiva, enter into the blood and causes skin rashes. Measles virus decreases immunity that usually leads to secondary infectious.

Rubeola ("red measles" or "hard measles"). Symptoms appear about 10-14 days after a person is infected with the rubeola virus. This is called the incubation period. During this period, the virus is multiplying. Symptoms occur in two phases.

The early phase begins with these symptoms: fever, run-down or lethargic feeling, cough, red eyes (conjunctivitis), runny nose.

The red measles rash develops from two to four days later. The rash usually starts on the face, spreading to the trunk and then to the arms and legs.

Catarrhal inflammation develops in fauces mucous membrane. It is characterized by congestion, edema, secretion of mucous and inflammatory infiltration. Sometimes necrosis croup and rashes appear on the mucous membrane (enanthema). Enanthema develops on internal surface of cheeks at the place of premolars (spots of Bilshow – Filatov-Kopilik) before appearance of skin rashes. After decrease of inflammation the necrotized epithelial layer is separated. There is enlargement of lymph nodes, spleen, tonsils with appearance of giant macrophages in them.

Interstitial pneumonia with appearance of giant macrophages develops in lungs. In rare cases encephalitis occurs.

Complications result from association with secondary infection and development of bronchitis, pneumonia, lung abscess. Patients die due to pulmonary complications and asphyxia in croup.

Rubella ("German measles"). German measles causes milder symptoms than red measles. The incubation period between getting the virus and getting sick is 10 days to two weeks.

Initially, some people experience fatigue, low-grade fever, headache, or red eyes several days before the rash appears. These symptoms are more common in adults than in children.

Swollen, tender lymph nodes may occur in the back of the neck.

The rash is light red to pink. It starts as individual spots that may merge together over time. The rash usually starts on the face and moves down to the trunk. The rash does not usually itch, but as it clears up, the skin may shed.

Adult women who get rubella may get painful joints for days to weeks after the infection. This typically affects the hands, wrists, and knees.

Symptoms may be so mild that they are not even noticed, especially in children. Most symptoms resolve in a few days, but swollen lymph nodes may persist for a few weeks.

The most feared complication of rubella is "congenital rubella," which occurs when an infected pregnant woman passes the virus to her unborn child. Among other problems and birth defects, affected infants may have cataracts, heart defects, hearing impairment, and learning disabilities. The risk of transmission is highest early in pregnancy. The virus may also cause miscarriage or stillbirth.

RABIES

Rabies is a viral disease that affects the central nervous system.

The fatal madness of rabies has been described throughout recorded history, and its association with rabid canines is well known. For centuries, dog bites were treated prophylactically with cautery, with predictable and unfortunate results. In the 19th century, Pasteur developed a vaccine that successfully prevented rabies after inoculation and launched a new era of hope in the management of this uniformly fatal disease.

The rabies virus is a bullet-shaped virion with a single-stranded RNA nucleocapsid core and lipoprotein envelope. Its nucleocapsid material consists of Negri bodies, which are observed as deeply eosinophilic inclusions in the cytoplasm of infected neurons. The virus is transmitted in saliva or in aerosolized secretions from infected animals, typically via a bite. The virus is not hardy and is quickly inactivated by drying, ultraviolet rays, x-rays, trypsin, detergents, and ether.

Human rabies reflects the prevalence of animal infection and the extent of contact this population has with humans. Less than 5% of cases in developed nations occur in domesticated dogs; however, unvaccinated dogs serve as the main reservoir worldwide. Undomesticated canines, such as coyotes, wolves, jackals, and foxes, are most prone to rabies and serve as reservoirs. Animal-control and vaccination strategies currently supersede postexposure prophylaxis in preventing the spread of rabies.

Rabies is more prevalent in the developing world than in industrialized countries. The World Health Organization (WHO) estimates that rabies is responsible for 35,000-50,000 deaths annually worldwide and that gross underreporting is likely. An estimated 10 million people receive postexposure prophylaxis each year after being exposed to animals with suspected rabies. Unvaccinated dogs are the major reservoir for rabies. Global reservoirs of rabies virus are as follows: Europe - foxes, bats; Middle East - wolves, dogs; Asia – dogs; Africa - dogs, mongooses, antelopes; North America - foxes, skunks, raccoons, insectivorous bats; South America - dogs, bats.

Rabies is a highly neurotropic virus that evades immune surveillance by its sequestration in the nervous system. Upon inoculation, it enters the peripheral nerves. A prolonged incubation follows, the length of which depends on the size of the inoculum and its proximity to the CNS. Amplification occurs until bare nucleocapsids spill into the myoneural junction and enter motor and sensory axons. At this point, prophylactic therapy becomes futile, and rabies can be expected to follow its fatal course, with a mortality rate of 100%.

The rabies virus travels along these axons at a rate of 12-24 mm/d to enter the spinal ganglion. Its multiplication in the ganglion is heralded by the onset of pain or paresthesia at the site of the inoculum, which is the first clinical symptom and a hallmark finding. From here, the rabies virus spreads quickly, at a rate of 200-400 mm/d, into the CNS, and spread is marked by rapidly progressive encephalitis. Thereafter, the virus spreads to the periphery and salivary glands.

Incubation period. The infected individual remains asymptomatic during this period. The average duration of incubation is 20-90 days. Rarely, incubation has been reported up to 7-19 years. In more than 90% of cases, incubation is less than 1 year. Patients may not recall exposure because of the prolonged incubation period.

The incubation period is less than 50 days if the patient is bitten on the head or neck or if a heavy inoculum is transferred through multiple bites, deep wounds, or large wounds. A person with a scratch on the hand may take longer to develop symptoms of rabies than a person who receives a bite to the head.

The rabies virus is segregated from the immune system during this period, and no antibody response is observed.

Prodromal period. The virus enters the CNS. The duration of this period is 2-10 days. Nonspecific symptoms and signs develop. Paresthesia, pain, or intense itching at the inoculation site is pathognomonic for rabies and occurs in 50% of cases during this phase; this may be the individual‘s only presenting sign. Symptoms may include the following: malaise, anorexia, headaches, fever, chills, pharyngitis, nausea, emesis, diarrhea, anxiety, agitation, insomnia, depression.

Acute neurologic period. This period is associated with objective signs of developing CNS disease. The duration is 2-7 days. Symptoms include muscle fasciculations, priapism, and focal or generalized convulsions. Patients may die immediately or may progress to paralysis, which may be present only in the bitten limb at first but usually becomes diffuse. The form of rabies known as furious rabies may develop during this period. Patients develop agitation, hyperactivity, restlessness, thrashing, biting, confusion, or hallucinations. After several hours to days, this becomes episodic and inter-

spersed with calm, cooperative, lucid periods. Furious episodes last less than 5 minutes. Episodes may be triggered by visual, auditory, or tactile stimuli or may be spontaneous. Seizures may occur. This phase may end in cardiorespiratory arrest or may progress to paralysis.

Another form of rabies, paralytic rabies, is also known as dumb rabies or apathetic rabies, because the patient is relatively quiet compared with a person with the furious form. Twenty percent of patients do not develop the furious form. Paralysis occurs from the outset, and fever and headache are prominent.

Coma. This begins within 10 days of onset, and the duration varies. Without intensive supportive care, respiratory depression, arrest, and death occur shortly after coma. Death occurs from global neurologic and organ dysfunction.

Histologic Findings. General findings on pathology include cerebral congestion and inflammation typical of encephalitis. Neuronal cell death is uncommon histopathologically.

Immunohistochemical or fluorescent antibody staining of nervous tissue, usually of unfixed brain or skin biopsy specimens with sensory nerve endings, reveals deposition of virion in the cytoplasm.

Negri bodies are observed in neurons on light microscopy and represent round cytoplasmic inclusions of assembling nucleocapsid. Only 70% of brain biopsy tissue exhibits this finding in human rabies encephalitis. Electron microscopy is more sensitive than light microscopy and reveals the characteristic bullet-shaped virion.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV is the causative agent for AIDS. The most common type is known as HIV-1 and is the infectious agent that has led to the worldwide AIDS epidemic. There is also an HIV-2 that is much less common and less virulent, but eventually produces clinical findings similar to HIV-1. The HIV-1 type itself has a number of subtypes (A through H and O) which have differing geographic distributions but all produce AIDS similarly. HIV is a retrovirus that contains only RNA.

HIV is a sexually transmitted disease. Infection is aided by Langerhans cells in mucosal epithelial surfaces which can become infected. Infection is also aided by the presence of other sexually transmitted diseases that can produce mucosal ulceration and inflammation. The CD4+ T-lymphocytes have surface receptors to which HIV can attach to promote entry into the cell. The infection extends to lymphoid tissues which contain follicular dendritic cells that can become infected and provide a reservoir for continuing infection of CD4+ T-lymphocytes. HIV can also be spread via blood or blood products, most commonly with shared contaminated needles used by persons engaging in intrave-

nous drug use. Mothers who are HIV infected can pass the virus on to their fetuses in utero or to infants via breast milk.

When HIV infects a cell, it must use its reverse transcriptase enzyme to transcribe its RNA to host cell proviral DNA. It is this proviral DNA that directs the cell to produce additional HIV virions which are released.

The genome of HIV contains only three major genes: env, gag, and pol. These genes direct the formation of the basic components of HIV. The env gene directs production of an enve-lope precursor protein gp160 which undergoes proteolytic cleavage to the outer envelope glycoprotein gp120, which is responsible for tropism to CD4+ receptors, and transmembrane glycoprotein gp41, which catalyzes fusion of HIV to the target cell's membrane. The gag gene directs formation of the proteins of the matrix p17, the "core" capsid p24, and the nucleocapsid p7. The pol gene directs synthesis of important enzymes including reverse transcriptase p51 and p66, integrase p32, and protease p11.

In addition to the CD4 receptor, a coreceptor known as a chemokine is needed for HIV infection. Chemokines are cell surface fusion-mediating molecules. Such coreceptors include CXCR4 and CCR5. Their presence on cells can aid binding of the HIV envelope glycoprotein gp120, promoting infection. Initial binding of HIV to the CD4 receptor is mediated by conformational changes in the gp120 subunit, but such conformational changes are not sufficient of fusion. The chemokine receptors produce a conformational change in the gp41 subunit which allows fusion of HIV. The differences in chemokine coreceptors that are present on a cell also explains how different strains of HIV may infect cells selectively. There are strains of HIV known as T-tropic strains which selectively interact with the CXCR4 chemokine coreceptor to infect lymphocytes. The M-tropic strains of HIV interact with the CCR5 chemokine coreceptor to infect macrophages. Dual tropic HIV stains have been identified. The presence of a CCR5 mutation may explain the phenomenon of resistance to HIV infection in some cases. Over time, mutations in HIV may increase the ability of the virus to infect cells via these routes. Infection with cytomegalovirus may serve to enhance HIV infection via this mechanism, because CMV encodes a chemokine receptor similar to human chemokine receptors.

Acquired Immunodeficiency Syndrome (AIDS). When the CD4 lymphocyte count drops below 200/microliter, then the stage of clinical AIDS has been reached. This is the point at which the characteristic opportunistic infections and neoplasms of AIDS appear. Listed below are some of the more common complications seen with AIDS with images that illustrate gross and microscopic pathologic findings.

The organ involvement of infections with AIDS represents the typical appearance of opportunistic infections in the immunocompromised host that

makes treatment more difficult. The strategies employed in AIDS patients to meet this challenge consist of (1) preserving immune function as long as possible with antiretroviral therapies, (2) using prophylactic pharmacologic therapies to prevent infections (such as Pneumocystis carinii pneumonia), and (3) diagnosing and treating acute infections as soon as possible.

Pneumocystis carinii. Pneumocystis carinii is the most frequent opportunistic infection seen with AIDS. It produces a pulmonary infection, called Pneumocystis carinii pneumonia (PCP), but rarely disseminates outside of lung. The most common clinical findings in patients with PCP are acute onset of fever, non-productive cough, and dyspnea. Chest radiograph may show perihilar infiltrates. Diagnosis is made histologically by finding the organisms in cytologic (bronchoalveolar lavage) or biopsy (transbronchial biopsy) material from lung, typically via bronchoscopy. The cysts of P.carinii stain brown to black with the Gomori methenamine silver stain. With Giemsa or Dif-Quik stain on cytologic smears, the dot-like intracystic bodies are seen.

Cytomegalovirus. Cytomegalovirus (CMV) is the most frequent disseminated opportunistic infection seen with AIDS. It causes the most serious disease as a pneumonia in the lung, but it can also cause serious disease in the brain and gastrointestinal tract. It is also a common cause for retinitis and blindness in persons with AIDS. CMV is identified by the presence of very large cytomegalic cells with enlarged nuclei that contain a violaceous intranuclear inclusion surrounded by a clear halo. Sometimes, basophilic stippling is present in the cytoplasm.

Mycobacteria. Mycobacterial infections are frequently seen with AIDS. Mycobacterium tuberculosis has been increasing in frequency since the start of the AIDS epidemic. The appearance of M.tuberculosis with AIDS is similar to that of non-AIDS patients, with granulomatous pulmonary disease, though the infection may be more extensive or may be disseminated to other organs. Mycobacte-rium avium complex (MAC) infection is more unique to AIDS and is characterized by involvement mostly of the organs of the mononuclear phagocyte system (lymph node, spleen, liver, marrow). MAC infections are less likely to produce visible granulomas, and the lesions often consist of clusters of macrophages filled with numerous mycobacteria. Definitive diagnosis of mycobacterial disease is made by culture.

Fungal Infections. There are many types of fungi that can complicate the course of AIDS. One of the most frequent (though uncommonly life-threatening) is Candida. Oral candidiasis is often seen with HIV infection and

may presage the progression to AIDS. Candida can occasionally produce invasive infections in esophagus, upper respiratory tract, and lung.

Infections with the dimorphic fungi Cryptococcus neoformans, Histoplasma capsulatum, and Coccidioides immitis are more serious infections that are often widely disseminated. C.neoformans often produces pneumonia and meningitis.

Toxoplasmosis. Toxoplasma gondii is a protozoan parasite that most often leads to infection of the brain with AIDS. The lesions are usually multiple and have the appearance of abscesses. Less commonly, T gondii infection is disseminated to other organs.

Herpes simplex

Herpes simplex virus infection with AIDS is most likely to involve the gastrointestinal tract, mainly the esophagus and the perianal region. Herpes zoster infection of the skin can also occur prior to the onset of clinical AIDS. Herpes infections are rarely life-threatening.

Gastrointestinal Protozoal Infections. Cryptosporidium, Microsporidium, and Isospora are all capable of producing a voluminous watery diarrhea in patients with AIDS. Diagnosis can be made by examination of stool specimens and/or intestinal biopsy.

Malignant Neoplasms. Kaposi's sarcoma (KS) produces reddish purple patches, plaques, or nodules over the skin and can be diagnosed with skin biopsy. Visceral organ involvement eventually occurs in 3/4 of patients with KS. Malignant lymphomas seen with AIDS are typically of a high grade and extranodal, often in the brain. They are very aggressive and respond poorly to therapy.

Miscellaneous. Lymphoid interstitial pneumonitis (LIP) is a condition involving the lung that can be seen in AIDS in children. By chest radiograph, bilateral reticulonodular interstitial pulmonary infiltrates are seen. The earliest pathologic finding is a hyperplasia of bronchial associated lymphoid tissue with aggregates of lymphocytes and plasma cells in a bronchovascular distribution. Later lesions demonstrate diffuse lung round cell infiltrates, and lymphoid aggregates can be present.

RICKETTSIOSIS

Rickettsiae comprise a group of microorganisms that phylogenetically occupy a position between bacteria and viruses. The genus Rickettsia is included in the bacterial tribe Rickettsiae, family Rickettsiaceae, and order Rickettsiales. They are obligate intracellular gram-negative coccobacillary forms that multiply within eukaryotic cells. Rickettsiae do not stain well with Gram stain, but they take on a characteristic red color when stained by the Giemsa or Gimenez stain. They have typical gram-negative cell walls and

lack flagella. Their genome is very small, composed of 1-1.5 million bases. A general characteristic of rickettsiae is that mammals and arthropods are natural hosts. Rickettsioses are usually transmitted to humans by arthropods.

EPIDEMIC TYPHUS

It is an acute rickettsiosis with the damage of small vessels, brain and appearance of generalized rash due to infection with a microorganism called Rickettsia prowazekii.

Source of infection – sick person transmitted by body louses which spread rickettsiae with their faeces. Incubation period is 10-12 days. After that high fever develops. Vasculitis, thrombosis, vascular paresis develop in vessels, that causes the decrease of blood pressure.

Damages of cerebral vessels lead to impairment in swallowing and respiration. If sympathetic nervous system is damaged the death of patient may occur due to impairment of heart activity.

Rashes on skin has represented by red or brown color spots. Rash presents mainly on the conjunctiva.

Serous meningitis may develop. In blood vessels vascular destruction, endothelial erosion, thrombi formation (warty vasculitis), then endothelial proliferation (proliferative vasculitis) occur. Sometimes necrotic patches on vessel wall (necrotic vasculitis) appear.

Inflammatory process in epidemic typhus has granulomatous character (epidemic typhus granuloma) except in liver, spleen, lymphnodes and bone marrow. There vessels are located in center and surrounded by proliferating glial cells (in brain) or by endothelium and adeventia of vessels, and by lymphoid elements in skin.

Complications result from impairment in blood circulation due to damaged vessels. That leads to trophism impairment in skin (bed sore development) and development of bronchitis and pneumonia.

BRILL-ZINSSER DISEASE – relapsing epidemic typhus. The pathology is similar to that described for the spotted fever group of rickettsial diseases. However, the organisms appear to lie dormant, most likely in the cells of the reticuloendothelial system, until they are reactivated by an unknown stressor, multiply and cause another acute but milder infection.

This reactivation event can then be transmitted to other individuals through fecal matter of the louse vector, and form the focus for a new epidemic of typhus.

DISEASES CAUSED BY BACTERIA

In order to gain an upper hand in human host, bacteria must resist early engulfment by neutrophils. They survive and damage the host in a variety of

ways such as by generation of toxins (e.g. gas-forming anaerobes), by forming a slippery capsule that resists attachment to macrophages (e.g. pneumococci), by inhibition of fusion of phagocytic vacuoles with lysosomes (e.g. tubercle bacilli) etc.

DIPHTHERIA

Diphtheria is an infection caused by the bacterium *Corynebacterium diphtheria*. It is a potentially fatal, contagious disease that usually involves the nose, throat, and air passages but may also infect the skin. The name of the disease is derived from the Greek ―diphtheria‖, meaning leather hide. The disease was described in the 5th century BCE by Hippocrates, and epidemics were described in the 6th century AD by Aetius. Its most striking feature is the formation of a grayish membrane covering the tonsils and upper part of the throat.

Source of infection are bacilli-carriers and rarely sick person. Children are more frequently affected.

Corynebacterium Diphtheriae multiplies in the place of invasion and releases exotoxin. Diphtheria toxin is produced by C. diphtheriae only when infected with a bacteriophage that integrates the toxin-encoding genetic elements into the bacteria. Exotoxin depresses tissue metabolism and impairs catecholamine synthesis and causes epithelial necrosis, vascular dilation and formation of fibrinous layer on the mucous membrane surface. Local tissue destruction enables the toxin to be carried lymphatically and hematologically to other parts of the body. Elaboration of the diphtheria toxin may affect distant organs such as the myocardium, nervous system, kidneys and adrenal glands. Sometimes it develops hyper toxic form due to hypersensitivity to exotoxin.

Local changes are localized in mucous membrane of fauces, tonsils, upper respiratory tract, sometimes in conjunctiva and on sex organs in girls.

Anterior Nasal Diphtheria

The onset of anterior nasal diphtheria is indistinguishable from that of the common cold and is usually characterized by a mucopurulent nasal discharge (containing both mucus and pus) which may become blood-tinged. A white membrane usually appears on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin in this location, and it can be terminated rapidly by diphtheria antitoxin and antibiotic therapy.

Pharyngeal and Tonsillar Diphtheria

The most common sites of diphtheria infection are the pharynx and the tonsils. Infection at these sites is usually associated with substantial systemic absorption of toxin.

The onset of pharyngitis is insidious. Early symptoms include malaise, sore throat, anorexia, and low-grade fever. Within 2–3 days, a bluish-white membrane appears and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted, the membrane is greyish-green, or black if bleeding has occurred. There is a minimal amount of mucosal erythema surrounding the membrane.

The pseudomembrane is firmly adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive pseudomembrane formation may result in respiratory obstruction.

While some patients may recover at this point without treatment, others may develop severe disease. Fever is usually not high, even though the patient may appear quite toxic. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic ―bullneck‖ appearance. If enough toxin is absorbed, the patient may develop severe prostration, striking pallor, rapid pulse, stupor, and coma, and may even die within 6 to 10 days.

Regional lymph nodes of neck are enlarged with necrotic patches. Cardiac toxicity typically occurs after 1-2 weeks of illness following improvement in the pharyngeal phase of the disease. It leads to death from cardiac insufficiency and this is known as early heart paralysis. If patients remain alive they finish with cardiosclerosis.

Nerves and ganglions of the vegetative nervous system, mainly which are located near the fauces (n.glossopharyngeal, n.vagus, n.phrenic) are damaged that causes the late paralysis of the soft palate, diaphragm and heart.

Necrosis and hemorrhage may appear in the adrenal medulla, and necrotic nephrosis - in the kidney.

Laryngeal Diphtheria can be either an extension of the pharyngeal form or can involve only this site. Symptoms include fever, hoarseness, and a barking cough. The membrane can lead to airway obstruction, coma, and death.

Fibrinous inflammation of larynx during diphtheria is known as croup. There is spread of process in to small branches of bronchial tree. Death may occur due to asphyxia or pneumonia.

Skin (cutaneous) diphtheria affects the skin, causing the typical pain, redness and swelling associated with other bacterial skin infections. Ulcers covered by a gray membrane also may develop in cutaneous diphtheria.

Although it's more common in tropical climates, cutaneous diphtheria also occurs in the United States, particularly among people with poor hygiene who live in crowded conditions.

Death occurs due to early heart paralysis, late heart paralysis and diaphragm paralysis.

SCARLET FEVER

Scarlet fever (known as scarlatina in older literature references) is a syndrome characterized by exudative pharyngitis, fever, and scarlatiniform rash. It is caused by an infection with group A beta-hemolytic streptococci. The bacteria make a toxin that can cause the scarlet-colored rash from which this illness gets its name. The disease occurs mostly in children between the ages of 2 and 10 years. Rout of transmission is air-droplet, sometimes through direct contact.

After entering into organism streptococci causes local inflammation at the portal of entry, then they spread along lymphatic way and causes regional lymphadenitis. Then streptococci enter into blood and causes intoxication. There is damage of C.N.S., internal organs and skin. This is first period of scarlet fever.

Degradation of microbes in blood causes development of autoimmunization that leads to appearance of 2nd period of disease (from 3rd week). This period appear with allergic processes in skin, joints, kidney, and heart. There may be formation of septic patches.

Local patches during scarlet are known as scarlet affect (located usually in fauces and tonsils) and in association with regional lymphadenitis - known as primary complex.

In 1st stage disease there is increased congestion of fauces and tonsils, oral mucosa, tongue and pharyngeal mucosa. Tonsils are enlarged, inflamed and then appears patches of necrosis. Necrosis may be present also in soft plate region, pharynx, and middle ear. Neck lymph nodes are enlarged with necrotic patches.

General changes:

1. Appearance of rash (appear on 2nd day of disease, small point like, red, covers whole body except nasolabial triangle)
2. Dystrophy of liver, kidney, heart and cerebral neurons

In severe toxic form death occur in 2-3 days. There is hyperemia in fauces. It involves esophagus. There is severe dystrophy of internal organs.

In severe septic form there is development of purulent processes in organs: retropharyngeal abscess, otitis, osteomyelitis of temporal bone, phlegmone in neck, abscesses of brain and meningitis.

2nd period of disease is connected with autoimmune processes and development not always. It begins with catarrhal tonsillitis and accompany with gromerulonephritis.

The microscopic findings of the eruption of scarlet fever are nonspecific and have an appearance similar to that of other exanthematous eruptions. A sparse perivascular infiltrate is present, usually consisting primarily of lymphocytes with a slight amount of spongiosis in the epidermis. Slight parakera-

tosis may be present, which probably correlates with the sandpaperlike texture of the skin.

The complications of scarlet fever include septic complications due to spread of streptococci in blood, and immune-mediated complications due to an aberrant immune response. Complications due to the spread of the infection can occur early in the infection and may include following: cervical lymphadenitis, otitis media and/or mastoiditis, ethmoiditis, peritonsillar abscess, sinusitis, bronchopneumonia, empyema thoracis, meningitis, brain abscess, intracranial venous sinus thrombosis, septicemia, osteomyelitis, and septic arthritis. Of these, otitis media, pneumonia, septicemia, osteomyelitis, rheumatic fever, and acute glomerulonephritis are the most common. Rare but lethal early toxin-mediated sequelae include myocarditis and toxic shock-like syndrome.

Immune complications include acute glomerulonephritis, rheumatic fever, and erythema nodosum. The secondary scarlatinous disease, or secondary malignant syndrome of scarlet fever, includes renewed fever, renewed angina, septic ear, nose, and throat complications, and kidney infection or rheumatic fever, and is seen around the 18th day of untreated scarlet fever.

An association between scarlet fever and hepatitis has been recognized for several decades. The causal mechanism is unknown.

MENINGOCOCCAL INFECTION

Meningococcal disease describes infections caused by the bacterium Neisseria meningitidis (also termed meningococcus). It carries a high mortality rate if untreated but is a vaccine-preventable disease. While best known as a cause of meningitis, widespread blood infection can result in sepsis, which is a more damaging and dangerous condition. Meningitis and meningococcemia are major causes of illness, death, and disability in both developed and under-developed countries.

There are approximately 2,600 cases of bacterial meningitis per year in the United States, and on average 333,000 cases in developing countries. The case fatality rate ranges between 10 and 20 percent. The incidence of endemic meningococcal disease during the last 13 years ranges from 1 to 5 per 100,000 in developed countries, and from 10 to 25 per 100,000 in developing countries. During epidemics the incidence of meningococcal disease approaches 100 per 100,000. Meningococcal vaccines have sharply reduced the incidence of the disease in developed countries.

The disease's pathogenesis is not fully understood. The pathogen colonises a large number of the general population harmlessly, but in some very small percentage of individuals it can invade the blood stream, and the entire body but notably limbs and brain, causing serious illness. Over the past few

years, experts have made an intensive effort to understand specific aspects of meningococcal biology and host interactions; however the development of improved treatments and effective vaccines is expected to depend on novel efforts by workers in many different fields.

While meningococcal disease is not as contagious as the common cold (which is spread through casual contact), it can be transmitted through saliva and occasionally through close, prolonged general contact with an infected person.

Some people have the bacteria living naturally in their nose and throat. In a small number of people, a dangerous strain of the bacteria can move through the lining of the throat, causing what is known as invasive meningococcal disease.

The three common presentations of meningococcal infection are:

1. Nasopharyngitis (inflammation of nasal and pharyngeal mucosa),
2. Purulent meningitis,
3. Meningococcemia.

Mainly disease develops in children up to 5 years of age.

Penetration of meningococci in nasopharyngeal mucosa causes nasopharyngitis. The fundamental pathologic change is widespread vascular injury characterized by endothelial necrosis, intraluminal thrombosis, and perivascular hemorrhage. Endotoxin, cytokines, and free radicals damage the vascular endothelium, producing platelet deposition and vasculitis. The deleterious effects of cytokines play a major role in the pathogenesis of meningococcemia by causing severe hypotension, reduced cardiac output, and increased endothelial permeability. Then meningococci spread hematogenically, crossing hematoencephalic barrier and causes purulent meningitis. It occurs presumably in children as they have weak hematoencephalic barrier. Sometimes meningococci may cause sepsis, so called meningococcemia.

Meningococcal nasopharyngitis – there is inflammation of nasopharyngeal mucosa. Nasopharingitis is characterized by hyperemia of the pharyngeal walls, edema of the epithelial cells, regional infiltration, hyperplasia and hypertrophy of lymphoid follicles. Signs of catarrhal inflammation are found in trachea and bronchi.

Meningococcal meningitis there is congestion of pia matter during meningococcal meningitis and turbid exudates.

The next stages may single out in pathogenesis of purulent meningitis:

1. Penetration of the agent through hematoencephalic barrier, irritation of receptors of soft cerebral membrane of the brain and systems, forming cerebrospinal fluid.

2. Hypersecretion of cerebrospinal fluid.

3. Disorder of circulation of the blood in the vessels of the brain and brain's membranes, delay of resorbtion of cerebrospinal fluid.

4. Swelling-edema of the brain hyperirritation of the brain's membranes and radices of cerebrospinal nerves.

Sometimes purulent process transfers from meninges to brain tissue and causes meningoencephalitis. On 3rd week exudates begins to resolve. This accompanies with spike formation in subarachnoid space and disturbs flow that leads to hydrocephaly and atrophy or brain. Death can occur from edema and swelling of brain, at last from cerebral cachexia due to hydrocephaly, connected with block of CSF tract.

Meningococcemia – there is damage of microcirculatory blood vessels. Multiple organ failure, shock, and death may ensue as a result of anoxia in vital organs and massive disseminated intravascular coagulation.

Patients with fulminant meningococcemia develop thrombosis and hemorrhage in the skin, the mucous membranes, the serosal surfaces, the adrenal sinusoids, and the renal glomeruli. Skin rash has hemorrhagic character, located on gluteal region and legs. Necrosis and hemorrhage in adrenal gland may cause acute adrenal insufficiency (Waterhouse-Frederickson syndrome). Thrombosis of the glomerular capillaries may cause renal cortical necrosis, the main characteristic of the generalized Schwartzman reaction. Thrombi containing numerous leukocytes are occasionally found in the lungs, and extensive intra-alveolar hemorrhage can occur. Myocarditis has been observed in adults with fatal meningococcal infections.

Microscopically, leukocytoclastic vasculitis, thrombosis, and organisms are often demonstrated in biopsy specimens from patients with acute meningococcemia.

Cutaneous petechiae and purpura correspond to thrombi in the dermal vessels composed of neutrophils, platelets, and fibrin. Acute vasculitis with neutrophils and nuclear dust present within and around vessels leads to hemorrhage into the surrounding tissue. Meningococci can often be seen in the luminal thrombi and vessel walls. Intraepidermal and subepidermal neutrophilic pustules also may be present.

Perivascular lymphocytic infiltrate with few neutrophils characterize a chronic meningococcemia, although leukocytoclastic vasculitis may be seen in biopsies of petechiae.

Chronic form of meningococcemia is rare. The duration of the disease is from some weeks till some years. One case was described with duration of meningococcemia during 25 years. The disease is accompanied by intermittent fever, polymorphic exudative erythema. During period of the remission rash becomes pale, it may disappear. The patient's state is improved. In chronic meningococcemia arthritis and polyarthritis are possible. Splenomegaly is revealed inrarely. Endocarditis (pancarditis) were described in chronic

meningococcemia. It is possible the development of meningitis after some weeks or month from the onset of the disease.

PERTUSSIS (WHOOPING COUGH)

Pertussis, commonly known as whooping cough, is a respiratory tract infection characterized by a paroxysmal cough. Paroxysms of cough occur with characteristic 'whoop'.

Whooping cough is a highly communicable acute bacterial disease of childhood caused by Bordetella pertussis. The use of DPT vaccination has reduced the prevalence of whooping cough in different populations. *B. pertussis* spreads via aerosolized droplets produced by the cough of infected individuals, attaching to and damaging ciliated respiratory epithelium. The causative organism, B. pertussis, has strong tropism for the brush border of the bronchial epithelium. The organisms proliferate here and stimulate the bronchial epithelium to produce abundant tenacious mucus. B. pertussis produces a heat-labile toxin, a heat-stable endotoxin, and a lymphocytosis-producing factor called histamine-sensitising factor.

Typically, the incubation period of pertussis ranges from 3-12 days. Pertussis is a 6-week disease divided into catarrhal, paroxysmal, and convalescent stages, each lasting from 1-2 weeks.

Older children, adolescents, and adults may not exhibit distinct stages. Symptoms in these patients include uninterrupted coughing, feelings of suffocation or strangulation, and headaches. Vaccinated adults usually develop only prolonged bronchitis without a whoop, whereas unvaccinated adults are more likely to have whooping and posttussive emesis.

Pathologic changes. The *initial (catarrhal) phase* is indistinguishable from common upper respiratory infections. It includes nasal congestion, rhinorrhea, and sneezing, variably accompanied by low-grade fever, tearing, and conjunctival suffusion. Pertussis is most infectious when patients are in the catarrhal phase, but pertussis may remain communicable for 3 or more weeks after the onset of cough.

Patients in the *second (paroxysmal) phase* present with paroxysms of intense coughing lasting up to several minutes. In older infants and toddlers, the paroxysms of coughing occasionally are followed by a loud whoop as inspired air goes through a still partially closed airway. Infants younger than 6 months do not have the characteristic whoop but may have apneic episodes and are at risk for exhaustion. Posttussive vomiting and turning red with coughing are common in affected children. The condition is self-limiting but may cause death due to asphyxia in infants.

Patients in the *third (convalescent) stage* have a chronic cough, which may last for weeks.

Microscopically, the lesions in the respiratory tract consist of necrotic bronchial epithelium covered by thick muco purulent exudate. In severe cases, there is mucosal erosion and hyperaemia. The peripheral blood shows marked lymphocytosis upto 90% and enlargement of lymphoid follicles in the bronchial mucosa and peribronchial lymph nodes.

STAPHYLOCOCCAL INFECTIONS

Staphylococci are gram positive cocci which are present everywhere in the skin, umbilicus, nasal vestibule, stool etc. Three species are pathogenic to human beings: Staph. aureus, Staph. epidermidis and Staph. saprophyticus. Most staphylococcal infections are caused by Staph. aureus. Staphylococcal infections are among the commonest antibiotic-resistant hospital-acquired infection in surgical wounds.

A wide variety of suppurative diseases are caused by Staph. aureus which includes the following:

1. Infections of skin. Staphylococcal infections of skin are quite common. The infection begins from lodgement of cocci in the hair root due to poor hygiene and results in obstruction of sweat or sebaceous gland duct. This is termed folliculitis. Involvement of adjacent follicles results in larger lesions called furuncle. Further spread of infection horizontally under the skin and subcutaneous tissue causes carbuncle or cellulitis. Styes are staphylococcal infection of the sebaceous glands of Zeis, the glands of Moll and eyelash follicles. Impetigo is yet another staphylococcal skin infection common in school children in which there are multiple pustular lesions on face forming honey-yellow crusts. Breast abscess may occur following delivery when Staphylococci are transmitted from infant having neonatal sepsis or due to stasis of milk.

2. Infections of burns and surgical wounds. These are quite common due to contamination from the patient's own nasal secretions or from hospital staff. Elderly, malnourished, obese and neonates have increased susceptibility.

3. Infections of the upper and lower respiratory tract. Small children under 2 years of age get staphylococcal infections of the respiratory tract commonly. These include pharyngitis, bronchopneumonia, staphylococcal pneumonia and its complications. Staphylococcal pneumonia predominantly affects people with underlying lung disease and can lead to abscess formation within the lungs.

4. Bacterial arthritis. Septic arthritis in the elderly is caused by Staph. aureus.

5. Infection of bone (Osteomyelitis). Young boys having history of trauma or infection may develop acute staphylococcal osteomyelitis.

6. Bacterial endocarditis. Acute and subacute bacterial endocarditis are complications of infection with Staph. aureus and Staph. Epidermidis. Its can lead to heart failure.

7. Bacterial meningitis. Surgical procedures on central nervous system may lead to staphylococcal meningitis.

8. Septicaemia. Staphylococcal septicaemia may occur in patients with lowered resistance or in patients having underlying staphylococcal infections. Patients present with features of bacteraemia such as shaking chills and fever.

9. Toxic shock syndrome. Toxic shock syndrome is a serious complication of staphylococcal infection characterized by fever, hypotension and exfoliative skin rash. The condition affects young menstruating women who use tampons of some brands which when kept inside the vagina cause absorption of staphylococcal toxins from the vagina.

STREPTOCOCCAL INFECTIONS

Streptococcal infections are communicable diseases that develop when bacteria normally found on the skin or in the intestines, mouth, nose, reproductive tract, or urinary tract invade other parts of the body and contaminate blood or tissue. Streptococci are also gram-positive cocci but unlike staphylococci, they are more known for their nonsuppurative autoimmune complications than suppurative inflammatory responses. Streptococcal infections occur throughout the world but their problems are greater in underprivileged populations where antibiotics are not instituted readily.

The following groups and subtypes of streptococci have been identified and implicated in different Streptococcal diseases:

1. ***Group A*** or Streptococcus pyogenes, also called (β-haemolytic streptococci, are involved in causing upper respiratory tract infection and cutaneous infections (erysipelas). Infection with this pathogen is also causally linked to 2 potentially serious nonsuppurative complications: acute rheumatic fever and acute glomerulonephritis. In addition, infection with *S. pyogenes* has reemerged as an important cause of toxic shock syndrome and of life-threatening skin and soft-tissue infections, especially necrotizingfasciitis.

2. ***Group B*** Streptococcus, also known as Streptococcus agalactiae, is best known as a cause of postpartum infection and as the most common cause of neonatal sepsis. This organism is also causes infection in nonpregnant adults. Group B streptococcal infection in healthy adults is extremely uncommon, except in young and middle-aged women, and is almost always associated with underlying abnormalities, with diabetes most commonly associated with infection in some series.

3. ***Group C*** is a common source of infection in animals. It rarely causes human illness.

4. ***Group D*** is a common cause of wound infections in hospital patients. *Streptococcus* group D infections in humans are most often associated with bacteremia, with or without endocarditis. Other less-common infections involving group D streptococci include urinary tract infections, meningitis, neonatal sepsis, spontaneous bacterial peritonitis, septic arthritis and vertebral osteomyelitis. Traditionally, group D streptococcal infections have predominantly been caused by *Streptococcus bovis.* This organism is well-established in the literature as a cause of bacteremia and endocarditis and has a well-known association with gastrointestinal malignancy.

5. ***Group G.*** Normally present on the skin, in the mouth and throat, and in the intestines and genital tract, Group G strep is most likely to lead to infection in alcoholics and in people who have cancer, diabetes mellitus, rheumatoid arthritis, and other conditions that suppress immune-system activity. It can cause a variety of infections, including: bacteria in the bloodstream (bacteremia); inflammation of the connective tissue structure surrounding a joint (bursitis); endocarditis (a condition that affects the lining of the heart chambers and the heart valves); meningitis; inflammation of bone and bone marrow (osteomyelitis); inflammation of the lining of the abdomen (peritonitis).

6. Untypable α-haemolytic streptococci such as ***Streptococcus viridans*** constitute the normal flora of the mouth and may cause bacterial endocarditis.

7. Pneumococci or ***Streptococcus pneumoniae*** are etiologic agents for bacterial pneumonias, meningitis and septicaemia.

CLOSTRIDIAL DISEASES

Clostridia are gram-positive spore-forming anaerobic microorganisms found in the gastrointestinal tract of herbivorous animals and man. These organisms may undergo vegetative division under anaerobic conditions, and sporulation under aerobic conditions. These spores are passed in faeces and can survive in unfavourable conditions. On degeneration of these microorganisms, the plasmids are liberated which produce many toxins responsible for the following clostridial diseases depending upon the species:

1. Gas gangrene by C. perfringens
2. Tetanus by C. tetani
3. Botulism by C. botulinum
4. Clostridial food poisoning by C. perfringens
5. Necrotising enterocolitis by C. perfringens.

Gas gangrene is a rapidly progressive and fatal illness in which there is myonecrosis of previously healthy skeletal muscle due to elaboration of myotoxins by some species of clostridia. In majority of cases (80-90%), the source of myotoxins is C. perfringens Type A; others are C. novyi and C. septicum. Generally, traumatic wounds and surgical procedures are followed

by contamination with clostridia and become the site of myonecrosis. The incubation period is 2 to 4 days. The most common myotoxin produced by C. perfringens Type A is the alpha toxin which is a lecithinase. The prevention of gas gangrene lies in debridement of damaged tissue in which the clostridia thrive. The lesion has serosanguineous discharge with odour and contains gas bubbles. Infections are characterized by a very low level of host inflammation in response to organism-associated exotoxins. Purulence is often absent. The process of myonecrosis can spread as fast as 2 cm/h. This results in systemic toxicity and shock that can be fatal within 12 hours. Overwhelming shock with accompanying renal failure usually leads to death.

TETANUS

Tetanus is characterized by an acute onset of hypertonia, painful muscular contractions (usually of the muscles of the jaw and neck), and generalized muscle spasms without other apparent medical causes. Tetanus is a severe acute neurological syndrome of humans and other mammals caused by tetanus toxin an extremely potent neurotoxin elaborated by plasmids of Cl.tetani.

Clostridium tetani is an obligate, anaerobic, motile, gram-positive bacillus. It is nonencapsulated and forms spores that are resistant to heat, desiccation, and disinfectants. Since the colorless spores are located at one end of the bacillus. They are found in soil, house dust, animal intestines, and human feces. Spores can persist in normal tissue for months to years. The vegetative bacilli are found in the gastrointestinal tracts of herbivorous animals and humans. Anaerobic condition promotes vegetative division, whereat aerobic ones lead to sporulation.

To germinate, the spores require specific anaerobic conditions, such as wounds with low oxidation-reduction potential (eg, dead or devitalized tissue, foreign body, active infection). Under these conditions, upon germination, they may release their toxin. Infection by *C. tetani* results in a benign appearance at the portal of entry because of the inability of the organism to evoke an inflammatory reaction

When the proper anaerobic conditions are present, the spores germinate and produce the following 2 toxins:

Tetanolysin – this substance is a hemolysin with no recognized pathologic activity;

Tetanospasmin – this toxin is responsible for the clinical manifestations of tetanus.

Tetanus remains a frequent and lethal disease in developing countries. More than 1 mln cases occur annually world-wide, most of which are fatal. Contributing factors include the presence of herbivorous animals (especially

horses and cattle), frequency of tetanus-prone wounds, abortion practices and immune status of population. Many deaths occur in newborns, owing to the custom of coating the umbilical stump with dirt or dung to prevent bleeding. In developed countries, tetanus is frequently associated with drug addiction.

Pathogenesis. At the site of injury, necrotic tissue and suppuration contribute to the creation of an anaerobic environment, a condition that causes spores to revert to vegetative cells, although the clostridia infection remains localized, the potent neurotoxin (tetanospasmin) undergoes retrograde transport through the ventral roots of peripheral nerves to the anterior horn cells of the spinal cord, the toxin crosses the synapse and binds to ganglioside receptors on presynaptic terminals of motor neurons in the ventral horns.

As a result the release of inhibitory neuro-transmitters is blocked, thereby permitting unopposed neural stimulation and sustained contraction of skeletal muscles (tetany). The block to release of inhibitory neuro-transmitters also includes acceleration of the heart rate, hypertension and cardio-vascular instability. Tetanospaspin produces no specific histopathology.

Clinical features. The incubation period of the disease is 1-3 weeks. Tetanus may be categorized into the following 4 clinical types: generalized, localized, cephalic and neonatal.

Approximately 50-75% of patients with *generalized tetanus* present with trismus (—lockjaw‖), which is the inability to open the mouth secondary to masseter muscle spasm. Nuchal rigidity and dysphagia are also early complaints that cause risus sardonicus, the scornful smile of tetanus, resulting from facial muscle involvement. As the disease progresses, patients have generalized muscle rigidity with intermittent reflex spasms in response to stimuli (e.g. noise, touch). Tonic contractions cause opisthotonos (i.e., flexion and adduction of the arms, clenching of the fists, and extension of the lower extremities). During these episodes, patients have an intact sensorium and feel severe pain. The spasms can cause fractures, tendon ruptures, and acute respiratory failure.

Patients with *localized tetanus* present with persistent rigidity in the muscle group close to the injury site. The muscular rigidity is caused by a dysfunction in the interneurons that inhibit the alpha motor neurons of the affected muscles. No further central nervous system involvement occurs in this form, and mortality is very low.

Cephalic tetanus is uncommon and usually occurs after head trauma or otitis media. Patients with this form present with cranial nerve palsies. The infection may be localized or may become generalized.

Neonatal tetanus is a major cause of infant mortality in underdeveloped countries. Infection results from umbilical cord contamination during unsanitary delivery, coupled with a lack of maternal immunization. At the end of the first

week of life, infected infants become irritable, feed poorly, and develop rigidity with spasms. Neonatal tetanus has a very poor prognosis.

Although at present, tetanus is rare, it has not been eradicated, and early diagnosis and intervention are lifesaving. Prevention is the ultimate management strategy for tetanus.

The outcome of tetanus depends on the age of the patient; the inoculums of toxin and the availability of medical support.

Administration of antibody to bind unabsorbed toxin, antibiotics to eliminate infection and supportive care, including respiratory support are the mainstays of therapy. Infants and persons older than 50 years of age have the highest mortality.

Complications of tetanus are pneumonia, rupture of muscles, compressive fracture of spinal column.

BOTULISM

It is characterized by symmetric paralysis of cranial nerves, limbs and trunk. The condition occurs following ingestion of food contaminated with neurotoxins of C. botulinum and less often by contamination of a penetrating wound. The spores of C. botulinum are capable of surviving in unfavourable conditions and contaminate vegetables and other foods, especially if improperly stored or canned. The symptoms of botulism begin to appear within 12 to 36 hours of ingestion of food containing the neurotoxins (type A to type G). Toxins are absorbed from the stomach and small intestine, where they are not denatured by digestive enzymes. Subsequently, they are hematogenously disseminated and block neuromuscular transmission in cholinergic nerve fibers. The nervous, gastrointestinal, endocrine, and metabolic systems are predominantly affected. Because the motor end plate responds to acetylcholine, botulinum toxin ingestion results in hypotonia that manifests as descending symmetric flaccid paralysis and is usually associated with gastrointestinal symptoms of nausea, vomiting, and diarrhea. Cranial nerves are affected early in the disease course. Later complications include paralytic ileus, severe constipation, and urinary retention.

CLOSTRIDIAL FOOD POISONING

It is caused by enterotoxin elaborated by C. perfringens. Out of five serotypes of C. perfringens, type A and C produce α-enterotoxin that causes food poisoning. These serotypes of organism are omnipresent in the environment and thus clostridial poisoning occurs throughout the world. Food poisoning from C. perfringens is mostly from ingestion of meat and its products which have been allowed to dry resulting in dehydration and anaerobic conditions suitable for growth of C. perfringens. The contaminated meat con-

tains vegetative form of the organism and no preformed enterotoxin (unlike botulism where preformed neurotoxin of C. botulinum is ingested). On ingestion of the contaminated meat, alpha-enterotoxin is produced in the intestine.

The gastroenteritis starts about 6 to 24 hours after contaminated food is eaten. The most common symptoms are watery diarrhea and abdominal cramps. Although usually mild, the infection also can cause abdominal pain, abdominal expansion (distention) from gas, severe diarrhea, dehydration, and a severe decrease in blood pressure (shock). Symptoms usually last about 24 hours.

Necrotising enterocolitis or 'pig bel' is caused by beta-enterotoxin produced by C. perfringens Type C. The condition occurs especially in undernourished children who suddenly indulge in overeating such as was first reported participation in pig feasts by poor children in New Guinea and hence the name 'pig bel'. Adults do not develop the condition due to good antibody response. Ingestion of contaminated pork by malnourished children who normally take protein-deficient vegetarian diet causes elaboration of beta-enterotoxin. The symptoms appear within 48 hours after ingestion of contaminated meat. These include: severe abdominal pain, distension, vomiting and passage of bloody stools. Milder form of disease runs a course similar to other forms of gastroenteritis while fulminant 'pig bel' may result in death of the child.

Grossly, the disease affects small intestine segmentally. The affected segment of bowel shows green, necrotic pseudomembrane covering the necrotic mucosa and there is associated peritonitis. Advanced cases may show perforation of the bowel wall. Microscopically, there is transmural infiltration by acute inflammatory cell infiltrate with changes of mucosal infarction, oedema and haemorrhage. The pseudomembrane consists of necrotic epithelium with entangled bacilli.

PLAGUE

Plague is caused by Yersinia (Pasteurella) pestis which is a small gram-negative coccobacillus that grows rapidly on most culture media. Direct identification of the organism in tissues is possible by fluorescence antisera methods.

Plague has been a great killer since 14th century and is known to have wiped out populations of cities. Unlike smallpox, the plague never will be eradicated. It lives in millions of animals and on billions of fleas that reside on them. It is a disease of the desert, the steppes, the mountains, and the forest.

Although, the plague has been considered a disease of the Middle Ages, multiple outbreaks in India and Africa during the last 20 years have stoked fears of another global pandemic. One reason may be the climatic change brought about by global warming. This change is ideal for increasing the prevalence of Ypestis in the host population. Another reason may be the increasing population explosion worldwide, which is bringing humans into

ever-increasing contact with wildlife. Lastly, the dramatic population increase will contribute to conditions of overcrowding and poor sanitation conditions ripe for plague hosts and vectors to flourish in.

Plague is a zoonotic disease and spreads by rodents, primarily by rats, both wild and domestic; others being squirrels and rabbits.

Once the flea bites a susceptible host, the bacilli migrate to the regional lymph nodes, are phagocytosed by polymorphonuclear and mononuclear phagocytes, and multiply intracellularly. Involved lymph nodes show dense concentrations of plague bacilli, destruction of the normal architecture, and medullary necrosis. This occurs within 24-48 hours of infection and is accompanied by chills, fever, myalgia, nausea, vomiting and marked prostration. With subsequent lysis of the phagocytes, bacteremia can occur and may lead to invasion of distant organs. If untreated, death occurs from disseminated intravascular coagulation (DIG) within 1 to 2 days with development of widespread petechiae and ecchymoses leading to gangrene and hence the name black death. In other cases, death results from multi-organ failure due to profound toxaemia. The patient and his fluids are highly infectious and can be transmitted by arthropods as well as person-to-person contact, giving rise to secondary cases.

Virulence of the organism Y. pestis is attributed to the elaboration of plague toxins: pesticin and lipopoly-saccharide endotoxin.

Pathologic changes. Three forms of the plague exist: bubonic plague the most common (60-80%), pneumonic plague (10-15%), and septicemic plague (10-15%).

Bubonic plague. The bacillus invades nearby lymphoid tissue, producing the bubo, an inflamed, necrotic, and hemorrhagic regional lymph node. Microscopically, the features are:

• Effaced architecture of lymph nodes due to necrosis in and around the affected nodes.

• Multiple necrotising granulomas.

• Characteristic mononuclear inflammatory response.

• Masses of proliferating bacilli in sinusoids of lymph nodes.

• Cellulitis in the vicinity.

Spread occurs along the lymphatic channels toward the thoracic duct, with eventual seeding of the vasculature. Bacteremia and septicemia ensue. The bacillus potentially seeds every organ, including the lungs, liver, spleen, kidneys, and rarely even the meninges.

The most virulent form, ***pneumonic plague,*** results from direct inhalation of the bacillus, which occurs from close contact of infected hosts or from aerosolized bacteria such as may occur if used as a biological weapon. A severe and rapidly progressive multilobar bronchopneumonia ensues with subsequent bacteremia and septicemia. Secondary pneumonic plague is caused when an in-

fected patient seeds his or her lungs and airways. Bronchopneumonia is characterized by the following conspicuous microscopic features:

- Necrosis of alveolar walls.
- Intense hyperaemia and haemorrhages.
- Numerous bacilli in the alveolar lumina.
- Characteristic mononuclear inflammatory response with very scanty neutrophils.

The third type of plague is a ***primary septicemic plague***. This is hypothesized to occur when the bacillus is deposited in the vasculature, bypassing the lymphatics. Early dissemination with sepsis occurs but without the formation of a bubo. This usually is observed in bites to the oral, tonsillar, and pharyngeal area and is believed to occur because of the vascularity of the tissue and short lymphatic distance to the thoracic duct.

Death occurs from cachexia and septicemia or from pulmonary complications.

ZOONOTIC INFECTIONS

TULAREMIA

Tularemia is an acute, febrile, granulomatous, infectious zoonosis caused by *Francisella tularensis*, an aerobic, gram-negative, pleomorphic bacillus *F tularensis* is one of the most infectious bacterial species known, as it can cause illness in humans with exposure to as few as 10-50 organisms. Four major subspecies, or biovars, exist; they differ in virulence and geographic range, with *F tularensis* biovar *tularensis*, found primarily in North America, being the most virulent. Worldwide, more than 100 species of animals, including mammals, birds, amphibians, and arthropods, host *F tularensis*. The bacillus, which causes acute infectious illness in humans, may also be found in mud and water.

Some authorities classify tularemia into 2 groups, which include the far more common ulceroglandular form (in which local or regional symptoms and signs predominate) and the more lethal typhoidal form (in which systemic symptoms dominate the clinical picture). More commonly, however, tularemia is divided into the following 6 forms: ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal. Each form reflects the mode of transmission. The organism gains access to the host by means of inoculation into skin or mucous membrane or through inhalation or ingestion.

A subcutaneous inoculum of 10 organisms is sufficient to induce disease, whereas an inhalational exposure of 25 organisms may cause a severely debilitating or fatal disease. Over the first 3-5 days after cutaneous exposure, the organism multiplies locally and a papule forms.

During the next 2-4 days, the site ulcerates. Organisms spread from the entry site to regional lymph nodes and may disseminate lymphohematogenously to involve multiple organs. Pulmonary findings may be primary after direct inhalation of aerosolized bacteria or may be present in up to half of all tularemia cases from hematogenous spread (secondary pneumonia). Patients are most likely bacteremic at this time, although this is not usually detected.

Infection produces an acute inflammatory response initially involving local macrophages, neutrophils, and fibrin. T lymphocytes, epithelioid cells, and giant cells then migrate into local necrotic tissue. As the area of necrosis expands, thrombosis of adjacent arteries and veins may occur. Granulomas develop, which may caseate and be mistaken for tuberculosis, and necrotic foci may coalesce to form abscesses. These changes occur in infected sites and have been demonstrated on autopsy in lymph nodes, the liver, the spleen, bone marrow, and the lungs. *F tularensis* may remain viable for prolonged periods. They may remain viable in the tissues, where they cause infection. The ability of *F tularensis* to impair phagocyte function and survive in infected cells is central to its virulence.

The incubation period for tularemia depends on the size of the inoculum, but ranges from 1-21 days (average 2-6 days). Individuals with tularemia may be asymptomatic or acutely septic with rapid death.

As with many other tick-borne diseases, tularemia may, early in its course, have a nonspecific presentation. Moreover, many individuals may not be aware of or recall having been bitten by a tick or fly. These factors illustrate the importance of routinely including queries regarding travel, work, and animal and arthropod exposure in the history when presented with a patient who potentially has tularemia. Delayed diagnosis and late administration of effective antibiotic therapy may result in increased morbidity and a greater risk of mortality in patients with the disease. Children infected with tularemia typically have a clinical presentation similar to that of adults. However, children have been reported to have fever, pharyngitis, hepatosplenomegaly, and constitutional symptoms more often than do adult patients.

The following are common findings in the various clinical forms of tularemia: abrupt onset of fever and chills - these symptoms typically last for several days, remit for a brief interval, and then recur; pulse-temperature disassociation; headache; anorexia; malaise and fatigue or prostration; myalgias; cough; vomiting; pharyngitis; abdominal pain; secondary pneumonitis - may occur in 45-83% of patients with the typhoidal form. As many as 20% of patients with tularemia have a rash, which may begin as blotchy, macular, or maculopapular and progress to pustular. Erythema nodosum and erythema multiforme are rare.

Ulceroglandular tularemia. In this form of tularemia, *F tularensis* usually enters the body via a scratch or abrasion and then spreads lymphatically, typically causing painful regional lymphadenopathy and an ulcerated skin lesion.

In most cases, 2-5 days following exposure to the disease bacterium (but with a range of 1-10 days) a small, erythematous, tender or pruritic papule occurs at the site of inoculation; the papule enlarges and becomes ulcerated 2-3 days later. Gradually, the tender necrotic base develops with a black eschar, often concomitantly with tender regional adenopathy.

The tick-borne form usually involves inguinal or femoral adenopathy, while the rabbit (animal)-associated form usually involves axillary or epitrochlear adenopathy. Systemic adenopathy may also occur. Some patients will exhibit a sporotrichoid picture of ascending, tender subcutaneous nodules. Lymphadenopathy, lymphadenitis, or both may occur, with tender, suppurative, local enlargement reflecting the site of entry. More than 20% of lymph nodes will suppurate if left untreated or treatment is delayed longer than 2 weeks.

The ulcer, which has raised edges and a jagged floor, is located on a finger or hand in more than 90% of patients with rabbit-associated disease. In tick-borne tularemia, the ulcer is found on a lower extremity or the perineal area in 50% of patients, on the trunk in 30% of cases, and on the head in 5-10% of patients.

Glandular tularemia. In the glandular form of tularemia, tender lymphadenopathy occurs without evidence of local cutaneous lesions. The bacterium presumably gains entry via microscopic abrasions or potentially through intact skin. It then spreads lymphatically or via the bloodstream.

Oculoglandular tularemia. In this form, *F tularensis* enters via the conjunctivae after the patient is either splashed with blood or rubs his or her eyes following contact with contaminated tissue fluids. Clinical manifestations are usually unilateral; they include the following: unilateral conjunctivitis - painful, purulent conjunctivitis; some patients experience chemosis, periorbital edema, and small, nodular or ulcerative lesions of the palpebral conjunctivae; corneal ulceration; lymphadenopathy - most commonly cervical, but preauricular and submandibular also observed; photophobia; lacrimation; lid edema; vision loss (rare)

Oropharyngeal tularemia. This is a rare form that may occur after consumption of infected, undercooked meat or contaminated water. Manifestations of oropharyngeal tularemia include the following: stomatitis and exudative pharyngitis or tonsillitis - the patient may occasionally develop a yellow-white pseudomembrane resembling diphtheria; abdominal pain (due to mesenteric lymphadenopathy), nausea, and vomiting; cervical lymphade-

nopathy, including deep neck infection; diarrhea; gastrointestinal bleeding - occasionally; caused by intestinal ulcerations

Pneumonic tularemia. Primary tularemia pneumonia, an uncommon condition, occurs after inhalation of *F tularensis*. Rarely acquired naturally, pneumonic tularemia may develop in laboratory workers. Patients with pneumonic tularemia usually report a dry cough, dyspnea, and pleuritic-type chest pain. Chest radiography may reveal patchy, ill-defined infiltrates in 1 or more lobes. Frank lobar pneumonia may also develop, and bilateral hilar adenopathy may be present. Bloody pleural effusions are characteristic and demonstrate a mononuclear cellular response. ARDS develops in some patients.

Typhoidal tularemia. This form of tularemia is particularly severe; it probably represents *F tularensis*bacteremia. Patients with this disease present with the following: fever; chills; myalgias; malaise; weight loss. Patients often have pneumonia. Diagnosis is difficult because ulcers and lymphadenopathy are usually absent.

Untreated tularemia has a mortality rate of 5-15%; if treated, the disease carries a mortality rate of 1-3%. The mortality rate is 2-3 times higher in patients with typhoidal tularemia than in those with other forms. Other factors associated with increased mortality include elevated creatine kinase levels, renal failure, and other serious comorbidities, as well as late diagnosis. The mortality rate also depends on the subspecies involved; *F tularensis* biovar *tularensis* is significantly more virulent than the others and is responsible for almost all reported deaths.

Complications of tularemia include the following: pneumonia; lung abscess; respiratory failure, including possible acute respiratory distress syndrome (ARDS); rhabdomyolysis; renal failure with possible hemodialysis; hemoptysis; meningitis; endocarditis; suppurative lymphadenitis; pericarditis; peritonitis; appendicitis; perisplenitis; osteomyelitis; guillain-barré syndrome; hepatitis; sepsis

BRUCELLOSIS

Brucellosis is a zoonotic infection caused by the bacterial genus *Brucella.* The bacteria are transmitted from animals to humans by ingestion through infected food products, direct contact with an infected animal, or inhalation of aerosols. The disease is an old one that has been known by various names, including Mediterranean fever, Malta fever, gastric remittent fever, and undulant fever. Humans are accidental hosts, but brucellosis continues to be a major public health concern worldwide and is the most common zoonotic infection.

Brucella organisms, which are small aerobic intracellular coccobacilli, localize in the reproductive organs of host animals, causing abortions and ste-

rility. They are shed in large numbers in the animal‘s urine, milk, placental fluid, and other fluids. To date, 8 species have been identified, named primarily for the source animal or features of infection. Of these, the following 4 have moderate-to-significant human pathogenicity:

- ✓ *Brucella melitensis (*from sheep; highest pathogenicity*)*
- ✓ *Brucella suis* (from pigs; high pathogenicity)
- ✓ *Brucella abortus* (from cattle; moderate pathogenicity)
- ✓ *Brucella canis* (from dogs; moderate pathogenicity)

Humans experience only limited risk from wild animals, mainly because of lack of proximity or intimate contact and infrequent use of milk and meat products from these animals. Concerns have been voiced that interaction of wild animals with domesticated ones may lead to infection of agricultural herds, though supportive evidence is quite limited.

The global burden of human brucellosis remains enormous: The infection causes more than 500,000 infections per year worldwide. Interest in brucellosis has been increasing because of the growing phenomena of international tourism and migration, in addition to the potential use of *Brucella* as a biologic weapon. Familiarity with the manifestations of brucellosis and knowledge of the optimal laboratory studies are essential for the recognition of this reemerging zoonosis. *B melitensis, B abortus,* and *B suis* have been completely sequenced, and these sequencing data will help improve our understanding of the pathogenesis and the manifestations of this complex disease.

Brucellae are aerobic gram-negative coccobacilli that possess a unique ability to invade both phagocytic and nonphagocytic cells and to survive in the intracellular environment by finding ways to avoid the immune system. This ability helps explain why brucellosis is a systemic disease and can involve almost every organ system.

Brucella can gain entry into the human body through breaks in the skin, mucous membranes, conjunctivae, and respiratory and gastrointestinal tracts. Sexual transmission has not been convincingly documented. Ingestion usually occurs by way of unpasteurized milk; meat products often have a low bacterial load.

Once within the bloodstream, the organisms quickly become intracellular pathogens contained within circulating polymorphonuclear cells and macrophages, making use of numerous mechanisms to avoid or suppress bactericidal responses. Animal data suggest that the lipopolysaccharide coat (smooth in *B melitensis*, *B abortus,* and *B suis;* rough in *B canis*) is likely to play a role in intracellular survival, perhaps because of adenine and guanine monophosphate production, which inhibits phagosomal fusion and oxidative burst activity.

In addition, *Brucella* species have relatively low virulence, toxicity, and pyrogenicity, making them poor inducers of some inflammatory cytokines, such as tumor necrosis factor and interferons. Furthermore, the bacteria do not activate the alternative complement system. Finally, they are thought to inhibit programmed cell death.

After ingestion by phagocytes, about 15-30% of brucellae survive. Susceptibility to intracellular killing differs among species, with *B abortus* readily killed and *B melitensis* rarely affected; these differences might explain the differences in pathogenicity and clinical manifestations in human cases of brucellosis.

Brucellae that survive are transported into the lymphatic system and may replicate there locally; they also may replicate in the kidney, liver, spleen, breast tissue, or joints, causing both localized and systemic infection. Any organ system can be involved (eg, central nervous system [CNS], heart, joints, genitourinary system, pulmonary system, and skin); localization of the process may cause focal symptoms or findings. After replication in the endoplasmic reticulum, the brucellae are released with the help of hemolysins and induced cell necrosis.

Development of cell-mediated immunity is the principal mechanism of recovery. The host response to infection with *B abortus* is characterized by the development of tissue granulomas indistinguishable from those of sarcoidosis. In contrast, infection with the more virulent species (*B melitensis* and *B suis*) more commonly results in visceral microabscesses.

Fever is the most common symptom and sign of brucellosis, occurring in 80-100% of cases. It is intermittent in 60% of patients with acute and chronic brucellosis and undulant in 60% of patients with subacute brucellosis. Constitutional symptoms of brucellosis include anorexia, asthenia, fatigue, weakness, and malaise, and weight loss and are very common.

Bone and joint symptoms include arthralgias, low back pain, spine and joint pain, and, rarely, joint swelling. Arthralgias may be diffuse or localized, with a predilection for bone ends and the sacroiliac joint. Acute monoarticular arthritis is uncommon but may be part of the presentation.

Neuropsychiatric symptoms of brucellosis are common despite the rare involvement of the nervous system. Headache, depression, and fatigue are the most frequently reported neuropsychiatric symptoms. In patients with advanced disease who have meningoencephalitis, these complaints may include changes in mental status, coma, neurologic deficit, nuchal rigidity, or seizures.

A significant percentage (approximately 50%) of patients have gastrointestinal) complaints, primarily dyspepsia, though abdominal pain from hepatic abscesses may occur. Hepatic abscesses should be suspected in patients with signs of systemic toxicity and persistently elevated liver enzymes. The

abscess can serve as a source of bacteremic seeding. Spontaneous bacterial peritonitis secondary to brucellosis infection has been reported. Constipation, diarrhea, and vomiting may occur.

Genitourinary infections with brucellae have been reported and include orchitis, urinary tract infection, and glomerulonephritis. Frank renal failure or sepsis is rare.

Neurologic symptoms of brucellosis can include weakness, dizziness, unsteadiness of gait, and urinary retention. Symptoms associated with cranial nerve dysfunction may affect persons with chronic central nervous system involvement.

Cough and dyspnea develop in up to 19% of persons with brucellosis; however, these symptoms are rarely associated with active pulmonary involvement. Pleuritic chest pain may affect patients with underlying empyema.

Endocarditis from brucellae is reported, with septic embolization a common complication of this form of brucellosis. Other cardiac complications, such as pulmonary edema or dysrhythmias, are rare. *Brucella* endocarditis is the form most commonly associated with fatalities.

With the chronic form of brucellosis, in which the illness has lasted longer than 1 year (undiagnosed and untreated brucellosis), an afebrile pattern is typical, with a history of myalgia, fatigue, depression, and arthralgias (chronic fatigue syndrome is the most important disease in the differential diagnosis). The chronic form is primarily caused by *B melitensis* and usually affects adults older than 30 years. The chronic form is rare in children.

Traditionally, brucellosis has been classified as subclinical, acute, subacute, or chronic; localized and relapsing forms have also been described. This classification system, though commonly used, is subjective and of limited clinical utility.

Subclinical brucellosis. Disease is usually asymptomatic, and the diagnosis is usually established incidentally after serologic screening of persons at high risk of exposure. Culture data are usually unrevealing.

Acute and subacute brucellosis. Disease can be mild and self-limited (eg, *B abortus*) or fulminant with severe complications (eg, *B melitensis*). Associated symptoms can develop 2-3 months before diagnosis in mild cases and 3-12 months before diagnosis in severe cases. Usually, acute brucellosis occurs without focal abnormalities. Nonfocal weakness may be noted. Tenderness, swelling, or effusion of joints may be evident. In some instances, orchitis appears after a few days of illness. Testicular swelling and tenderness in the wake of chills and high fever thus resemble mumps orchitis.

Some patients manifest constipation. Occasionally, abdominal tenderness suggests an acute abdomen. In some more severe cases, tender enlargement of the spleen may be detected.

Murmurs, friction rubs, acute-onset blindness or visual field disturbance, tachycardia, oropharyngeal or conjunctival petechiae (some with pale centers), Roth spots, splinter hemorrhages of the nail beds, Osler nodes, Janeway lesions, or hepatosplenomegaly may develop as manifestations of bacterial endocarditis, a complication that is much rarer as an aspect of acute or subacute brucellosis than as an element of focal or diffuse chronic brucellosis.

Rarely, disease of the lungs or pleura is a feature of acute brucellosis, manifestations of which could include rales, wheezes, abnormalities of percussion or egophony, or pleural friction rubs.

Meningismus, papilledema, mental status changes, and long-tract signs are found in a small fraction of cases of acute brucellosis as manifestations of acute neurobrucellosis.

Radicular sensory or motor changes may arise in individuals with brucellotic osteomyelitis with associated epidural abscess. Focal tenderness or pain in the perispinous region may precede fever and objective sensory or motor findings. Brucellotic cervical epidural abscess may produce tenderness and movement restriction without the classic triad (fever, neck pain, and radiculopathy) of streptococcal or other types of epidural abscess. However, such findings may eventually develop, prompting delayed consideration of this diagnostic entity.

Chronic brucellosis. The diagnosis of chronic brucellosis is typically made after symptoms have persisted for 1 year or more. Low-grade fevers and neuropsychiatric symptoms predominate. Results of serologic studies and cultures are often negative; without confirmatory evidence, many authorities doubt the existence of chronic disease. Many patients have persistent disease caused by inadequate initial therapy, and underlying localized disease may be present.

Localized and relapsing brucellosis. Localized complications of brucellosis are typically observed in patients with acute disease or chronic untreated infection. Osteoarticular, genitourinary, and hepatosplenic involvement are most common. Cultures of involved tissue sites and serology can be diagnostic.

Bone marrow aspiration and biopsy may be required to establish a diagnosis in certain patients. Bone marrow examination may reveal erythrophagocytosis. Microangiopathic hemolytic anemia, thrombocytopenic purpura, and Coombs-positive hemolytic anemia have been reported in brucellosis. Percutaneous liver biopsy may be needed in the patient with liver granulomas to obtain a specimen for diagnosis. Analysis of liver biopsy specimens may reveal granulomatous hepatitis and hepatic microabscesses. Histologic findings in brucellosis usually include mixed inflammatory infiltrates with lymphocytic predominance and granulomas with necrosis

The prognosis is generally excellent. Although initial symptoms of brucellosis may be debilitating, if they are treated appropriately and within the first few months of onset, the disease is easily curable, with a low risk of relapse or chronic disease. However, the prognosis is poor in persons who present with congestive heart failure due to endocarditis, in whom mortality approaches 85%. In some patients, brucellosis can cause chronic debilitating illness with extensive morbidity.

In uncomplicated cases of acute brucellosis, fever, malaise, and many other manifestations improve rapidly with bed rest, whereas sustained physical activity may prolong or worsen the degree of illness. Considerable improvement from the symptoms of the acute phase of illness typically occurs within a few weeks, with or without treatment. In many cases, this is followed by complete remission within 2-6 months. Recovery tends to be more rapid with B abortus infection than with *B melitensis* or *B suis* infection.

Overall mortality in recognizably symptomatic acute or chronic cases of brucellosis is very low, certainly less than 5% and probably less than 2%. It is usually the result of the rare instance of *Brucella* endocarditis or is the result of severe CNS involvement, often as a complication of endocarditis.

Recurrence of symptoms of acute brucellosis is not uncommon. The recurrent disease may be systemic or localized. In some of these patients, the condition evolves into chronic brucellosis, which may be progressive if untreated. Chronic brucellosis includes systemic and specific localized forms (including various types of neurobrucellosis). Chronic brucellosis may continue to trouble patients for as long as 25 years, but such cases are quite rare.

ANTHRAX

Anthrax is a zoonotic infection caused by *Bacillus anthracis.* Most anthrax is cutaneous (95%). The remaining cases of the disease are inhalational (5%) and gastrointestinal (< 1%). Cutaneous anthrax results from exposure to the spores of *B anthracis* while handling sick animals or contaminated wool, hair, or animal hides. Pulmonary anthrax results from inhaling anthrax spores. GI anthrax results from ingesting meat products that contain anthrax. Anthrax is present in areas where animals, particularly herbivores, graze. Anthrax caused by inhalation is usually fatal, and symptoms usually begin days after exposure. This delay makes the initial exposure to *B anthracis* difficult to track.

Anthrax was described in the early literature of the Greeks, Romans, Egyptians, and Hindus. The term *anthrakis* means coal in Greek, and the disease is named after the black appearance of its cutaneous form. A modern concern is use of anthrax as a biologic warfare agent.

Anthrax is primarily a disease of herbivores (eg, cattle, sheep, goats, horses). Pigs are not immune, but they are more resistant, as are dogs and

cats. Birds are usually naturally resistant to anthrax. Buzzards and vultures are naturally resistant to anthrax but may transmit the spores on their talons and beaks.

Anthrax (*B anthracis*) is a large, spore-forming, gram-positive rod. Persistence of spores is aided by nitrogen and organic soil content, environmental pH greater than 6, and ambient temperature greater than 15°C. Spores can exist indefinitely in the environment. Optimal growth conditions result in a vegetative phase and bacterial multiplication. Drought or rainfall can trigger anthrax spore germination, while flies and vultures spread the spores.Virulence depends on the bacterial capsule and the toxin complex. The capsule is a poly-D-glutamic acid that protects against leukocytic phagocytosis and lysis.

Anthrax toxins are composed of 3 entities: a protective antigen, a lethal factor, and an edema factor. The protective antigen is an 83-kd protein that binds to cell receptors within a target tissue. Once it is bound, a fragment is cleaved free to expose an additional binding site. The binding of edema factor at this site results in the formation of edema toxin; the binding of lethal factor results in the formation of lethal toxin.

Edema toxin acts by converting adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Cellular cAMP levels are increased, leading to cellular edema within the target tissue. Lethal factor is not well understood; it may inhibit neutrophil phagocytosis, lyse macrophages, and cause release of tumor necrosis factor and interleukin-1. Death from anthrax occurs as a result of the effects of lethal toxin. Near death or just after death, animals bleed from all body orifices.

Cutaneous anthrax

Humans are relatively resistant to cutaneous invasion by *B anthracis*, but the organisms may gain access through microscopic or gross breaks in the skin. In cutaneous anthrax, a malignant pustule develops at the infection site. Cutaneous anthrax develops 1-7 days (usually 2-5 days) after skin exposure and penetration of *B anthracis* spores This pustule is a central area of coagulation necrosis (ulcer) surrounded by a rim of vesicles filled with bloody or clear fluid. A black eschar forms at the ulcer site. Extensive edema surrounds the lesion.

The organisms multiply locally and may spread to the bloodstream or other organs (eg, spleen) via the efferent lymphatics. *B anthracis* remains in the capillaries of invaded organs, and the local and fatal effects of the infection are due, in large part, to the toxins elaborated by *B anthracis*. Dissemination from the liver, spleen, and kidneys back into the bloodstream may result in bacteremia. Secondary hemorrhagic intestinal foci of anthrax result from *B anthracis* bacteremia.

Intestinal anthrax is a rare form of infection. It occurs from eating infected, undercooked meat. Ingesting *B anthracis* spores may cause intestinal

anthrax 2-5 days following ingestion. Abdominal pain and fever occur first, followed by nausea, vomiting, malaise, anorexia, hematemesis, bloody diarrhea, and, less often, watery diarrhea. Primary intestinal anthrax predominantly affects the cecum and produces a local lesion similar to the lesion produced in the cutaneous form.

As spores are transported to mesenteric lymph nodes, replication and bacteremia begin. Ascites and ileus follow as the lymphatic system becomes occluded with the large number of bacilli. Peritoneal fluid is turbid with the presence of leukocytes and red blood cells from hemorrhagic adenitis. Vascular stasis occurs, and the stomach and intestine become edematous. Shock may occur from interstitial and intraperitoneal volume losses. Anthrax toxin further causes intrinsic renal failure independent of prerenal azotemia. Death is rapid without antibiotic therapy and aggressive volume resuscitation. The mortality rate is 50%.

Oropharyngeal anthrax is a more common form of GI anthrax and has occurred in epidemic settings. Ingestion of *B anthracis* spores may result in oropharyngeal anthrax 2-7 days after exposure. Typically, 2 days after ingestion of contaminated meat, fever and neck swelling occur in the presence of an oral cavity lesion. The lesion starts as an edematous area that becomes necrotic and forms a pseudomembrane within 2 weeks. Sore throat, dysphagia, respiratory distress, and oral bleeding also occur. Soft-issue edema and dramatic cervical lymph node enlargement follow. Recovery usually takes 3 weeks with antibiotic therapy. The reason the disease limits itself to the oropharyngeal area is unknown.

Inhalational anthrax occurs after a person inhales spores into the lungs. Primate studies suggest that the minimum infective dose ranges from 4000-8000 inhaled spores. Inhalational anthrax usually occurs in textile and tanning industries among workers handling contaminated animal wool, hair, and hides. Inhalational anthrax begins abruptly, usually 1-3 days (range, 1-60 days) after inhaling anthrax spores. Inhaled spores are ingested by pulmonary macrophages and then carried to hilar and mediastinal lymph nodes.

The spores undergo germination and multiplication and begin to elaborate toxins. Anthrax in the lungs does not cause pneumonia, but it does cause hemorrhagic mediastinitis and pulmonary edema. Hemorrhagic pleural effusions frequently accompany inhalational anthrax. After the lymph nodes become overwhelmed, bacteremia and death quickly ensue. Without treatment, the mortality rate of inhalational anthrax is approximately 95%.

Bacteremic anthrax with hematogenous spread most commonly follows inhalational anthrax. In bacteremic anthrax, hemorrhagic lesions may develop anywhere on the body. Septicemic anthrax refers to overwhelming

infection resulting from bloodstream invasion secondary to inhalation or intestinal anthrax.

Anthrax meningitis may complicate any form of anthrax, with bacteremia and hematogenous spread to the CNS. It also has occurred without a primary focus. The meninges are characteristically hemorrhagic and edematous. The mortality rate is near 100%.

Septicemic anthrax refers to overwhelming infection by anthrax bacilli. This form of anthrax may complicate inhalational anthrax. The anthrax bacilli multiply in the blood and proliferate to outnumber red blood cells. Another name for anthrax is black blood, which refers to the very dark color of the blood of animals or humans with overwhelming septicemic anthrax.

Because humans are relatively resistant to invasion by *B anthracis*, most cases of septicemic anthrax occur following inhalational anthrax. The number of organisms released from the liver or spleen into the bloodstream overwhelms host defenses and produces massive amounts of lethal toxin that cause shock and death.

Histologic Findings. The characteristic finding in anthrax is the presence of the organisms in the capillaries at the infection site; therefore, if a patient is infected, expect *B anthracis* in the capillaries of the skin, intestines, liver, spleen, lungs, or leptomeninges. Pathological findings are not in proportion to the numbers of bacilli present, which is best explained by the effects of one or more of the toxins associated with *B anthracis*. Hemorrhage may be evident.

Most cases of anthrax are the cutaneous type, are mild, and resolve with or without treatment. If treated early with appropriate antibiotics, the mortality rate of cutaneous anthrax is less than 1%. However, other forms of anthrax are potentially fatal, with inhalational anthrax carrying the worst prognosis. Inhalational anthrax and its subsequent systemic infection (eg, septicemia, hemorrhagic leptomeningitis) have a mortality rate approaching 100%.

Oropharyngeal or intestinal anthrax carries a less favorable prognosis than cutaneous anthrax but a more favorable prognosis than inhalational anthrax. Patients with oropharyngeal anthrax may develop airway obstruction (as may those with inhalational anthrax or cutaneous anthrax involving the neck). Intestinal anthrax is difficult to diagnose and is associated with higher morbidity (mortality rate 20-60%).

INTESTINAL INFECTIONS

As the name indicates, intestinal infections affect the gastrointestinal tract. Most intestinal infections are caused by bacteria, virus, protozoans, and parasites. An intestinal infection spreads through contact with the pathogen in

food, water, or fecal matter. While other causes, such as contacting with polluted water and poor hygiene can also trigger intestinal infection.

Pathogens. Intestinal infections are caused when pathogens enter your system and begin irritating the tissue in your digestive tract. The gastrointestinal tract can become inflamed and sore, which typically begins to cause additional symptoms of digestive distress. Pathogens which cause intestinal infections are ingested, typically from a contaminated food source. Spoiled dairy products, unpasteurized dairy products, spoiled meat, contaminated shellfish, or any food which was exposed to microbial pathogens and not sterilized properly with the cooking process can increase the risk of developing an infection.

Contaminated water. Coming into contact with contaminated water can also lead to an intestinal infection. Water from natural sources such as lakes should not be consumed unless it has been thoroughly boiled to sterilize it. Swimming pools can also become infested with microbes which can cause infection if they are not sanitized properly to accommodate the large population.

Poor hygiene. This can also spread microbes that cause intestinal infections. Failing to wash your hands after visiting the restroom is a common way to contract an infection. Touching surfaces, silverware or food after failing to wash your hands increases the risk that others will come into contact with these microbes, spreading the risk of disease further.

Bacterial infection. Bacterial intestinal infections occur through consumption of food that is contaminated with the infection causing or pathogenic bacteria. Bacterial infections most commonly occur in cases wherein food is not prepared or handled hygienically. Typically, these kinds of infections are seen in places where food is prepared for masses such as cafeterias in schools, fairs, and so on. Bacterial intestinal infection is usually because of not cooking meat products adequately as well as poor hygiene practices such as not washing hands before handling foods, not boiling drinking water and so on. Listed below are some of common causes of intestinal bacterial infection.

- ✓ Cholera, caused by the bacteria vibrio cholera
- ✓ Typhoid (Salmonella enteritis)
- ✓ Parathyroid infections.
- ✓ Shigellosis (Shigella enteritis)
- ✓ E. coli infections
- ✓ Intestinal staph infection (Staphylococcus)
- ✓ Botulism (Clostridium botulinum)
- ✓ Enteritis (Campylobater enteritis)

Viral infections. Viruses also cause a lot of stomach infections as well. The rota virus is the leading cause of intestinal infections in the world

and has a high death rate in children under the age of 5. The ill effects of viral intestinal infections are greater in developing nations where general sanitation is very poor. With transmission being through contact, viral intestinal infections can spread very quickly. Some of the common intestinal infections are caused by the following viruses.

- ✓ Rotavirus infections
- ✓ Norovirus infections
- ✓ Adenovirus infections
- ✓ Astrovirus infections

Parasites and protozoans. Parasites and protozoans are another reason for intestinal infections. These however are usually not self-limiting and need medication to kill the pathogens. Some of the common intestinal infections caused by parasites and protozoans are listed below.

- ✓ Amoebiasis (Entamoeba hystolytica)
- ✓ Balantidiasis
- ✓ Giardiasis (Giardia lamblia)
- ✓ Cryptosporidiosis (Cyrptosporidium)
- ✓ Intestinal trichomoniasis.

The most common symptoms of an intestinal infection are diarrhea, abdominal pain, cramps, nausea, and vomiting.

TYPHOID FEVER

Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by *Salmonella typhi*. Source of infection – sick person.

S.typhi enters the host's system primarily through the distal ileum. *S typhi* has specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. After crossing lymphatic barrier S.typhi enter into blood and leads to generalization of infectious process. The Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by *Salmonella typhi*. Source of infection – a sick person. Microbes are present in urine, faeces, sweat. Route of transmission is a fecal-oral.

Pathogenesis. The typhoid bacilli are ingested through contaminated food or water. During the initial asymptomatic incubation period of about 2 weeks, the bacilli invade the lymphoid follicles and Peyer's patches of the small intestine and proliferate. Following this, the bacilli invade the blood stream causing bacteraemia, and the characteristic clinical features of the disease like continuous rise in temperature and 'rose spots' on the skin are ob-

served. Immunological reactions (Widal's test) begin after about 10 days and peak titres are seen by the end of the third week. Eventually, the bacilli are localised in the intestinal lymphoid tissue (producing typhoid intestinal lesions), in the mesenteric lymph nodes (leading to haemorrhagic lymphadenitis), in the liver (causing foci of parenchymal necrosis), in the gall bladder (producing typhoid cholecystitis), and in the spleen (resulting in splenic reactive hyperplasia).

S typhi enters the host's system primarily through the distal ileum. *S typhi* has specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. After crossing lymphatic barrier S.typhi enter into blood and leads to generalization of infectious process. The bacteria then infect the gallbladder via either bacteremia or direct extension of *S typhi* –infected bile. The result is that the organism reenters the gastrointestinal tract in the bile and reinfects Peyer`s patches and lymphatic nodules and causes necrosis of Payer‘s patches. After that microbes excreted with urine faeces, bile, sweat, with milk in feeding mothers. In this period the patient is more infective and can cause infection of others.

Pathologic changes. The lesions are observed in the intestines as well as in other organs.

Intestina (local) changes develop in mucous membrane and lymphatic tissue of intestine. Macroscopically, terminal ileum is affected most often, but lesions may be seen in the jejunum and colon. The Peyer's patches show oval typhoid ulcers with their long axis along the length of the bowel. The base of the ulcers is black due to sloughed mucosa. The margins of the ulcers are slightly raised due to inflammatory oedema and cellular proliferation. There is never significant fibrosis and hence fibrous stenosis seldom occurs in healed typhoid lesions. The regional lymph nodes are invariably enlarged.

Microscopically, there is hyperaemia, oedema and cellular proliferation consisting of phagocytic histiocytes (showing characteristic erythrophagocytosis), lymphocytes and plasma cells. Though enteric fever is an example of acute inflammation, neutrophils are invariably absent from the cellular infiltrate and this is reflected in the leucopenia with neutropenia and relative lymphocytosis in the peripheral blood.

So, 5 stages of intestinal lesion may be described:

1. *Stage of brain like swelling.*
2. *Necrosis of enteric fever granulomas.*
3. *Ulcer formation.*

4. *Stage of pure ulcers.*
5. *Ulcer healing and formation of scars.*

Other lesions. Typhoid red papular rash appears on 7-11th day at first on the abdomen. Besides the intestinal involvement, various other organs and tissues showing pathological changes in enteric fever are:

i) Mesenteric lymph nodes — haemorrhagic lymphadenitis.
ii) Liver — foci of parenchymal necrosis,
iii) Gallbladder — typhoid cholecystitis,
iv) Spleen — splenomegaly with reactive hyperplasia.
v) Kidneys — nephritis.
vi) Abdominal muscles — Zenker's degeneration,
vii) Joints — arthritis,
viii) Bones — osteitis,
ix) Meninges — Meningitis.
x) Testis — Orchitis.

There is dystrophy in internal organs.

Complications usually result from intestine damage (intestinal complications)/ These are perforation of the ulcers and haemorrhage. Beside broncho pneumonia (due to association of secondary infection), osteomyelitis, sepsis may develop.

Persistence of organism in the gallbladder or urinary tract may result in passage of organisms in the faeces or urine creating a 'carrier state' which is a source of infection to others.

The prognosis among persons with typhoid fever depends primarily on the speed of diagnosis and initiation of correct treatment. Generally, untreated typhoid fever carries a mortality rate of 10%-20%. In properly treated disease, the mortality rate is less than 1%.

SALMONELLOSIS

It is a group of intestinal infections caused by salmonellae. They are seen in humans as weel as in animals – atropozoonosis. Most frequent causative agents are Salmonella typhymurium, S.enteritidis, S.cholerae sues.

The transmission of salmonella to a susceptible host usually occurs via consumption of contaminated foods. The most common sources of salmonella include beef, poultry, and eggs. Improperly prepared fruits, vegetables, dairy products, and shellfish have also been implicated as sources of Salmonella.

Although the infectious dose varies among Salmonella strains, a large inoculum is thought to be necessary to overcome stomach acidity and to compete with normal intestinal flora. Large inocula are also associated with higher rates of illness and shorter incubation periods. In general, about 10^6

bacterial cells are needed to cause infection. Low gastric acidity, which is common in elderly persons and among individuals who use antacids, can decrease the infective dose to 10^3 cells, while prior vaccination can increase the number to 10^9 cells.

After ingestion, infection with salmonella is characterized by attachment of the bacteria by fimbriae or pili to cells lining the intestinal lumen. Salmonella selectively attach to specialized epithelial cells (M cells) of the Peyer patches. The bacteria are then internalized by receptor-mediated endocytosis and transported within phagosomes to the lamina propria, where they are released. Once there, salmonella induce an influx of macrophages (typhoidal strains) or neutrophils (nontyphoidal strains).

The incubation period depends on the host and the inoculum is generally 6-72 hours. In most cases, stools are loose and bloodless. In rare cases, Salmonella infections cause large-volume cholera like diarrhea or may be associated with tenesmus. The diarrhea is typically self-limiting and resolves within 3-7 days. Fever, abdominal cramping, chills, headache, and myalgia are common. Fever usually resolves within 48 hours.

There are 3 main clinical forms of salmonellosis:

1. *Intestinal* – develops as acute gastritis with the dehydratation because of vomiting and diarrhea,
2. *Septic* – intestinal changes are not well marked but there is haematogenic spread of causative agent. Purulent inflammation in lungs and brain occur.
3. T*yphoid* – it resembles enteric fever. The changes in intestine, lymph nodes and spleen appear as in enteric fever but are less marked. There is rare intestinal hemorrhage and perforation of intestinal wall.

DYSENTERIES

The term 'dysentery' is used to mean diarrhoea with abdominal cramps, tenesmus and passage of mucus in the stools, from any cause. There are 2 main forms of dysenteries — bacillary and amoebic.

1. Bacillary dysentery. Bacillary dysentery is the term used for infection by shigella species: S. dysenteriae, S. flexneri, S. boydii and S. sonnei. Infection occurs by foecooral route and is seen with poor personal hygiene, in densely populated areas, and with contaminated food and water. The common housefly plays a role in spread of infection.

Large intestine (colon sigmoideum and rectum) is more frequently affected. Bacteria affect the large intestinal epithelium and lead to necrosis of mucous membrane. Bacterial endotoxin shows vasoneuroparalytic action that leads to increased exudation, necrotic changes in the intestinal wall and formation of ulcer.

Microscopically, the lesions are mainly found in the colon and occasionally in the ileum. Superficial transverse ulcerations of the bowel wall mucosa occur in the area of lymphoid follicles but perforation is seldom seen. The intervening intact mucosa is hyperaemic and oedematous. Following recovery from the acute attack, complete healing usually takes place. Microscopically, the mucosa overlying the lymphoid follicles is necrosed. The surrounding mucosa shows congestion, oedema and infiltration by neutrophils and lymphocytes. The mucosa may be covered by greyish-yellow 'pseudomembrane' composed of fibrino-suppurative exudate.

According to local changes, seen in large intestines, 4 stages may be diagnozed:

1. Stage of catarrhal colitis – there are congestion and edema of intestinal mucous membrane and small putches of necrosis. It continues for 2-3 days.
2. Stage of fibrinous colitis – there are necrosis and leukocyte infiltration, appearance of fibrin layer on the mucous membrane and dystrophic changes in nerve plexus. It continues for 5-10 days.
3. Ulceration stage – ulcers develop after the fibrinous layer and necrotic masses rejection. There may be complicated with intestinal hemorrhage and perforation.
4. Stage of ulcer healing – defect is filled with granulation tissue, which develops and converted into connective tissue scar. Large ulcers healing may cause the deformation and stenosis of intestinal lumen.

Sometimes there may be catarrhal colitis only. In children‘s it affects lymphoid tissue of intestines. If healing process is slow, chronic dysentery may develop.

General changes are hyperplasia of spleen, liver dystrophy, dystrophy of the heart and kidney.

Complication include perforation of intestine with development of peritonitis, phlegmone of intestine, intestinal hemorrhage, stenosis of intestine, development of pneumonia, pyelonephritis, intoxication, polyarthritis and iridocyclitis.

2. Amoebic dysentery (Amoebiasis)

Amoebiasis is caused by Entamoeba histolytica, named for its lyric action on tissues. It is the most important intestinal infection of man. The condition is particularly more common in tropical and subtropical areas with poor sanitation.

The parasite occurs in 2 forms: a trophozoite form which is active adult form seen in the tissues and diarrhoeal stools, and a cystic form seen in formed stools but not in the tissues. The trophozoite form can be stained positively with PAS procedure in tissue sections while amoebic cysts having four

nuclei can be identified in stools. The cysts are the infective stage of the parasite and are found in contaminated water or food. Ingestion of E histolytica cysts from the environment is followed by excystation in the terminal ileum or colon to form highly motile trophozoites. Upon colonization of the colonic mucosa, the trophozoite may encyst and is then excreted in the feces, or it may invade the intestinal mucosal barrier and gain access to the bloodstream, whereby it is disseminated to the liver, lung, and other sites. Excreted cysts reach the environment to complete the cycle.

Pathologic changes. The incubation period for E histolytica infection is commonly 2-4 weeks but may range from a few days to years. The clinical spectrum of amebiasis ranges from asymptomatic infection to fulminant colitis and peritonitis to extraintestinal amebiasis (liver abscess, pleuropulmonary disease, peritonitis, pericarditis, brain abscess, genitourinary disease), the most common form of which is amebic liver abscess.

Amoebic colitis, the most common type of amoebic infection begins as a small area of necrosis of mucosa which may ulcerate. These ulcerative lesions may enlarge, develop undermining of margins of the ulcer due to lytic action of the trophozoite and have necrotic bed. Such chronic amoebic ulcers are described as flask-shaped ulcers due to their shape. The margin of the ulcer shows inflammatory response consisting of admixture of polymorphonuclear as well as mononuclear cells. Complications of amebic colitis include the following: fulminant or necrotizing colitis, toxic megacolon, ameboma, rectovaginal fistula.

Amoebic liver abscess may be formed by invasion of the radicle of the portal vein by trophozoites. Amoebic liver abscess may be single or multiple. The amoebic abscess contains a yellowish-grey amorphous liquid material in which trophozoites are identified at the junction of the viable and necrotic tissue. Complications of amebic liver abscess include the following: intraperitoneal, intrathoracic, or intrapericardial rupture, with or without secondary bacterial infection; direct extension to pleura or pericardium; dissemination and formation of brain abscess.

Amoeboma a less common form of intestinal disease, arises from the formation of annular colonic granulation in response to the infecting organisms, which results in a large local lesion of the bowel. Microscopically, the lesion consists of inflammatory granulation tissue, fibrosis and clusters of trophozoites at the margin of necrotic with viable tissue.

CHOLERA

It is the infection which affects the stomach and small intestine. Causative agent is Vibrio cholera. They multiplicate and secrete exotoxin – cholerogen which leads to increased release of isotonic fluid and disturbances of

water reabsorption. The hallmark of the disease is profuse secretory diarrhea. Although the disease may be asymptomatic or mild, severe cholera can cause dehydration and death within hours of onset.

In the developed countries, because of advanced water and sanitation systems, cholera is not a major threat. Despite all the major advances in research, the condition still remains a challenge to the modern medical world.

Cholera is transmitted by the fecal-oral route. Source of infection is a sick person.

Cholera is typically transmitted to humans by either contaminated food or water. Most cholera cases in developed countries are a result of transmission by food, while in the developing world it is more often water. Food transmission can occur when people harvest seafood such as oysters in waters infected with sewage, as Vibrio cholerae accumulates in planktonic crustaceans and the oysters eat the zooplankton.

Cholera can be endemic, epidemic, or pandemic.

When consumed, most bacteria do not survive the acidic conditions of the human stomach. The few surviving bacteria conserve their energy and stored nutrients during the passage through the stomach by shutting down much protein production. When the surviving bacteria exit the stomach and reach the small intestine, they must propel themselves through the thick mucus that lines the small intestine to reach the intestinal walls where they can attach and thrive.

Once the cholera bacteria reach the intestinal wall they no longer need the flagella to move. The bacteria stop producing the protein flagellin to conserve energy and nutrients by changing the mix of proteins which they express in response to the changed chemical surroundings. On reaching the intestinal wall, V. cholerae start producing the toxic proteins that result in constitutive cAMP production, which in turn leads to secretion of H_2O, Na^+, K^+, Cl^-, and HCO_3^- into he lumen of the small intestine and rapid dehydration.

Stages of cholera:

1. *Choleric enteritis* – it has serous character. Mucous membrane is edematous, congested. There is increased formation of mucous and hemorrhages.

2. *Choleric gastroenteritis* – there is necrosis of mucous membrane, damage of microvillus and dehydration

3. *Alhyde period* – more expressive morphological changes. Mucous membrane has necrosis and sloughing of epithelium, expressive inflammatory infiltration and hemorrhages.

In the intestinal lumen there is large amount of liquid which looks like rice water and contains vibrio. Diarrhea leads to dehydration and loss of minerals. There may be development of hypovolemic shock, increased blood vis-

cosity, oliguria, hypothermia. All these changes lead to choleric coma and patient‘s death.

Signs of dehydration seen in cadavers are dry skin, wrinkles, mainly on hands, dry serous and mucous membrane.In the liver, kidney and myocardium thare are severe dystrophic changes.

Complications are choleric typhoid, fibrinous colitis, liver necrosis, subacute extracapillary glomerulonephritis or necrotic nephrosis with uremia development, postcholeric uremia, development of pneumonia, abscesses.

Death occurs due to dehydration in alhyde period, coma, uremia.

Before the development of effective regimens for restoration of fluid and electrolyte losses, the mortality in severe form of cholera was more than 50%. Mortality is higher in pregnant women and children

YERSINIOSIS

Yersiniosis is a relatively uncommon infection contracted through the consumption of undercooked meat products (especially pork), unpasteurized milk, or contaminated water. Usually, someone with an infection caused by *Yersinia* bacteria recovers within a few days without medical treatment.

Of the three main types of yersiniosis that affect people, *Yersinia enterocolitica* (bacteria that thrive in cooler temperatures) are responsible for most infections. The infection seems to be more common in cooler climates.

Yersinia enterocolitica is a pleomorphic, gram-negative bacillus that belongs to the family Enterobacteriaceae. As a human pathogen, *Y.enterocolitica* is most frequently associated with enterocolitis, acute diarrhea, terminal ileitis, mesenteric lymphadenitis, and pseudoappendicitis, with the spectrum of disease ranging from asymptomatic to life-threatening sepsis, especially in infants. The bacterium was first reported by Mclver and Picke, in 1934.

Y.enterocolitica most commonly affects young individuals (approximately 75% of patients with *Y.enterocolitica* infection are aged 5-15 years), but whether this represents an increased susceptibility or a greater likelihood of developing symptomatic illness is unclear. Most cases of *Y.enterocolitica* infection are sporadic, but reports have documented large outbreaks centered on a single contaminated source.

Human yersiniosis is attributed to contaminated pork, milk, water, and tofu consumption, as well as to blood transfusion. Infected individuals may shed *Y.enterocolitica* in stools for 90 days after the symptom resolution, suggesting that early detection of *Y.enterocolitica* from diarrheal stool samples is critical in preventing its transmission and an eventual outbreak.

As with other members of the genus *Yersinia*, *Y.enterocolitica* is an invasive organism that appears to cause disease by tissue destruction. Re-

searchers have elucidated several potential pathogenic properties, including chromosomally mediated effects (eg, attachment to tissue culture, production of enterotoxin) and plasmid-mediated mechanisms (eg, production of Vw antigens, calcium dependency for growth, autoagglutination).

As a foodborne pathogen, *Y.enterocolitica* can efficiently colonize and induce disease in the small intestine. Following ingestion, the bacteria colonize the lumen and invade the epithelial lining of the small intestine, resulting in the colonization of the underlying lymphoid tissues known as Peyer patches. A direct lymphatic link between the Peyer patches and mesenteric lymph nodes may result in bacterial dissemination to these sites, resulting in mesenteric lymphadenitis or systemic infection.

Dissemination to extraintestinal sites, such as the spleen, is hypothesized to occur via 2 main mechanisms: (1) colonization of the Peyer patches, which can then be used as a staging ground for spread into the blood and/or lymph, ultimately resulting in the appearance of bacteria in other tissues, and (2) bypass of the Peyer patches, with *Y.enterocolitica* going straight to systemic colonization. The possibilities of additional avenues for dissemination have yet to be excluded.

The enterotoxin produced by *Y.enterocolitica* is similar to that produced by the heat-stable *Escherichia coli*; however, it likely plays a minor role in causing disease, as diarrheal syndromes have been observed in the absence of enterotoxin production. In addition, the toxin does not appear to be produced at temperatures higher than 30°C. The plasmid-mediated outer membrane antigens are associated with bacterial resistance to opsonization and neutrophil phagocytosis.

One unique property of *Y.enterocolitica* is its inability to chelate iron, which is an essential growth factor for most bacteria and is obtained through the production of chelators known as siderophores. *Y.enterocolitica* does not produce siderophores but can utilize siderophores produced by other bacteria.

The usual presentation of *Y.enterocolitica* infection includes diarrhea (the most common clinical manifestation of this infection), low-grade fever, and abdominal pain lasting 1-3 weeks. Diarrhea may be bloody in severe cases. Vomiting is present in approximately 15-40% of cases. The existence of extraintestinal symptoms after a gastrointestinal illness may also indicate the possibility of yersiniosis.

Enterocolitis, the most common presentation of *Y.enterocolitica*, occurs primarily in young children, with a mean age of 24 months. The incubation period is 4-6 days, typically with a range of 1-14 days.

Prodromal symptoms of listlessness, anorexia, and headache may be present. Such symptoms are followed by watery, mucoid diarrhea; fever ; colicky abdominal pain; bloody stools; and white blood cells in the stool. The diarrhea

generally has a duration of 1 day to 3 weeks. Most cases are self-limited. However, concomitant bacteremia may occur in 20-30% of infants younger than 3 months.

Complications of enterocolitis include appendicitis, diffuse ulceration and inflammation of the small intestine and colon, peritonitis, meningitis, intussusception, and cholangitis.

Histologic findings in *Y.enterocolitica* infection are consistent with acute and chronic inflammation. Yersiniosis does not produce unique histologic findings. Epithelial cell granulomas with suppuration of the centers of the granulomas (central microabscesses) have been reported. These granulomas were composed of numerous histiocytes with or without epithelioid cell features, along with scattered small T-lymphocytes and plasmacytoid monocytes

GIARDIASIS

Giardiasis is a major diarrheal disease found throughout the world. The flagellate protozoan *Giardia intestinalis* - (previously known as *G. lamblia*), its causative agent, is the most common protozoal intestinal parasite isolated worldwide. Infection is more common in children than in adults.

G.intestinalis can cause asymptomatic colonization or acute or chronic diarrheal illness. The organism has been found in as many as 80% of raw water supplies from lakes, streams, and ponds and in as many as 15% of filtered water samples. It is a common cause of chronic diarrhea and growth retardation in children in developing countries.

Giardiasis usually represents a zoonosis with cross-infectivity between animals and humans. *Giardia intestinalis* has been isolated from the stools of beavers, dogs, cats, and primates. Beavers may be an important reservoir host for *G.intestinalis*. Other *Giardia* species include *G .muris* in rodents; *G.agilis* in amphibians; *G.psittaci* and *G ardeae* in birds; and *G .microti* in voles and muskrats. Although *G. intestinalis* was the first protozoan parasite described, its role as a pathogenic organism was not recognized until the 1970s, after community outbreaks and after the appearance of the disease in travelers returning from endemic regions. Prior to that time, the organism was thought to be a harmless commensal organism of the intestine.

Giardia species are endemic in areas of the world that have poor sanitation. In developing countries, the disease is an important cause of morbidity. Water-borne and food-borne outbreaks are common. Because ingestion of as few as 10 *Giardia* cysts may be sufficient to cause infection, giardiasis is common in daycare center attendees and institutionalized patients in developed countries. *G.intestinalis* is a particularly significant pathogen for people with malnutrition, immunodeficiency, or cystic fibrosis.

Infection with *Giardia intestinalis* most often results from fecal-oral transmission or ingestion of contaminated water. Contaminated food is a less common etiology. Person-to-person spread is common, with 25% of family members with infected children themselves becoming infected.

Most infections are asymptomatic. The rate of symptomatic infection in the natural setting varies from 5-70%. *Giardia* is found in healthy people in endemic areas, and asymptomatic carriage with excretion of high numbers of cysts in stools is common. Predisposing factors to symptomatic infection include hypochlorhydria, various immune system deficiencies, blood group A, and malnutrition. The incubation period averages 1-2 weeks, with a mean of 9 days. The average duration of symptoms in all ages ranges from 3-10 weeks.

Giardia life cycle. *Giardia* has one of the simplest life cycles of all human parasites. The life cycle is composed of 2 stages: (1) the trophozoite, which exists freely in the human small intestine; and (2) the cyst, which is passed into the environment. No intermediate hosts are required.

Upon ingestion of the cyst, contained in contaminated water or food, excystation occurs in the stomach and the duodenum in the presence of acid and pancreatic enzymes. The trophozoites pass into the small bowel where they multiply rapidly, with a doubling time of 9-12 hours. As trophozoites pass into the large bowel, encystation occurs in the presence of neutral pH and secondary bile salts. Cysts are passed into the environment, and the cycle is repeated.

Mechanism of injury. The mechanisms by which *Giardia* causes diarrhea and intestinal malabsorption are probably multifactorial and not yet fully elucidated. Postulated mechanisms include damage to the endothelial brush border, enterotoxins, immunologic reactions, and altered gut motility and fluid hypersecretion via increased adenylate cyclase activity.

Adhesion of trophozoites to the epithelium has been demonstrated to cause increased epithelial permeability. *Giardia*- induced loss of intestinal brush border surface area, villus flattening, inhibition of disaccharidase activities, and eventual overgrowth of enteric bacterial flora appear to be involved in the pathophysiology of giardiasis but have yet to be causatively linked to the disease's clinical manifestations.

Marked or moderate partial villous atrophy in the duodenum and jejunum can be observed in histologic sections from asymptomatic individuals who are infected. In addition to disrupting the mucosal epithelium, effects in the intestinal lumen may contribute to malabsorption and the production of diarrhea. Nevertheless, diarrhea can occur in individuals in the absence of obvious light microscopic changes in small intestinal structure.

Varying degrees of malabsorption of sugars (e.g., xylose, disaccharides), fats, and fat-soluble vitamins (e.g., vitamins A and E) may contribute

to substantial weight loss. The histopathologic response to giardiasis varies and imperfectly correlates with the clinical symptoms.

G.intestinalis may release cytopathic substances that damage the intestinal epithelium. *Giardia* species contain thiol-dependent and thiol-independent proteinases, which may find substrates in the microvillus membrane. In addition, the surface mannose-binding lectin of *G.intestinalis* may contribute to epithelial damage. Whatever the mechanism by which *G.intestinalis* damages villous epithelial cells, the result consistently appears to be an increase in crypt length and crypt cell proliferation.

Enterocytic injury is mediated by activated host T lymphocytes. Pathophysiological activation of lymphocytes is secondary to *Giardia* -induced disruption of epithelial tight junctions, which, in turn, increases intestinal permeability. Loss of epithelial barrier function is a result of *Giardia* -induced enterocyte apoptosis.

Epithelial barrier dysfunction in cases with chronic giardiasis is associated with increased rates of enterocyte apoptosis. Consistent with these observations, microarray analyses of the effects of *G. intestinalis* on human CaCo2 cells found that the parasite–host interactions lead to a pronounced up-regulation of genes implicated in the apoptotic cascade and the formation of reactive oxygen species.

Giardia can also prevent the formation of nitric oxide, a compound known to inhibit giardial growth, by consuming local arginine, which effectively removes the substrate needed by enterocytes to produce nitric oxide. This mechanism may contribute to *Giardia* -induced enterocyte apoptosis because arginine starvation in these cells is known to cause programmed cell death.

The prognosis for patients with giardiasis is generally excellent. Most patients are asymptomatic, and most infections are self-limited. Giardiasis is not associated with mortality except in rare cases of extreme dehydration, primarily in infants or malnourished children. Several antibiotic agents are available with good efficacy rates to shorten the disease course, although drug resistance has been observed in clinical experience. Untreated, giardiasis can last for weeks. The parasite persists in the stool. Reinfection is possible. Weight loss, disaccharidase deficiency, malabsorption, and growth retardation are possible complications. *G. intestinalis* has been implicated as the chief cause of growth retardation in infected children, even after other diarrhea-causing agents are controlled. Some patients may experience persistent symptoms (e.g., chronic diarrhea/steatorrhea, malabsorption) despite apparently effective antibiotic treatment, although these usually subside over weeks to months. Patients reported bloating, diarrhea, and abdominal pain, which were exacerbated by specific foods or by physical or mental stress.

Complications of giardiasis may include the following: development of chronic illness with weight loss; malabsorption syndrome in adults; failure to thrive in children; disaccharidase deficiency; zinc deficiency in schoolchildren; growth retardation; persistent gastrointestinal symptoms.

The traditional basis of diagnosis is identification of *Giardia intestinalis* trophozoites or cysts in the stool of infected patients via a stool ova and parasite examination. Stool antigen enzyme-linked immunosorbent assays also are available. Standard treatment for giardiasis consists of antibiotic therapy.

ESCHERICHIA COLI INFECTIONS

Escherichia coli is one of the most frequent causes of many common bacterial infections, including cholecystitis, bacteremia, cholangitis, urinary tract infection, and traveler's diarrhea, and other clinical infections such as neonatal meningitis and pneumonia.

Escherichia organisms are gram-negative bacilli that exist singly or in pairs. E. coli is facultative anaerobic with a type of metabolism that is both fermentative and respiratory. They are either non motile or motile by peritrichous flagella. E. coli is a major facultative inhabitant of the large intestine.

As a cause of enteric infections, 6 different mechanisms of action of 6 different varieties of E. coli have been reported. *Enterotoxigenic E coli* (ETEC) is a cause of traveler's diarrhea. *Enteropathogenic E. coli* (EPEC) is a cause of childhood diarrhea. *Enteroinvasive E. coli* (EIEC) causes a Shigella-like dysentery. *Enterohemorrhagic E. coli* (EHEC) causes hemorrhagic colitis or hemolytic-uremic syndrome. *Enteroaggregative E. coli* (EAggEC) is primarily associated with persistent diarrhea in children in developing countries, and *Enteroadherent E coli* (EAEC) is a cause of childhood diarrhea and traveler's diarrhea in Mexico and North Africa. ETEC, EPEC, EAggEC, and EAEC colonize the small bowel, and EIEC and EHEC preferentially colonize the large bowel prior to causing diarrhea.

Shiga toxin–producing E. coli (STEC) is among the most common causes of foodborne diseases. This organism is responsible for several gastrointestinal illnesses, including nonbloody and bloody diarrhea. Patients with these diseases, especially children, may be affected by neurologic and renal complications, including hemolytic-uremic syndrome.

BALANTIDIASIS

Balantidiasis (also known as balantidiosis) is defined as large-intestinal infection with Balantidium coli, which is a ciliated protozoan (and the largest protozoan that infects humans). *B. coli* is known to parasitize the colon, and pigs may be its primary reservoir. Balantidiasis tends to be more common among persons who handle pigs.

B. coli exists as a trophozoite and a cyst and usually affects the large intestine, from the caecum to the rectum. The trophozoites replicate by binary fission and conjugation, and they subsist on bacteria. Humans ingest infective cysts, which then migrate to the large intestine, cecum, and terminal ileum. The organisms primarily dwell in the lumen but can also penetrate the mucosa and cause ulcers. *B. coli* produces hyaluronidase, potentially enhancing its ability to invade the mucosa.

Patients with balantidiasis may present with abdominal tenderness, fever, and prolonged diarrhea, which may result in signs of dehydration.

Histologic findings. B coli can invade the mucosa and submucosa, causing ulceration and infiltration with polymorphonuclear cells, lymphocytes, and eosinophils. Trophozoites can be observed at the invading edge of ulcers or at the periphery of submucosal abscesses.

Complications. Intestinal perforation and extraintestinal spread to liver and mesenteric lymph nodes are rare. Pulmonary involvement has been reported and appears to be more common in patients with underlying illnesses such as diabetes, cancer, or impaired lymphocyte function.

Most cases of balantidiasis in immunocompetent individuals are asymptomatic. Mortality rates associated with acute and fulminating types of balantidiasis.

GRANULOMATOUS INFECTIONS

RHINOSCLEROMA

Rhinoscleroma is a chronic granulomatous bacterial disease of the nose and other parts of the upper respiratory tract, caused by Klebsiella rhinoscleromatis.

Rhinoscleroma is endemic to areas of Africa (Egypt, tropical areas), Southeast Asia, Mexico, Central and South America, and Central and Eastern Europe. It is rare in Western Europe.

Rhinoscleroma develops due to direct inhalation of droplets or contaminated material. The disease probably begins in areas of epithelial transition such as the vestibule of the nose, the subglottic area of the larynx, or the area between the nasopharynx and oropharynx. Cellular immunity is impaired in patients with rhinoscleroma; however, their humoral immunity is preserved.

Rhinoscleroma usually affects the nasal cavity, but lesions associated with rhinoscleroma may also affect the larynx; nasopharynx; oral cavity; paranasal sinuses; or soft tissues of the lips, nose, trachea, and bronchi.

Classic histopathologic findings include large vacuolated Mikulicz cells and transformed plasma cells with Russell bodies. The Mikulicz cell is a

large macrophage with clear cytoplasm that contains the bacilli; this cell is specific to the lesions in rhinoscleroma.

TUBERCULOSIS

Tuberculosis (TB), a multisystemic disease with myriad presentations and manifestations, is the most common cause of infectious disease–related mortality worldwide. The World Health Organization (WHO) has estimated that 2 billion people have latent TB and that globally, in 2009, the disease killed 1.7 million people.

Despite great advances in immunology, microbiology, and drug development, TB remains among the great public health challenges. Poverty; lack of functioning public health infrastructure; lack of funding to support basic research aimed at developing new drugs, diagnostics, and vaccines; and the co-epidemic of HIV continue to fuel the ongoing epidemic of TB.

The lungs are the most common site for the development of TB; 85% of patients with TB present with pulmonary complaints. Extrapulmonary TB can occur as part of a primary or late, generalized infection.

*Etiology***.** TB is caused by *Mycobacterium tuberculosis (TBM),* a slow-growing obligate aerobe and a facultative intracellular parasite.

The first description of TBM is credited to Robert Whytt, on the basis of his 1768 monograph, Observations of Dropsy in the Brain. TBM first was described as a distinct pathological entity in 1836, and Robert Koch demonstrated that TB was caused by *M.tuberculosis* in 1882.

M.tuberculosis is an aerobic gram-positive rod that stains poorly because of its thick cell wall that contains lipids, peptidoglycans, and arabinomannans.

Mycobacteria vary in appearance from spherical to short filaments, which may be branched. Although they appear as short to moderately long rods, they can be curved and frequently are seen in clumps. Individual bacilli generally are 0.5-1 µm in diameter and 1.5-10 µm long. They are nonmotile and do not form spores.

One of the distinct characteristics of mycobacteria is their ability to retain dyes within the bacilli that usually are removed from other microorganisms by alcohols and dilute solutions of strong mineral acids such as hydrochloric acid. This ability is attributed to a waxlike layer composed of long-chain fatty acids, the mycolic acids, in their cell wall. As a result, mycobacteria are termed acid-fast bacilli.

The organism is spread primarily as an airborne aerosol from an individual who is in the infectious stage of TB. In immunocompetent individuals, exposure to *M.tuberculosis* usually results in a latent/dormant infection. Only about 5% of these individuals later show evidence of clinical disease. Altera-

tions in the host immune system that lead to decreased immune effectiveness can allow *M.tuberculosis* organisms to reactivate, with tubercular disease resulting from a combination of direct effects from the replicating infectious organism and from subsequent inappropriate host immune responses to tubercular antigens.

Mycobacteria are highly antigenic, and they promote a vigorous, nonspecific immune response. Their antigenicity is due to multiple cell wall constituents, including glycoproteins, phospholipids, and wax D, which activate Langerhans cells, lymphocytes, and polymorphonuclear leukocytes

When a person is infected with *M. tuberculosis*, the infection can take 1 of a variety of paths, most of which do not lead to actual TB. The infection may be cleared by the host immune system or suppressed into an inactive form called latent tuberculosis infection (LTBI), with resistant hosts controlling mycobacterial growth at distant foci before the development of active disease. Patients with LTBI cannot spread TB.

Predisposing factors for the development of active TB include malnutrition, alcoholism, substance abuse, diabetes mellitus, corticosteroid use, malignancy, head trauma, and HIV infection.

Homeless persons, people in correctional facilities, and residents of long-term care facilities also have a higher risk of developing active TB compared with the general population.

*Pathogenes***is.** The typical TB lesion is an epithelioid granuloma with central caseation necrosis. The most common site of the primary lesion is within alveolar macrophages in subpleural regions of the lung. Bacilli proliferate locally and spread through the lymphatics to a hilar node, forming the Ghon complex.

Early tubercles are spherical, 0.5- to 3-mm nodules with 3 or 4 cellular zones demonstrating the following features:

1. A central caseation necrosis,
2. An inner cellular zone of epithelioid macrophages and Langhans giant cells admixed with lymphocytes,
3. An outer cellular zone of lymphocytes, plasma cells, and immature macrophages,
4. A rim of fibrosis (in healing lesions).

Initial lesions may heal and the infection become latent before symptomatic disease occurs. Smaller tubercles may resolve completely. Fibrosis occurs when hydrolytic enzymes dissolve tubercles and larger lesions are surrounded by a fibrous capsule. Such fibrocaseous nodules usually contain viable mycobacteria and are potential lifelong foci for reactivation or cavitation. Some nodules calcify or ossify and are seen easily on chest radiographs.

Tissues within areas of caseation necrosis have high levels of fatty acids, low pH, and low oxygen tension, all of which inhibit growth of the tubercle bacillus.

If the host is unable to arrest the initial infection, the patient develops progressive, primary TB with tuberculous pneumonia in the lower and middle lobes of the lung. Purulent exudates with large numbers of acid-fast bacilli can be found in sputum and tissue. Subserosal granulomas may rupture into the pleural or pericardial spaces and create serous inflammation and effusions.

With the onset of the host immune response, lesions that develop around mycobacterial foci can be either proliferative or exudative. Both types of lesions develop in the same host, since infective dose and local immunity vary from site to site.

Proliferative lesions develop where the bacillary load is small and host cellular immune responses dominate. These tubercles are compact, with activated macrophages admixed, and are surrounded by proliferating lymphocytes, plasma cells, and an outer rim of fibrosis. Intracellular killing of mycobacteria is effective, and the bacillary load remains low.

Exudative lesions predominate when large numbers of bacilli are present and host defenses are weak. These loose aggregates of immature macrophages, neutrophils, fibrin, and caseation necrosis are sites of mycobacterial growth. Without treatment, these lesions progress and infection spreads.

There are 3 main kinds of the clinicomorhologic forms of tuberculosis: primary, haematogenic and secondary.

PRIMARY TUBERCULOSIS

Primary tuberculosis develops due to primary contact of organism with M.tuberculosis. Mode of transmission – mostly air-droplet, rarely with food of direct contact. The way of infection spred – aerogenic; but alimentary way is possible too. More frequently the children are affected.

To appearance of primary tuberculosis belongs primary TB complex. There are inflammatory patches in affected organ (primary focus on affect), inflammation of lymphatic vessels (lymphagnitis) and regional lymph nodes (lymphadenitis).

The most typical places of primary the focus localization in case aerogenic damage are the sub pleural segments of lungs (3,8,9,10). It consists of focus of exudative inflammation with the repid development of necrosis. The focus of caseous pneumonia, blundered by the zone of peritocal inflammation is formed. The sizes of affect are different: sometimes this is alveolitis, more frequently the damage of acinus or lobule, rarely – segment and hole lobe.

The elastic fibres are kept long time in the caseous. Inflammatory process involves the pleurae resulting in fibrinous or serous-fibrinous pleuritis.

Specific inflammatory process speeds on the neighbor lymphatic vessels (the lymphangitis). Lymphostasis and the tuberculus formation along the lymphatic vessels in perivascular tissue are observed. So, the way from the primary focus to hilus lymph nodes is formed. Then inflammatory process spreads father and involves the regional bronchopulmonary, bronchial, bifurcation lymph nodes, where the specific inflammatory process with the caseous necrosis appears. It is total caseous the lymphadenitis.

If *M.tuberculosis* penetrates with food, then there is formation of same primary complex in intestines. Tubercular tubercles are formed in the intestines with necrosis and ulcer formation, development of lymphangitis of mesenterial lymph vessels and caseous lymphadenitis.

Thus primary tuberculosis is characterized by:

1. Development of disease due to first meeting of organism and infection;
2. Sensitization and allergy reactions of hypersensitivity of immediate type;
3. Predominance of exudative-necrotic changes;
4. Inclination to haematogenic and lymphogenic generalization;
5. Para specific reactions such as vasculitis, arthritis, serositis and other.

Variants of primary tuberculosis duration:

1. Attenuation of primary tuberculosis and healing of primary complex,
2. Progressive primary tuberculosis with generalization of process,
3. Chronic duration.

I. Attenuation of primary tuberculosis it begins from damaged patch of pulmonary tissue. Caseous necrosis patches – are surrounded by epithelioid and lymphoid cells, and then by fibrous capsule. Necrotic masses tear away. At their place forms fragments of bone tissue (ossification of primary spot). Healed primary patch is known as Hon`s patch. There is sclerosis of lymph vessel with the formation of fibrous cord; healing process in lymph node occurs as well as in lungs, but slowly. *M. tuberculosis* then remains in these patches. This gives immunity and prevents from new attack. If steroids and immunosuppressants are given to these patients then these patches may be activated with development of tuberculosis infection.

II. Progressive primary TB it is with generalization of process. It may have four forms:

1. Haematogenic – causative agent enters into blood and spread in whole organism that leads to formation of tuberculous patches of different size in different organs.
2. Lymphoglandular – in this groups of lymph nodes are involved and they squeezes bronchi that leads to atelectasis and pneumonia

3. Growth of primary affect – it is more severe progressive form. Caseous necrotic patch increases continuously that leads to death of patient or cavity in lungs – primary pulmonary cavern.

4. Mixed form – develops in weak patients from one of the previous forms. Necrotic patch is seen in lungs. There is damage of lymph nodes, tuberculous patches are present in many organs.

III. Chronic duration develops in prolonged inflammation process in lymph nodes. Periods of recurrence are alternated with remission periods. There is sensibilization of organism – increased sensitivity to different nonspecific actions. This is confirmed by skin probes (Mont, perk). Paraspecific reactions develop – fibrinoid changes in CT, dystrophy in organs, amyloidosis, hyperplasia of bone marrow.

Peculiarities of primary chronic tuberculosis of lungs:

1. Total caseous necrosis of lymph nodes;

2. Inclination to generalization with metastatic foci of extra pulmonary tuberculosis formation;

3. Hematogenous generalization of infection is accompanied with tuberculosis inflammation of serous coats (tuberculosis poliserositis – pleuritis, pericarditis) and activity of process in lymph nodes.

Chronic primary tuberculosis arises in case of slowly progressive wavy course of specific process. It results in organism sensitization: increase of its sensitivity to nonspecific agents and development of paraspecific reactions (diffuse and nodular proliferation of lymphocytes and macrophagocytes, fibrinoid changes in blood vessel wall, hyperplastic changes of hemopoietic tissue, disproteinosis, and sometime amyloidosis.

HEMATOGENOUS TUBERCULOSIS

Arises and develops in organism after primary infection and healing, but in patients secondary foci or not fully healed foci are kept in different organs and lymph nodes. Due to action of negative factors and hypersensitivity to tuberculosis latent process exacerbation arises.

Subvariants:

1) generalized hematogenous tuberculosis;
2) hematogenous tuberculosis with lungs lesion mainly;
3) hematogenous tuberculosis with extrapulmonary lesions mainly.

Generalized hematogenous tuberculosis is severe form of disease in which multiple tuberculosis tuberculum and necrotic foci appear.

Depending on morphological substrate its 3 kinds are distinguished:

I. Acute tuberculosis sepsis (necrotic type),

II. Acute general miliary tuberculosis,

III. Acute general large focal tuberculosis.

Hematogenous tuberculosis with lungs lesion mainly – most frequent form of pulmonary tuberculosis.

Variants:

а) acute miliary lung tuberculosis;

б) chronic miliary lung tuberculosis;

в) chronic large focal tuberculosis of lungs.

Chronic large focal tuberculosis of lungs is one of intermediate form of hematogenous tuberculosis with kept immunological features (appear in adult persons).

Main morphological signs:

1. Symmetric damage of both lungs;
2. Mainly corticopleural localization of pathological process in lungs;
3. Predominance of proliferative reactions;
4. Development of diffuse net sclerosis;
5. Development of emphysema;
6. Hypertrophy of right heart;
7. Absence of inclination to destruction;
8. Formation of caverns in the borderline zones of lungs and their symmetric localization;
9. Presence of extrapulmonary metastatic foci.

SECONDARY TUBERCULOSIS

Secondary tuberculosis (reinfectious, after primary) develops in organism of adult persons, who have suffered primary tuberculosis infection in childhood. It is characterized by lungs lesion. Progression of process is possible by contact way or intracanalicular (in swallowing or aspiration of sputum), but not by the blood or lymph.

Forms of secondary tuberculosis:

1. Acute focal tuberculosis;
2. Fibrous- focal tuberculosis;
3. Infiltrative- pneumonic;
4. Tuberculoma;
5. Caseous pneumonia;
6. Acute cavernous tuberculosis;
7. Fibrous- cavernous tuberculosis;
8. Cirrhotic tuberculosis.

Complications:

- In primary tuberculosis: tuberculosis meningitis, pleuritis, pericarditis, peritonitis.
- In tuberculosis of bones: sequesters, abscess, deformations, fistula.

➢ In secondary tuberculosis complications are provided by caverns: hemorrhage, rupture of wall and spreading into pleural cavity (empyema and pneumothorax).

➢ Amyloidosis (complication of chronic purulent processes).

Causes of death:

- progression of specific process, which is accompanied with severe intoxication and dystrophy of parenchymatous organs,

- brain edema in tuberculosis generalization and miliary tuberculosis with tuberculosis meningitis, hydrocephaly and fibrosis in pia mater encephali;

- decompensation of renal failure with uremia in bilateral kidney tuberculosis;

- pulmonary bleedings from erosive blood vessels of cavern wall in progression of pulmonary tuberculosis;

- amyloid-lipoid nephrosis with progressing renal failure in general amyloidosis;

- chronic pulmonary-cardiac failure, which may result in the left type of acute pulmonary-cardiac failure.

LEPROSY

Leprosy is a chronic infection caused by the acid-fast, rod-shaped bacillus Mycobacterium leprae. Leprosy can be considered 2 connected diseases that primarily affect superficial tissues, especially the skin and peripheral nerves. Initially, a mycobacterial infection causes a wide array of cellular immune responses. These immunological events then elicit the second part of the disease, a peripheral neuropathy with potentially long-term consequences.

In the 1990s, the World Health Organization (WHO) launched a campaign to eliminate leprosy as a public health problem by 2000. Elimination, as defined by the WHO, was defined as a reduction of patients with leprosy requiring multidrug therapy to fewer than 1 per 10,000 population. This goal was achieved in terms of global prevalence by 2002, but 15 of the 122 countries where leprosy was endemic in 1985 still have prevalence rates of greater than 1 per 10,000 population

According to WHO figures and as reported by 130 countries, the global annual detection rates have declined from 2004-2010. Of the new cases, 95% were detected worldwide during 2010 in the following countries: Angola, Bangladesh, Brazil, China, Democratic Republic of the Congo, India, Ethiopia, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, Philippines, Sri Lanka, Sudan, and United Republic of Tanzania. These countries still exhibit pockets of high endemicity.

M leprae was discovered as the causative agent in 1873. The acid fast, gram-positive bacillus is an obligate intracellular organism with a predilection for Schwann cells and macrophages.

The route of transmission has not been definitively established, although human-to-human aerosol spread of nasal secretions is thought to be the most likely mode of transmission in most cases. Leprosy is not spread by touch, since the mycobacteria are incapable of crossing intact skin. Living near people with leprosy is associated with increased transmission. Among household contacts, the relative risk for leprosy is increased 8- to 10-fold in multibacillary and 2- to 4-fold in paucibacillary forms. Animal reservoirs do exist (armadillos, certain nonhuman primates), and cases of suspected zoonotic transmission have been reported.

The incubation period of leprosy is long, ranging from a few months to 20-50 years. The mean incubation time is estimated to be 10 years for lepromatous leprosy and 4 years for tuberculoid leprosy.

Leprosy can manifest in different forms, depending on the host response to the organism.

Individuals who have a vigorous cellular immune response to M. leprae have the tuberculoid form of the disease that usually involves the skin and peripheral nerves. The number of skin lesions is limited, and they tend to be dry and hypoesthetic. Nerve involvement is usually asymmetric. This form of the disease is also referred to as paucibacillary leprosy because of the low number of bacteria in the skin lesions (i.e., < 5 skin lesions, with absence of organisms on smear).

Individuals with minimal cellular immune response have the lepromatous form of the disease, which is characterized by extensive skin involvement. Skin lesions are often described as infiltrated nodules and plaques, and nerve involvement tends to be symmetric in distribution. The organism grows best at 27-30°C; therefore, skin lesions tend to develop in the cooler areas of the body, with sparing of the groin, axilla, and scalp. This form of the disease is also referred to as multibacillary leprosy because of the large number of bacteria found in the lesions (i.e., >6 lesions, with possible visualization of bacilli on smear).

Leprosy is rarely fatal, and the primary consequence of infection is nerve impairment and debilitating sequelae. Although both lepromatous leprosy and tuberculoid leprosy involve the skin and peripheral nerves, tuberculoid leprosy has more severe manifestations. Nerve involvement results in loss of sensory and motor function, which may lead to frequent trauma and amputation. The ulnar nerve is most commonly involved.

Damage in the following nerves is associated with characteristic impairments in leprosy:

- Ulnar and median - Clawed hand,
- Posterior tibial - Plantar insensitivity and clawed toes,
- Common peroneal -Foot drop,
- Radial cutaneous, facial, and greater auricular nerves may also be involved.

Infiltration by bacteria may lead to destruction of nasal cartilage (lepromatous leprosy), ocular involvement, and diffuse thickening of the skin. Advanced cases of leprosy involve the loss of eyebrows and lashes, but these deformities are less common today.

*Histologic Findings***.** Findings vary but can include dermatitis, giant cells, infiltration of nerve bundles with mononuclear cells, and granulomas. Lepromatous lesions generally contain numerous acid-fast bacilli and fat-laden macrophages with a paucity of lymphocytes.

In contrast, tuberculoid lesions contain few-to-no acid-fast bacilli but manifest granulomatous changes with epithelial cells and lymphocytes.

GRANULOMA INGUINALE

Granuloma inguinale is a chronic bacterial infection that frequently is associated with other sexually transmitted diseases. Granuloma inguinale is characterized by intracellular inclusions in macrophages referred to as Donovan bodies. Granuloma inguinale usually affects the skin and mucous membranes in the genital region, where it results in nodular lesions that evolve into ulcers.

The disease is common in tropical and subtropical countries such as New Guinea, Australia and India. The organism inhabits the intestinal tract. The infection is transmitted through vaginal or anal intercourse and by autoinoculation. The incubation period varies from 2 to 4 weeks. Initially, the lesion is in the form of a papule, a subcutaneous nodule or an ulcer. Within a few weeks, it develops into a raised, soft, painless, reddish ulcer with exuberant granulation tissue. Depending upon whether the individual is heterosexual or homosexual, the lesions are located on the penis, scrotum, genitocrural folds and inguinal folds, or in the perianal and anal area respectively. Regional lymphadenopathy generally does not occur.

Microscopically, the margin of the ulcer shows epithelial hyperplasia. The ulcer bed shows neutrophilic abscesses. The dermis and subcutaneous tissues are infiltrated by numerous histiocytes containing many bacteria called Donovan bodies, and lymphocytes, plasma cells and neutrophils. These organisms are best demonstrated by silver impregnation techniques.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is a sexually-transmitted disease caused by *Chlamydia trachomatis* and is characterized by mucocutaneous lesions and regional lymphadenopathy. C. trachomatis is an obligate intracellular gram-negative bacteria. LGV is endemic in certain areas of Africa, Southeast Asia, India, the Caribbean, and South America.

Infection occurs after direct contact with the skin or mucous membranes of an infected partner. The organism does not penetrate intact skin. The organism then travels by lymphatics to regional lymph nodes, where it replicates within macrophages and causes systemic disease.

Pathologic changes. LGV has three stages. In its primary stage, the disease is more likely to be detected in men; it may go unnoticed in women. After an incubation period of four to 30 days, a small painless ulcer or blister develops in the genital area. Second-stage LGV develops between one and six weeks later. In this stage, the infection spreads to the lymphatic system, forming buboes (swellings) in the lymph nodes of the groin area. The buboes often merge, soften, and rupture, forming sinuses and fistulas (hollow passages and ducts) that carry an infectious bloody discharge to the outside of the body. Patients with second-stage LGV may also have fever, nausea, headaches, pains in their joints, skin rashes, and enlargement of the spleen or liver. Third-stage LGV, which is sometimes called anogenitorectal syndrome, develops in about 25% of patients. Third-stage LGV is marked by rectal pain, constipation, a discharge containing pus or bloody mucus, and the development of strictures (narrowing or tightening of a body passage) in the rectum or vagina.

LGV can have a number of serious **complications**. C. trachomatis infections of any subtype are associated with long-term fertility problems in women. Strictures in the rectum can completely close off the lower bowel, producing eventual rupture of the bowel and inflammation of the abdominal cavity. The patient can develop chronic abscesses or fistulae in the anal area or in the vagina in women. Long-term blockages in the lymph nodes can produce elephantiasis, a condition in which the patient's upper legs and groin area become greatly enlarged. Patients with chronic LGV infection have a higher risk of developing cancer in the inflamed areas.

Microscopically, the lymph nodes have characteristic stellate-shaped abscesses surrounded by a zone of epithelioid cells (granuloma). Healing stage of the acute lesion takes place by fibrosis and permanent destruction of lymphoid structure.

SYPHILIS

Syphilis (lues) is a chronic, sexually transmitted, systemic infection caused by Treponema pallidum. The disease was first recognized in Europe in the 1490s and has been related to the return of Christopher Columbus and his seamen from the New World. Urbanization and mass movements of people caused by war contributed to its rapid spread. Originally, syphilis was an acute disease that caused destructive skin lesions and early death, but it has become milder, with a more protracted and insidious clinical course.

Syphilis has a myriad of presentations and can mimic many other infections and immune-mediated processes in advanced stages. Hence, it has earned the nickname ―the great impostor.‖ The complex and variable manifestations of the disease prompted Sir William Osler to remark, ―The physician who knows syphilis knows medicine.‖ Many famous personages throughout history are thought to have suffered from syphilis, including Bram Stoker, Henry VIII, and Vincent Van Gogh. Since the discovery of penicillin in the mid-20th century, the spread of this once very common disease has been largely controlled, but efforts to eradicate the disease entirely have been unsuccessful.

The cause of syphilis is infection with the spirochete *Treponema pallidum.* Transmission of *T.pallidum* occurs via penetration of the spirochetes through mucosal membranes and abrasions on epithelial surfaces. It is primarily spread through sexual contact but can be spread by exposure to blood products and transferred in utero. *T. pallidum* is a labile organism that cannot survive drying or exposure to disinfectants; thus, fomite transmission (e.g., from toilet seats) is virtually impossible.

T. pallidum is a thin, long spirochete, which cannot be grown in artificial media. The organism is too thin to be seen by routine light microscopy, and techniques that amplify the width of the organism (e.g., dark-field microscopy, silver impregnation stains) must be employed to demonstrate the organism in tissue of fluids.

Epidemiology. Syphilis is a world wide disease, which is transmitted almost exclusively by sexual contact. The infection is also spread from an infected mother to her fetus (congenital syphilis). Blood transfusions, direct inoculation, and nonsexual contact are only rare causes of syphilis.

Risk factors of syphilis include the following: unprotected sex, promiscuous sex, and intravenous drug use are the major risk factors. Health care workers are at occupational risk.

Pathogenesis. Treponema pallidum is very fragile and is killed by soap, antiseptics, drying, and cold. Person-to-person transmission requires direct contact between a rich source of spirochetes (e.g., an open lesion) and mucous membranes or abraded skin of the genital organs, rectum, mouth, fingers, or nipples.

In acquired syphilis, *T. pallidum* rapidly penetrates intact mucous membranes or microscopic dermal abrasions and, within a few hours, enters the lymphatics and blood to produce systemic infection. Incubation time from exposure to development of primary lesions, which occur at the primary site of inoculation, averages 3 weeks but can range from 10-90 days. Studies in rabbits show that spirochetes can be found in the lymphatic system as early as 30 minutes after primary inoculation, suggesting that syphilis is a systemic disease from the outset. Although *T.pallidum* incites a vigorous inflammatory response, it persists and proliferates. Chronic infection and inflammation cause tissue destruction, sometimes for decades.

Regardless of the stage of disease and location of lesions, histopathologic hallmarks of syphilis include endarteritis (which in some instances may be obliterative in nature) and a plasma cell–rich infiltrate. Endarteritis is caused by the binding of spirochetes to endothelial cells, mediated by host fibronectin molecules bound to the surface of the spirochetes. The resultant endarteritis can heal with scarring in some instances.

The syphilitic infiltrate reflects a delayed-type hypersensitivity response to *T.pallidum*, and in certain individuals with tertiary syphilis, this response by sensitized T-lymphocytes and macrophages results in gummatous ulcerations and necrosis. Antigens of *T.pallidum* induce host production of treponemal antibodies and nonspecific reagin antibodies. Immunity to syphilis is incomplete.

The course of syphilis is classically divided into three stages:

1. *Primary syphilis:* the first lesion (a chancre) appears within several weeks of exposure at the inoculation site, where the number of organisms is initially greatest.
2. *Secondary syphilis:* From the primary lesion, the spirochetes are disseminated throughout the body, producing systemic manifestations and widespread lesions
3. *Tertiary syphilis:* The continued presence of spirochetes at some sites and the associated immunologic response produce chronic destructive lesions, which often manifest years after primary and secondary disease

PRIMARY SYPHILIS

The classic lesion of primary syphilis is the chancre; a characteristic ulcer located at the site of T. pallidum inoculation, usually the penis, vulva, anus, or mouth. It appears 1 week to 3 months after exposure, with an average incubation period of 3 weeks. The chancre tends to be solitary and has a firm, raised border. Unless secondarily infected, the chancre lacks a purulent exudate. Microscopically, spirochetes may be anywhere in the chancre but tend to be concentrated in the walls of vessels and in the epidermis around the ulcer. Chancres, as well as the lesions of the other stages of syphilis, display a characteristic "luetic vascu-

litis," in which endothelial cells proliferate and swell and the walls of the vessels become thickened by lymphocytes and fibrous tissue.

The chancre begins as a papule that quickly erodes to a characteristic ulcer. Chancres are painless and can go unnoticed in some locations, such as the uterine cervix, anal canal, and mouth. The chancre lasts from 3 to 12 weeks and is frequently accompanied by inguinal lymphadenopathy. It heals without scarring. Penicillin remains effective therapy.

SECONDARY SYPHILIS

Secondary syphilis is characterized by lesions in a variety of organs, especially the skin, mucous membranes, lymph nodes, meninges, stomach, and liver. This stage is the result of the systemic dissemination and proliferation of T. pallidum. Because almost any organ or combination of organs can be involved in secondary syphilis, this stage of the disease is enormously diverse in its clinical presentation, earning syphilis its nickname as "The Great Imitator." Histopathologically, the lesions of secondary syphilis show a chronic inflammatory infiltrate and endarteritis obliterans.

- *Skin:* The most common presentation of secondary syphilis is a rash, accompanied by constitutional symptoms, which appears 2 weeks to 6 months after the chancre heals. The rash is erythematous and maculopapular, involving the trunk and extremities and often including the palms and soles. There are a variety of other skin lesions in secondary syphilis, including condylomata lata (exudative plaques in the perineum, vulva, or scrotum, which abound in spirochetes; follicular syphilids (small popular lesions around hair follicles that cause loss of hair); and nummular syphilids (coinlike lesions involving the face and perineum).
- *Mucous membranes:* lesions on mucosal surfaces of the mouth and genital organs, called ―mucous patches‖, teem with organisms and are highly infectious. The mucocutaneous lesions are accompanied by fever malaise, pharyngitis, weight loss and lymphadenopathy.
- *Lymph nodes:* characteristic changes in lymph nodes include a thickened capsule, follicular hyperplasia, increased numbers of plasma cells and macrophages and luetic vasculitis. Numerous spirochetes are present in the lymph nodes of secondary syphilis. Swelling of the epitrochlear lymph nodes, uncommon in other diseases, has long been associated with syphilis.
- *Meninges:* although the meninges are commonly seeded with T. Pallidum, this involvement is frequently asymptomatic. Occasionally patients complain of headache and stiff neck.

The symptoms of secondary syphilis may begin before the chancre of primary syphilis has resolved and persist for varying periods of time ranging from a few days to many months. If untreated, secondary syphilis can relapse.

TERTIARY SYPHILIS

After the lesions of secondary syphilis have subsided, an asymptomatic period lasts for years or decades. However during this latent period, spirochetes continue to multiply, and the deep-seated lesions of tertiary syphilis gradually develop and expand. During this stage of apparent well-being, spirochetes may be passed in blood transfusions or across the placenta to the fetus.

A third of untreated patients with syphilis develop tertiary lesions. Most of the pathologic processes associated with tertiary syphilis derive from focal ischemic necrosis secondary to obliterating endarteritis. T. Pallidum incites a mononuclear inflammatory infiltrate predominantly composed of lymphocytes and plasma cells. These cells infiltrate small arteries and arterioles, producing a characteristic obstructive vascular lesion (endarteritis obliterans). The small arteries are inflamed and their endothelial cells are swollen. They are surrounded by concentric layers of proliferating fibroblasts, which confer an ―onion skin‖ appearance to the vascular lesions.

Syphilitic aortitis: this lesion results from a slowly progressive endarteritis obliterans of the vasa vasorum that eventually leads to necrosis of the aortic media, a gradual weakening and stretching of the aortic wall, and the formation of an aortic aneurysm. The syphilitic aneurysm is saccular and involves the ascending aorta, an unusual site for the much more common atherosclerotic aneurysms. On gross examination, the intima of the aorta appears rough and pitted (tree-bark appearance). The specialized arrangement of the aortic media, which includes a delicate and intimate weave elastica, smooth muscle and collagen, is gradually replaced by scar tissue. It is the specialized tissues of the media that gives the aorta its strength and resilience. When these are replaced by scar tissue, the aorta gradually stretches, becoming progressively thinner to the point of rupture, massive hemorrhage, and sudden death. Damage to and scarring of the ascending aorta also commonly lead to dilatation of the aortic ring, separation of the valve cusps, and regurgitation of blood through the aortic valve (aortic insufficiency).

Luetic vasculitis of the coronary arteries may narrow or occlude these vessels and cause myocardial infarction.

• *Neurosyphilis:* The slowly progressive infection damages the meninges, cerebral cortex, spinal cord, cranial nerves, or eyes. Tertiary syphilis involving the central nervous system is subclassified according to the predominant tissue affected. Thus, there are references to meningovascular syphilis (meninges), tabes dorsalis (spinal cord), and general paresis (cerebral cortex).

• *Gumma:* A gumma is a characteristic lesion of tertiary syphilis, which may form in any organ or tissue. These granulomatous lesions are composed of a central area of coagulative necrosis, epithelioid histiocytes, occasional giant cells, and peripheral fibrous tissue. Gummas are most com-

monly found in the skin, bone, and joints, although lesions can occur at any body site. Gummas are usually localized lesions, which do not significantly damage the patient.

CONGENITAL SYPHILIS

Syphilis may be acquired in utero. The treponemes readily cross the placental barrier and infect the fetus, causing a high rate of spontaneous abortion and stillbirth. When T. pallidum is transmitted from an infected mother to the fetus, the organism disseminates in fetal tissues, which are injured by the proliferating organisms and accompanying inflammatory response. Fetal infection produces stillbirth, neonatal illness or death, or progressive postnatal disease.

Histopathologically, the lesions of congenital syphilis are identical to those of adult disease. Infected tissues show a chronic inflammatory infiltrate, composed of lymphocytes and plasma cells, and endarteritis obliterans. Virtually any tissue can be affected, but skin, bones, teeth, joints, liver, and central nervous systems are characteristically involved.

The clinical features of congenital syphilis are highly variable, and infected newborns are often completely asymptomatic. Within the first 2 years of life, symptoms are similar to severe adult secondary syphilis with widespread condylomata lata and rash. ―Snuffles‖ describes the mucopurulent rhinitis caused by involvement of the nasal mucosae. Later manifestations of congenital syphilis include bone and teeth deformities, such as ―saddle nose‖ (due to destruction of the nasal septum), ―saber shins‖ (due to inflammation and bowing of the tibia), ―Clutton‘s joints‖ (due to inflammation of the knee joints), ―Hutchinson‘s teeth‖ (in which the upper incisors are widely spaced and notched), and ―mulberry molars‖ (in which the molars have too many cusps). Tabes dorsalis and general paresis may develop as in adults, with 8th cranial nerve deafness and optic nerve atrophy as well as a variety of other ophthalmologic involvement leading to blindness being additional features.

DISEASES CAUSED BY FUNGI

Of the large number of known fungi, only a few are infective to human beings. Many of the human fungal infections are opportunistic i.e. they occur in conditions with impaired host immune mechanisms. Such conditions include defective neutrophil function, administration of corticosteroids, immunosuppressive therapy and immunodeficiency states (congenital and acquired).

CANDIDIASIS

Candidiasis is an opportunistic fungal infection caused most commonly by Candida albicans and occasionally by Candida tropicalis. In human beings, Candida species are present as normal flora of the skin and muco-

cutaneous areas, intestines and vagina. The organism becomes pathogenic when the balance between the host and the organism is disturbed. Various predisposing factors are: impaired immunity, prolonged use of oral contraceptives, long-term antibiotic therapy, corticosteroid therapy, diabetes mellitus, obesity, pregnancy etc.

Pathologic changes. Candida produces superficial infections of the skin and mucous membranes, or may invade deeper tissues as described under:

1. *Oral thrush*. This is the commonest form of muco-cutaneous candidiasis seen especially in early life. Full-fledged lesions consist of creamy white pseudo-membrane composed of fungi covering the tongue, soft palate, and buccal mucosa. In severe cases, ulceration may be seen.

2. *Candidal vaginitis*. Vaginal candidiasis or monilial vaginitis is characterised clinically by thick, yellow, curdy discharge. The lesions form pseudomembrane of fungi on the vaginal mucosa. They are quite pruritic and may extend to involve the vulva (vulvovaginitis) and the perineum.

3. *Cutaneous candidiasis.* Candidal involvement of nail folds producing change in the shape of nail plate (paronychia) and colonisation in the intertriginous areas of the skin, axilla, groin, infra- and intermammary, intergluteal folds and interdigital spaces are some of the common forms of cutaneous lesions caused by Candida albicans.

4. *Systemic candidiasis*. Invasive candidiasis is rare and is usually a terminal event of an underlying disorder associated with impaired immune system. The organisms gain entry into the body through an ulcerative lesion on the skin and mucosa or may be introduced by iatrogenic means such as via intravenous infusion, peritoneal dialysis or urinary catheterisation. The lesions of systemic candidiasis are most commonly encountered in kidneys as ascending pyelonephritis and in heart as candidal endocarditis.

SUPERFICIAL MYCOSIS

The superficial (cutaneous) mycoses are usually confined to the outer layers of skin, hair, and nails, and do not invade living tissues. The fungi are called dermatophytes. Dermatophytes, or more properly, keratinophilic fungi, produce extracellular enzymes (keratinases) which are capable of hydrolyzing keratin. Dermatophytes are the most important example of cutaneous mycosis caused by Microsporum, Trichophyton and Epidermophyton. These superficial fungi are spread by direct contact or by fomites and infect tissues. Examples of diseases pertaining to these tissues are as under:

- Tinea capitis characterized by patchy alopecia affecting the scalp and eye brows.
- Tinea barbae is acute folliculitis of the beard.
- Tinea corporis is dermatitis with formation of erythematous papules.

- Tinea cruris - "jock itch". Infection of the groin, perineum or perianal area.
- Tinea pedis - "athlete's foot". Infection of toe webs and soles of feet.
- Tinea versicolor - characterized by a blotchy discoloration of skin which may itch. Up to 25% of the general population may have this lesion at any one time. Tinea versicolor is caused by Malassezia furfur.

The diagnosis of dermatophytosis is made by light microscopic examination of skin scrapings after addition of sodium or potassium hydroxide solution. Other methods include fungal culture and demonstration of fungus in tissue sections.

Trichophyton species. These infect skin, hair and nails. They rarely cause subcutaneous infections, in immunocompromised individuals. Trichophyton species take 2 to 3 weeks to grow in culture. The conidia are large (macroconidia), smooth, thin-wall, septate (0-10 septa), and pencil-shaped; colonies are a loose aerial mycelium that grow in a variety of colors. Identification requires special biochemical and morphological techniques. It can rarely cause subcutaneous infections (kerion) in immunocompromized individuals, particularly patients with chronic myelogenous leukemia.

Microsporum species. These may infect skin and hair, rarely nails. The prevalence of infection has decreased significantly in recent years. When prevalent (15-20 years ago), this organism could be easily identified on the scalp because infected hairs fluoresce a bright green color when illuminated with a UV-emitting Wood's light. The loose, cottony mycelia produce macroconidia which are thick-walled, spindle-shaped, multicellular, and echinulate (spiny). Microsporum canis is one of the most common dermatophyte species infecting humans.

Epidermophyton floccosum. These infect skin and nails and rarely hair. They form yellow-colored, cottony cultures and are usually readily identified by the thick, bifurcated hyphae with multiple smooth, club-shaped macroconidia.

MYCETOMA

Mycetoma is a chronic suppurative infection involving a limb, shoulder or other tissues and is characterized by draining sinuses. The material discharged from the sinuses is in the form of grains consisting of colonies of fungi or bacteria. Mycetomas are of 2 main types:

• ***Mycetomas*** caused by actinomyces (higher bacteria) comprising about 60% of cases. This infection results in a granulomatous inflammatory response in the deep dermis and subcutaneous tissue, which can extend to the underlying bone. Mycetoma is characterized by the formation of grains containing aggregates of the causative organisms that may be discharged onto

the skin surface through multiple sinuses. The body parts affected most commonly in persons with mycetoma include the foot or lower leg, with infection of the dorsal aspect of the forefoot being typical. After several months of infection, the affected site, most commonly foot, is swollen and hence the name 'madura foot'. The lesions extend deeply into the subcutaneous tissues, along the fascia and eventually invade the bones. They drain through sinus tracts which discharge purulent material and grains. The surrounding tissue shows granulomatous reaction. The hand is the next most common location; however, mycetoma lesions can occur anywhere on the body. The causative organism enters through sites of local trauma. A neutrophilic response initially occurs, which may be followed by a granulomatous reaction. Spread occurs through skin facial planes and can involve the bone. Hematogenous or lymphatic spread is uncommon.

• ***Eumycetomas*** caused by true fungi comprising the remaining 40% of the cases. The disease is marked by progressive destruction of soft tissue and nearby anatomic structures. The foot is the most common site of infection, and 70% of all mycetomas affect the foot. Other reported sites of involvement include the upper extremities, trunk, buttocks, eyelids, lacrimal glands, paranasal sinuses, mandible, scalp, neck, perineum, and testes. The disease is initially limited to the skin and subcutaneous tissue but may eventually spread through the fascial planes to contiguous structures such as muscle, bone, blood and lymphatic vessels, and nerves. Rarely, the disease may spread to the regional lymph nodes or viscera.

Most common fungi causative for eumycetoma are Madurella mycetomatis or Madurella grisea, both causing black granules from discharging sinuses. Eumycetomas are particularly common in Northern and tropical Africa, Southern Asia and tropical America. The organisms are inoculated directly from soil into bare feet, from carrying of contaminated sacks on the shoulders, and into the hands from infected vegetation.

DISEASES CAUSED BY PARASITES

Diseases caused by parasites (protozoa and helminths) are quite common and comprise a very large group of infestations and infections in human beings. Parasites may cause disease due to their presence in the lumen of the intestine, due to infiltration into the blood stream, or due to their presence inside the cells.

AMOEBIASIS, BALANTIDIASIS

See above (Intestinal infections)

MALARIA

Malaria is a protozoal disease caused by any one or combination of four species of plasmodia: Plasmodium vivax, Plasmodium falciparum, Plasmodium

ovale and Plasmodium malariae. While Plasmodium falciparum causes malignant malaria, the other three species produce benign form of illness. These parasites are transmitted by bite of female Anopheles mosquito. The disease is endemic in several parts of the world, especially in tropical Africa, parts of South and Central America, India and South-East Asia.

P. falciparum differs from other forms of plasmodial species in 4 respects:

I) It does not have exo-erythrocytic stage,

II) Erythrocytes of any age are parasitised while other plasmodia parasitize juvenile red cells,

III) One red cell may contain more than one parasite,

IV) The parasitized red cells are sticky causing obstruction of small blood vessels by thrombi, a feature which is responsible for extraordinary virulence of P. falciparum.

The main clinical features of malaria are cyclic peaks of high fever accompanied by chills, anaemia and splenomegaly.

Pathologic changes. Parasitisation and destruction of erythrocytes are responsible for major pathologic changes as under:

1. Malarial pigment liberated by destroyed red cells accumulates in the phagocytic cells of the reticuloendothelial system resulting in enlargement of the spleen and liver (hepatosplenomegaly).

2. In falciparum malaria, there is massive absorption of haemoglobin by the renal tubules producing blackwater fever (haemoglobinuric nephrosis).

3. At autopsy, cerebral malaria is characterized by congestion and petechiae on the white matter.

4. Parasitized erythrocytes in falciparum malaria are sticky and get attached to endothelial cells resulting in obstruction of capillaries of deep organs such as of the brain leading to hypoxia and death. If the patient lives, microhaemorrhages and microinfarcts may be seen in the brain.

Complications. Most complications are caused by *P.falciparum*. One of them is cerebral malaria, defined as coma, altered mental status, or multiple seizures with *P.falciparum* in the blood. The symptoms of cerebral malaria are similar to those of toxic encephalopathy. Other complications of *P.falciparum* infection include the following:

✓ *Seizures*. Secondary to either hypoglycemia or cerebral malaria.

✓ *Renal failure.* As many as 30% of nonimmune adults infected with *P.falciparum* suffer acute renal failure.

✓ *Hypoglycemia*.

✓ *Hemoglobinuria (blackwater fever).* It is the passage of dark urine, hemolysis, hemoglobinemia, and the subsequent hemoglobinuria and hemozoinuria cause this condition.

✓ *Noncardiogenic pulmonary edema.* This affliction is most common in pregnant women and results in death in 80% of patients.

✓ *Hemolysis resulting in severe anemia and jaundice.*

✓ *Bleeding (coagulopathy).*

The diagnosis of malaria is made by demonstration of malarial parasite in thin or thick blood films or sometimes in histologic sections.

FILARIASIS

Filariasis is a disease group affecting humans and animals, caused by filariae. Filarial parasites can be classified according to the habitat of the adult worms in the vertebral host, as follows:

➢ Cutaneous group – includes *Loa loa, Onchocerca volvulus,* and *Mansonella streptocerca*,

➢ Lymphatic group – includes *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori,*

➢ Body-cavity group – includes *Mansonella perstans* and *Mansonella ozzardi.*

Filariae have a specific geographic distribution. For example, *W.bancrofti* is found in sub-Saharan Africa, Southeast Asia, India, and the Pacific Islands. *B.malayi* is found in similar locations but not in sub-Saharan Africa. *B.timori* occurs on Timor Island, in Indonesia.

Filarial infection generates significant inflammatory immune responses that participate in the development of symptomatic lymphatic obstruction. The lymphatic vessels inhabit the adult worm, especially in the lymph nodes, testis and epididymis. Microfilariae seen in the circulation are produced by the female worm. Majority of infected patients remain asymptomatic. Symptomatic cases may have two forms of disease an acute form and a chronic form.

• Acute form of filariasis presents with fever, lymphangitis, lymphadenitis, epididymo-orchitis, urticaria, eosinophilia and microfilariaemia.

• Chronic form of filariasis is characterized by lymphadenopathy, lymphoedema, hydrocele and elephantiasis.

The most commonly affected nodes are in the femoral and epitrochlear regions. Abscess formation may occur at the nodes or anywhere along the distal vessel. Cellular invasion with plasma cells, eosinophils, and macrophages, together with hyperplasia of the lymphatic endothelium, occurs with repeated inflammatory episodes. The consequence is lymphatic damage and chronic leak-

age of protein-rich lymph in the tissues, thickening and verrucous changes of the skin, and chronic streptococcal and fungal infections, which all contribute to the appearance of elephantiasis. (The skin of individuals with elephantiasis is characterized by hyperkeratosis, acanthosis, lymph and fatty tissue, loss of elastin fibers, and fibrosis.) Chylous ascites and chyluria may occur due to rupture of the abdominal lymphatics.

CYSTICERCOSIS

Cysticercosis is infection by the larval stage of Taenia solium, the pork tape-worm. The adult tape-worm resides in the human intestines. The eggs are passed in human faeces which are ingested by pigs or they infect vegetables. These eggs then develop into larval stages in the host, spread by blood to any site in the body and form cystic larvae termed cysticercus cellulosae. Human beings may acquire infection by the larval stage by eating undercooked pork ('measly pork'), by ingesting uncooked contaminated vegetables, and sometimes, by autoinfection.

Pathologic changes. The cysticercus may be single or there may be multiple cysticerci in the different tissues of the body. The cysts may occur virtually anywhere in body and accordingly produce symptoms; most common sites are brain, skeletal muscle and skin. The cysticercus consists of a round to oval white cyst, about 1 cm in diameter, contains milky fluid and invaginated scolex with birefringent booklets. The cysticercus may remain viable for a long time and incite no inflammation. But when the embryo dies, it produces granulomatous reaction with eosinophils. Later, the lesion may become scarred and calcified.

OTHER INFECTIONS

TORCH COMPLEX

The original TORCH complex described similar congenital infections caused by Toxoplasma gondii, Rubella virus, Cytomegalovirus, and Herpes simplex virus. The letter «O» in TORCH refers to «other» organisms that cause perinatal infections such as Parvovirus B19, Varicella Zoster Virus, Syphilis, and HIV.

TORCH infections are caused significant morbidity and mortality in neonates. It has been estimated that TORCH complex infections have an overall incidence of 1-5% of all live born children. These infections are acquired by the mother and passed either transplacentally or during the birth process.

Common clinical manifestations that are suggestive of specific congenital infections in the neonate are listed in a table 7.

Table 7. Clinical Features Associated with TORCH Infections

Infection	Clinical Features
Toxoplasmosis	• Intracranial calcifications in a diffuse pattern • Hydrocephalus • Chorioretinitis • Mononuclear CSF pleocytosis or elevated CSF protein
Rubella	• Cataracts, glaucoma, pigmented retinopathy • Congenital heart disease (patent ductus arteriosus and peripheral pulmonary artery stenosis) • Radiolucent bone disease • Sensorineural hearing loss
Cytomegalovirus (CMV)	• Periventricular intracranial calcifications • Microcephaly • Thrombocytopenia
Herpes Simplex Virus (HSV)	• Mucocutaneous vesicles or scarring • CSFpleocytosis • Thrombocytopenia • Elevated liver transaminases • Conjunctivitis or keratoconjunctivitis
Syphilis	• Skeletal abnormalities such as osteochondritis and peri- ostitis • Pseudoparalysis • Persistent rhinitis • Maculopapular rash (most notably on palms and soles or in diaper area)

Since the symptoms produced by TORCH group of organisms are indistinguishable from each other, it is a common practice in a suspected pregnant mother or infant to test for all the four main TORCH agents. The fetal damage caused by TORCH complex infection is irreparable and, therefore, prevention is the best mode of therapy.

CAT SCRATCH DISEASE

Cat Scratch disease (CSD), also known as cat scratch fever or subacute regional lymphadenitis, is a bacterial infection affecting lymph nodes that drain the sites of inoculation. *Bartonella henselae,* a gram-negative rod, is considered the principal etiologic agent. B. henselae is organism linked to rickettsiae but unlike rickettsiae this organism can be grown in culture.

The condition occurs more commonly in children (under 18 years of age). Patients with CSD usually have a history of sustaining a scratch or bite from a cat. The initial symptom is formation of a papule at the inoculation site, followed by solitary or regional lymphadenopathy within 1-2 weeks. In most patients, the disease resolves spontaneously within 2-4 months. A small percentage of immunocompetent patients develop severe systemic disease or

other atypical manifestations. These may include oculoglandular syndrome, encephalitis, neuroretinitis, pneumonia, osteomyelitis, erythema nodosum, arthralgia, arthritis, and thrombocytopenic purpura.

Lymph nodes. In general, lymph nodes become enlarged in the 1-2 weeks after exposure. They are often tender and occasionally become fluctuant. Lymphoid hyperplasia with arteriolar proliferation and reticular cell hyperplasia is seen early in the disease. As the disease progresses, granulomas appear, with central necrosis surrounded by lymphocytes. Histiocytes and multinucleated giant cells are often present. Finally, stellate microabscesses form, and nodes can become fluctuant.

Central nervous system. Encephalopathy is the most common neurologic manifestation, occurring in 2-3% of patients. The onset is usually abrupt and occurs 1-6 weeks after the lymphadenopathy becomes apparent. Patients can become confused and disoriented, and their condition can deteriorate to coma. About 50% of patients have a fever. Focal findings of hemiparesis and reflex abnormalities may be noted. Seizures, which occur in as many as 80% of patients with neurologic sequelae, are often prolonged and recurrent.

Neuroretinitis. Patients with neuroretinitis generally present with painless, unilateral visual loss. Examination reveals decreased visual acuity, decreased color vision, and centrocecal scotoma. The optic disc appears edematous, and exudates frequently surround the macula. Neuroretinitis is possibly due to a subretinal angiomatous nodule similar to that seen in bacillary angiomatosis.

Pulmonary. Six cases of CSD with pneumonia and 8 cases with pleural thickening and/or effusion have been reported. In these cases, pulmonary features developed 1-5 weeks after lymphadenopathy occurred. Systemic signs of infection, including fever, were present in 85%. One case in which a massive abscess involved the chest wall has been reported.

Histopathologic findings of the lymph nodes depend on the stage of infection. Lymphoid hyperplasia with arteriolar proliferation, reticulum cell hyperplasia, and widening of arteriolar walls are seen early in the disease. Progression of the disease is manifested by granulomas. The centers of these granulomas are acellular and necrotic with surrounding histiocytes and lymphocytes. Microabscesses may develop as the granulomas and areas of necrosis coalesce. The organism is extracellular and can be identified by silver stains.

The prognosis for immunocompetent patients with CSD is excellent. Complete recovery without sequelae occurs in nearly all patients. Significant morbidity occurs in 5-10% of cases, usually because of involvement of the central or peripheral nervous system or because of multisystem disseminated disease. Even in patients with CNS involvement, however, recovery without neuro-

logic sequelae within weeks to months can be expected. Death caused by CSD in patients who are immunocompetent is extremely rare.

SEPSIS

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, and killing as many as one in four (and often more). Similar to polytrauma, acute myocardial infarction, or stroke, early identification and appropriate management in the initial hours after sepsis develops improves outcomes.

Sepsis is now defined as a ‗life-threatening organ dysfunction due to a dysregulated host response to infection'. In this new definition the concept of the non-homeostatic host response to infection is strongly stressed while the SIRS criteria have been removed. The SIRS criteria are considered overly non-specific and of poor clinical utility: i.e. they may be present in simple, non-complicated infection, or in response to non infectious-triggers (i.e. trauma, pancreatitis, post-cardiac arrest syndrome), or may even be absent in critically ill patients with obvious evidence of a life-threatening infection. While recognition and treatment of the infectious trigger obviously remain important, the attention with sepsis is now more focused on the pathobiology of the host response and the related organ dysfunction. The inflammatory response accompanying infection (pyrexia, neutrophilia, etc.) often represent an appropriate host response to any infection, and this may not necessarily be life-threatening.

The key element of sepsis-induced organ dysfunction is defined by ‗an acute change in total SOFA score ≥ 2 points consequent to infection, reflecting an overall mortality rate of approximately 10%'. The baseline Sepsis-related Organ Failure Assessment (SOFA) score may be taken as zero unless the patient is known to have previous comorbidity (e.g. head injury, chronic kidney disease, etc.). In light of this, the current definition of 'severe sepsis' becomes obsolete, as does the term.

The Sepsis-related Organ Failure Assessment (SOFA) score is widely used in the critical care setting and is a reliable tool to clinical characterise septic patients, but it requires some laboratory investigations and may be less useful for a quick screening patients in settings outside of the ICU. A simple bedside score (‗qSOFA', for quick SOFA) has been proposed, which incorporates hypotension (systolic blood pressure ≤100mmHg), altered mental status and tachypnea (respiratory rate > 22/min): the presence of at least two of these criteria strongly predicts the likelihood of poor outcome in out-of-ICU patients with clinical suspicion of sepsis.

Septic shock is now defined as a ‗subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially

increase mortality‘. Clinical criteria identifying such condition include the need for vasopressors to obtain a MAP≥ 65mmHg and an increase in lactate concentration > 2 mmol/L, despite adequate fluid resuscitation. This new definition is mainly focused on the importance to both distinguish septic shock from other forms of circulatory shock and underline the detrimental clinical impact of sepsis-induced cellular metabolism abnormalities.

Given the urgent need to widely spread education campaigns and better inform the public about the clinical and economic implications of such condition, a lay definition of sepsis as ‗a life-threatening condition that arises when the body‘s response to infection injures its own tissue‘ has been also endorsed. Finally, all these new definitions are recommended for coding and research purposes.

Despite the unavoidable limits affecting any definition of syndromes that do not have any specific diagnostic clinical, imaging, laboratory or biochemical marker, this new classification includes the most recent deep understanding of sepsis biology and stresses the clinical relevance of organ dysfunction. In addition, similarly to software updates, the Sepsis-3 definition has been established with the aim of fostering future updates.

Pathomorphological characteristics are based on 3 factors:

1. Etiology;
2. Entrance gate;
3. Clinico-morphological appearances.

According to entrance gate there are therapeutic (parainfectious), tonsillogenic, surgical, uterine, otogenic, odontogenic, umbilical, cryptogenic forms of sepsis.

Morhologicaly, sepsis can be in the form of septicaemia, seticopyemia, septic endocarditis.

Septicaemia means presence of rapidly multiplying, highly pathogenic bacteria in the blood e.g. pyogenic cocci (more frequently streptococci), bacilli of plague etc. It is generally accompanied by systemic effects like toxaemia, multiple small haemorrhages, neutrophilic leucocytosis and disseminated intravascular coagulation (DIC). Main features of septicemia are: 1) rapid course, severe toxicosis; 2) absence of purulent focus (or it is very small), purulent metastasis; 3) is accompanied with severe hyperergic reaction; 4) more frequently it results from streptococci infection.

Pathological anatomy:

1. Absence of purulent focus;
2. Hemolytic jaundice, skin and sclera are yellowish with hemorrhagic rush (hemorrhagic syndrome);
3. Hyperplasia of red bone marrow (changes in myelogramma), lymphatic nodes and spleen (―septic spleen‖);

4. Interstitial inflammation in parenchymatous organs (liver, kidney, heart);

5. Allergic vasculitis.

Septicopyemia is characterized:

1. Purulent processes in infectious gate and in different organs and tissues (metastatic foci of inflammation);

2. Hyperergic reaction is moderate, and due to this there is no rapid course;

3. Is caused by staphylococci and haemophilus influenzae;

4. Intoxication is week more frequently;

5. Results in chronic sepsis.

Pathological anatomy:

1. The dissemination of small septic thrombi in the blood which cause their effects at the site where they are lodged. This can result in pyaemic abscesses or septic infarcts.

3. Hyperplastic processes are more week as in septicaemya. In red bone marrow there is no leukemoid reaction (in myelogramma). May be ―septic spleen‖, but lymphatic nodes may be normal.

4. Interstitial inflammation in parenchymatous organs (liver, kidney, heart) is moderate or week;

5. Allergic vasculitis.

It is characterized by presence of purulent focus with changes in lymph vessels (lymphangitis), lymph nodes (lymphadenitis), changes in blood vessels (purulent trombophlebitis).

In case of systemic circulation in veins first metastatic purulent foci appear in pulmonary veins, then in organs: liver, kidney, skin fat tissue, bone marrow, synovial coats and heart valves (acute septic polipous- ulcerative endocarditis.

Septic endocarditis is characterized by septic damage of the valvular and mural endocardium (heart valves) with typical infected and friable vegetations. It appears more frequently in males. It may be caused by different forms of bacteria (Streptococci, Staphylococci, Enterococci).

Acute bacterial endocarditis (ABE) is the fulminant and destructive acute infection of the endocardium by highly virulent bacteria in a previously normal heart and almost invariably runs a rapidly fatal course in a period of 2-6 weeks.

Subacute bacterial endocarditis (SABE) or endocarditis lenta (lenta = slow) is caused by less virulent bacteria in a previously diseased heart and has a gradual downhill course in a period of 6 weeks to a few months and sometimes years.

Predisposing factors of both forms of bacterial endocarditis development are:

1. Conditions initiating transient bacteraemia, septicemia and pyaemia;
2. Underlying heart disease; and
3. Impaired host defenses.

Pathologic changes are characterized by presence of typical vegetations or verrucae on the valve cusps or leaflets, and less often, on mural endocardium.

Macroscopically, the lesions are found commonly on the valves of the left heart, most frequently on the mitral, followed in descending frequency, by the aortic, simultaneous involvement of both mitral and aortic valves, and quite rarely on the valves of the right heart. The vegetations of bacterial endocarditis vary in size from a few millimeters to several centimeters, grey-tawny to greenish, irregular, single or multiple, and typically friable. They may appear flat, filiform, fungating or polypoid. The vegetations in ABE tend to be bulkier and globular than those of SABE and are located more often on previously normal valves, may cause ulceration or perforation of the underlying valve leaflet, or may produce myocardial abscesses.

Microscopically, the vegetations of bacterial endocarditis consist of 3 zones:

1. The outer layer or cap consists of eosinophilic material composed of fibrin and platelets,
2. Underneath this layer is the basophilic zone containing colonies of bacteria. However, bacterial component of the vegetations may be lacking in treated cases.
3. The deeper zone consists of non-specific inflammatory reaction in the cusp itself, and in the case of SABE there may be evidence of repair.

Its peripheral signs are:

1. Test of Konchalovsky (appearance of petechia in the places of skin compression).
2. Petechiae in the inferior eyelid conjunctive of medial angle.
3. Osler`s nodules (features of septic vasculitis) – painful nodules on the manus palmar surfaces.
4. Thickness of the falanges – due to vegetation of periosteum.
5. Hemorrhages in the skin (spots of Jenuay).
6. Jaundice (hemolytic).
7. Very often thromboembolic complications (sometimes thromboembolic syndrome).

Complications of BE:

Cardiac complications.

i) Valvular stenosis or insufficiency,

ii) Perforation, rupture and aneurysm of valve leaflets,

iii) Abscesses in the valve ring,

iv) Myocardial abscesses,

v) Suppurative pericarditis,

vi) Cardiac failure from one or more of the foregoing complications.

Extra-cardiac complications:

i) Emboli originating from the left side of the heart and entering the systemic circulation affect organs like the spleen, kidneys and brain causing infarcts, abscesses and mycotic aneurysms.

ii) Emboli arising from right heart enter the pulmonary circulation and produce pulmonary abscesses.

iii) Petechiae may be seen in the skin and conjunctiva due to either emboli or toxic damage to the capillaries.

iv) Painful, tender nodules on the finger tips of hands and feet called Osler's nodes, while in ABE there is appearance of painless, non-tender sub-cutaneous maculopapular lesions on the pulp of the fingers called Janeway's spots. In either case, their origin is due to toxic or allergic inflammation of the vessel wall.

v) Focal necrotising glomerulonephritis is seen more commonly in SABE than in ABE. Occasionally diffuse glomerulonephritis may occur. Both these have their pathogenesis in circulating immune complexes (hyper-sensitivity phenomenon).

PATHOMORPHOSIS

A man in the era of scientific and technical revolution is exposed by powerful, long, various influences of aggressive factors of the environment, that affect on the integration systems of maintenance of the homeostasis, interrelation of the human body with microorganisms and medical products. There are previously unknown features of the course of various diseases, new diseases, new syndromes, thus the phenomena of pathomorphosis develops.

Pathomorphosis (from Greek pathos - suffering, disease and morphe - kind, shape) - essential and steady changes of character of the disease, causes of death and properties of various diseases under the influence of various factors.

The term "pathomorphosis" has been used for the first time in the 30 years of the twentieth century in the foreign literature as the amendment to the presentation accepted in the pathology about stability of nosological forms. W. Hellpach meant first of all changes of clinical and morphological forms of syphilis under the influence of active chemotherapy.

In 1956 W. Doerr specified such forms of pathomorphosis, as natural pathomorphosis (spontaneous changes in the course of the disease arising from changes of external and internal causes of the disease) and induced or therapeutic pathomorphosis (changes in the disease caused by therapeutic effects).

In literature the term "pathomorphosis" was introduced by Ya.L. Rapoport only in 1962. Professor Ya.L. Rapoport singled out one important feature - induced pathomorphosis was not fixed genetically, therefore are possible the reversal of the disease, returning to its classical forms and manifestations after removal of the therapeutic factor.

V.V. Serov gave the following definition of pathomorphosis: ‖Pathomorphosis is nosomorphosis as in wide ("panorama" of diseases) and narrow (some disease) sense‖.

At the present stage scientists identify two forms of pathomorphosis: spontaneous (idiopathic, natural) and induced (therapeutic). Spontaneous pathomorphosis are transformations in the course of nosological forms which are caused by changes of external causes of disease, influence of factors of environment (ecology), action of the internal causes (the constitution, features of the reactivity of the organism), changes of properties of the pathogenic organism. Manifestations of induced pathomorphosis arise in relatively short periods of time under the influence of treatment by new drugs, radiation therapy and other.

IATROGENIC REACTIONS AND DISEASES

From the Greek words ―iatros‖ meaning "medical" and ―genea‖ meaning "origin", ―iatrogenic‖ means the occurrence of negative effects caused by a medical procedure. According to The ICD-10, iatrogenic diseases are any undesirable or adverse effects of preventive, diagnostic, therapeutic interventions or

procedures which lead to the infringement of functions of the body, limiting of usual activity, disablement or even death; complications of medical interventions which may arise as a result of false and correct actions of doctors.

It is frequently thought that iatrogenic means "error" or "neglect", but iatrogenic effects and medical errors are opposite terms, not synonymous ones. An error is a mistake or the result of ignorance and, thus, opposes the concept of medical attitude, whereas an iatrogenic effect is the consequence of an accurate action based on a correct orders, indication and adequate criteria and can be predicted by the physician. When, in trying to heal, relieve or treat a patient, the physician (like any other health care worker) generates psychological, functional or organic illness that takes the from of pain, disease or disturbance, he is being iatrogenic. The diagnosis may be difficult, delayed or initially missed as iatrogenic illness can be generated directly from the doctor-patient relationship or by means of agents used in the diagnostic search, or as a consequence of a therapeutic, instrumental (technical) or drug-related measure.

Iatrogenic disease is a serious problem with a great social impact. The world literature shows that the incidence of iatrogenic events in the hospitalized population varies widely, ranging from 6 to 65%. It occurs very frequently, is expensive and is potentially responsible for high morbidity and mortality. In the U.S., it is estimated that iatrogenic causes are responsible for 225,000 deaths each year, thus being the third leading cause of death after heart disease and cancer.

Causes of iatrogenesis include:

1. Side effects of possible drug interactions,
2. Complications arising from a procedure or treatment,
3. Medical error,
4. Negligence,
5. Unexamined instrument design,
6. Anxiety or annoyance in the physician or treatment provider in relation to medical procedures or treatments,
7. Unnecessary treatment for profit.

Professionals who may cause harm to patients include physicians, pharmacists, nurses, dentists, psychologists, psychiatrists, medical laboratory scientists and therapists. Iatrogenesis can also result from complementary and alternative medicine treatments.

Among the causes of iatrogenic diseases objective and subjective factors are distinguished. The objective factors are the imperfection of medicine, the incurability of some pathology, the necessity of the realization of invasive procedures for confirmation or refutation of the diagnosis. The subjective factors of the beginning of iatrogenic diseases are connected with the individual qualities of the medical worker (the insufficiency of professional

skills, the inability to collect correctly the information about the disease of the patient, disinterest in the estimation of the condition of the patient).

Iatrogenic reactions and diseases are divided into 4 groups:

1. Connected with diagnostic procedures: instrumental damage of organs by endoscopes and other diagnostic appliances, radiation damage of a patient during X- ray and radiological examination, allergic and toxic reactions to contrast substances.

2. Connected with therapeutic actions: drug disease due to drug intoxication; allergic reactions to drugs; radiation damage during radiation therapy; puncture, injection, infusion damages of organs and tissues; operational stress and mechanical damage of organs.

3. Connected with preventive measures: reaction to vaccination; infectious and inflammatory damages due to injections.

4. Information: reaction to words of medical workers; effects of modern literature, medical books, articles; self-treatment under the influence of newspapers, appeals to witch doctors.

The risk factors for the occurrence of iatrogenesis during hospitalization are: age, number of comorbidities, complexity of the diseases, use of multiple drugs, length of hospital stay, severity of illness at admission and functional status.

Patients 65 years and older suffer twice as many diagnostic complications, two and one half times as many medication reactions, four times as many therapeutic mishaps, and nine times as many falls as those younger patients. Age-related factors that predispose the older patient to iatrogenesis include:

1. Diminished physiologic reserve.
2. Impaired compensatory mechanisms.
3. Atypical presentation of illness, which complicates accurate diagnosis and treatment.
4. More co-morbid, chronic medical conditions that require more diagnostic procedures and medications.
5. Polypharmacy - The prescription, administration or use of more medications than clinically indicated.
6. Increased cognitive and functional impairment.
7. Other risk factors for iatrogenic complications include:

a. Increased severity of illness and complexity of care,
b. Greater numbers of prescribed medications,
c. Admission from nursing home or other acute care facility,
d. Longer length or stay,
e. Lack of attention to functional impairment by physicians upon admission.

The role of the pathologist in the investigation of dead bodies is central to the identifying and monitoring of iatrogenic pathology.

REFERENS:

1. Pathology / Eds. E. Rubin, J.L. Farber - Philadelphia: Lippincott-Raven Publ., 1998.
2. Pathology Illustrated / Govan A.D.T., Macflane P.S., Callander R. - Edinburgh: Churchill Livingstone, 1995.
3. Robbins & Cotran Pathologic Basis of Disease (Robbins Pathology) 9th Edition. 2014.- 1408p.
4. Rosai J: Ackerman`s Surgical Pathology (2 vols), 11th ed. Elsevier 2018.
5. Textbook of Pathology / H. Mochan - India, New Dehi: Jaypee Brothers, Med. Publ., 2005.
6. Wheater's Basic Histopathology. A Colour Atlas and Text / Burkitt H.G., Stevens A.J.S.L., Young B. - Edinburgh: Churchill Livingstone, 1996.

CONTENTS

Учебное издание

Самсонова Инна Васильевна, **Клопова** Виктория Александровна

ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ
КУРС ЛЕКЦИЙ. ЧАСТЬ 2. ЧАСТНАЯ ПАТОЛОГИЯ

PATHOLOGICAL ANATOMY
LECUTURE COURSE. PART II. SYSTEMIC PATHOLOGY

учебно-методическое пособие на английском языке

Редактор И.В.Самсонова
Компьютерная верстка И.В.Самсонова

Подписано в печать 1.06.2020. Формат бумаги 64x84 1/16.
Бумага типографская № 2. Гарнитура Times New Roman.
Усл. печ. листов 28,66. Уч. изд. л. 30,81.
Тираж 500. Заказ № 364.

Издатель и полиграфическое исполнение
УО «Витебский государственный медицинский университет»
ЛП №02330/453 от 30.12.2013 г.
пр. Фрунзе, 27, 210023, Витебск