CHAPTER THREE
HEMATOPATHOLOGY
DR Haytham, Dr Saad, Dr Jaffar

RED CELL DISORDERS
WHITE CELL DISORDERS
BLEEDING DISORDERS
TRANSFUSION MEDICINE

RED CELL DISORDERS
Disorders of red cells can result in either anemia or polycythemia (an increase in the number of red cells).

Anemia is a reduction in the oxygen-carrying capacity of blood, which usually stems from a reduction of the total circulating red cell mass to below-normal amounts.

Classification of anemia
a. etiologic classification
   1. Excessive bleeding
   2. Increased red cell destruction, or
   3. Decreased red cell production.

These mechanisms serve as a basis for classifying anemias. The decrease in tissue oxygen tension that is associated with anemia usually triggers increased erythropoietin production (the exception is that of anemia related to chronic renal failure, in which erythropoietin-producing cells in the kidney are lost). Increased erythropoietin production leads to compensatory hyperplasia of erythroid precursors in the bone marrow and, in severe anemias, the appearance of extramedullary hematopoiesis within the secondary hematopoietic organs (the spleen, liver, and lymph nodes).

Anemia that results from acute bleeding or increased red cell destruction (hemolysis) leads to compensatory regeneration of red cells 5-8 times normal. The hallmark of increased marrow output is reticulocytosis, the appearance of increased numbers of newly formed red cells (reticulocytes) in the peripheral blood. In contrast, disorders of decreased red cell production (regenerative anemias) are characterized by reticulocytopenia.

b. Morphologic classification, which is based on the morphology of red cells; this is often correlates with the cause of their deficiency. Specific red cell features that provide etiologic clues include the
   1. Cell size (normocytic, microcytic, or macrocytic)
   2. Degree of hemoglobinization, which is reflected in the color of the cells (normochromic or hypochromic)
   3. Shape of the cells

These features are judged subjectively by visual inspection of peripheral smears (blood film) and are also expressed quantitatively through the following indices:

Mean cell volume (MCV): the average volume per red cell, expressed in femtoliters (cubic microns)
Mean cell hemoglobin (MCH): the average content (mass) of hemoglobin per red cell, expressed in picograms
Mean cell hemoglobin concentration (MCHC): the average concentration of hemoglobin in a given volume of packed red cells, expressed in grams per deciliter

Red cell distribution width (RDW): the coefficient of variation of red cell volume.

In modern clinical laboratories, specialized instruments directly measure or automatically calculate the red cell indices. Adult reference ranges are shown in (Fig. 3-1)

The clinical consequences of anemia
These are determined by
1. The severity of the anemia
2. Its speed of onset, and
3. Underlying pathogenic mechanism.

• If the onset is slow, adaptations take place that partially compensate for the deficit in O₂ carrying capacity, such as increases in plasma volume, increased cardiac output, increased respiratory rate (manifested as shortness of breath), and red cell 2,3-diphosphoglycerate levels. These changes can largely reduces the effects...
of mild to moderate anemia in otherwise healthy individuals, but are less effective in those with impaired pulmonary or cardiac function.

- **Pallor, fatigue, and exhaustion** are common to all anemias, and are the primary presenting symptoms of the most common types, such as that caused by iron deficiency.

- Additional features depend on the mechanism of anemia evolution for e.g.
  - Anemias caused by the premature destruction of red cells in the peripheral blood (hemolytic anemias) are associated with hyperbilirubinemia, jaundice, and pigment gallstones.
  - Anemias of ineffective hematopoiensis (the premature death of erythroid progenitors in the marrow) are associated with inappropriately high levels of iron absorption from the gut, which can lead to iron overload (secondary hemochromatosis) and eventual damage to endocrine organs and the heart.
  - If left untreated, severe congenital anemias, such as β-thalassemia major, inevitably result in growth retardation, skeletal abnormalities, and cachexia.

**ANEMIA OF BLOOD LOSS: HEMORRHAGE**

**Acute blood loss**
The immediate threat to the patient is hypovolemia (shock) rather than anemia. If the patient survives, hemodilution begins at once and achieves its full effect within 2 to 3 days, unmasking the extent of the red cell loss. The anemia is normocytic and normochromic. Recovery from blood loss anemia is enhanced by a rise in the erythropoietin level, which stimulates increased red cell production within several days. The onset of the marrow response is marked by reticulocytosis.

**Chronic blood loss**
The iron stores are gradually depleted. Iron is essential for hemoglobin synthesis and effective erythropoiesis, and its deficiency thus leads to a chronic anemia of underproduction.

**THE HEMOLYTIC ANEMIAS**

Normal red cells have a life span of about 120 days. Anemias that are associated with accelerated destruction of red cells are termed hemolytic anemias. Destruction can be caused by

1. **Inherent (intracorporscular) red cell defects**, which are usually inherited, or
2. **External (extracorporscular) factors**, which are usually acquired.

There are certain general features of hemolytic anemias. All are characterized by

1. an increased rate of red cell destruction
2. a compensatory increase in erythropoiesis that results in reticulocytosis, and
3. the retention by the body of the products of red cell destruction (including iron). Because the iron is conserved and recycled readily, red cell regeneration can keep pace with the hemolysis. Consequently, these anemias are almost invariably associated with a marked erythroid hyperplasia within the marrow and an increased reticulocyte count in peripheral blood. In severe hemolytic anemias, extramedullary hematopoiensis often develops in the spleen, liver, and lymph nodes.

Destruction of red cells can occur within the vascular compartment (intravascular hemolysis) or within the cells of the mononuclear phagocyte (reticuloendothelial) system (extravascular hemolysis).

**Intravascular hemolysis** can result from mechanical trauma (e.g., a defective heart valve) or biochemical or physical agents that damage the red cell membrane (e.g., fixation of complement, exposure to clostridial toxins, or heat). Regardless of cause, hemolysis leads to hemoglobinemia, hemoglobinuria, and hemosiderinuria. The conversion of the heme pigment to bilirubin can result in unconjugated hyperbilirubinemia and jaundice. Massive intravascular hemolysis sometimes leads to renal acute tubular necrosis. Haptoglobin, a circulating protein that binds and clears free hemoglobin, is often absent from the plasma.

**Extravascular hemolysis**, the more common mode of red cell destruction, takes place largely within the phagocytic cells of the spleen and liver. The mononuclear phagocyte system removes damaged or immunologically targeted red cells from the circulation. Because extreme alterations of shape are necessary for
red cells to successfully navigate the splenic sinusoids, any reduction in red cell deformability makes this passage difficult and leads to splenic sequestration, followed by phagocytosis. As will be described, diminished deformability is an important cause of red cell destruction in a variety of hemolytic anemias. Extravascular hemolysis is not associated with hemoglobinemia and hemoglobinuria, but it often produces jaundice and, if long-standing, can lead to the formation of bilirubin-rich gallstones (so-called pigment stones). Haptoglobin amounts are always decreased, because some hemoglobin invariably escapes into the plasma. In most forms of hemolytic anemia there is a reactive hyperplasia of the mononuclear phagocyte system, which results in splenomegaly.

In chronic hemolytic anemias, changes in iron metabolism lead to increases in iron absorption from the gut. Because the pathways for the excretion of excess iron are limited, this often causes iron to accumulate, giving rise to systemic hemosiderosis or, in very severe cases, secondary hemochromatosis.

Common examples of hemolytic anemias

1. Hereditary Spherocytosis (HS) is characterized by an inherited (intrinsic) defect in the red cell membrane that renders the cells spheroidal, less deformable, and vulnerable to splenic sequestration and destruction. It is transmitted most commonly as an autosomal dominant trait; approximately 25% of patients have a more severe autosomal recessive form of the disease.

Pathogenesis

- The primary abnormality resides in one of a group of proteins that form a meshlike supportive skeleton on the intracellular face of the red cell membrane (Fig. 3-2). The major protein in this skeleton is spectrin, a long, flexible structure that is linked to the membrane. The horizontal spectrin-spectrin and vertical spectrin-intrinsic membrane protein interactions serve to stabilize the membrane and are responsible for the normal shape, strength, and flexibility of the red cell.
- The spleen plays a major role in the destruction of spherocytes. Red cells must undergo extreme degrees of deformation to leave the cords of Billroth and enter the splenic sinusoids. The discoid shape of normal red cells allows considerable freedom for changes in cell shape. In contrast, because of their spheroidal shape and limited deformability, spherocytes are sequestered in the splenic cords and eventually destroyed by macrophages, which are plentiful.
- The critical role of the spleen is illustrated by the invariably beneficial effect of splenectomy; although the red cell defect and spherocytes persist, the anemia is corrected.

Pathological features

- On smears, the red cells lack the central zone of pallor because of their spheroidal shape (Fig. 3-3).
- Spherocytosis, though distinctive, is not diagnostic; it is seen in other conditions, such as immune hemolytic anemias, in which there is a loss of cell membrane relative to cell volume.
- Because of their spheroidal shape, HS red cells show increased osmotic fragility when placed in hypotonic salt solutions, a characteristic that is helpful for diagnosis.
- The excessive red cell destruction and resultant anemia lead to a compensatory hyperplasia of marrow red cell progenitors and an increase in red cell production, which is marked by peripheral blood reticulocytosis.
- Splenomegaly is greater and more common in HS than in any other form of hemolytic anemia. The splenic weight is usually between 500 and 1000 gm and can be even greater. The enlargement results from marked congestion of the cords of Billroth and increased numbers of mononuclear phagocytes. Phagocytosed red cells are frequently seen within macrophages lining the sinusoids and, in particular, within the cords.
- In long-standing cases there is prominent systemic hemosiderosis. The other general features of hemolytic anemias described earlier are also present, pigmented gall stone, which occurs in up to 50% of HS patients.

Clinical Course

The characteristic clinical features are anemia, splenomegaly, and jaundice. The severity of the anemia is highly variable; most commonly it is of moderate degree. The clinical course is often stable but may be punctuated by aplastic crises. Such episodes are often triggered by the infection of bone marrow erythroblasts by parvovirus B19, which causes a transient cessation of red cell production. Because HS red cells have a shortened life span, the failure of erythropoiesis for even a few days results in a rapid worsening of the anemia.
2. Sickle cell anemia

The hemoglobinopathies are “a group of hereditary disorders that are defined by the presence of structurally abnormal hemoglobins”. The prototypical (and most prevalent) hemoglobinopathy is caused by a mutation in the β-globin chain gene that creates sickle hemoglobin (HbS). The disease associated with HbS is sickle cell anemia. HbS, like 90% of other abnormal hemoglobins, results from a single amino acid substitution in the globin chain. On average, the normal adult red cell contains 96% HbA (α2β2), 3% HbA2 (α2δ2), and 1% fetal Hb (HbF, α2γ2). Substitution of valine for glutamic acid of the β-chain produces HbS. In homozygotes all HbA is replaced by HbS, whereas in heterozygotes only about half is replaced. In parts of Africa where malaria is endemic the gene frequency approaches 30%, as a result of a small but significant protective effect of HbS against Plasmodium falciparum malaria. Worldwide, sickle cell anemia is the most common form of familial hemolytic anemia.

Etiology and Pathogenesis

- Upon deoxygenation, HbS molecules undergo polymerization (gelation or crystallization). These polymers distort the red cell, which assumes an elongated crescentic, or sickle, shape (Fig. 3-4).
- Sickling of red cells is initially reversible upon reoxygenation; however, membrane damage occurs with each episode of sickling, and eventually the cells accumulate calcium, lose potassium and water, and become irreversibly sickled.

Many variables influence sickling of RBCs. The three most important ones are as follows:

1. The presence of hemoglobins other than HbS. In heterozygotes approximately 40% of Hb is HbS. The presence of HbA slows the rate of polymerization greatly, and as a result the red cells of heterozygotes have little tendency to sickle in vivo. Such individuals are said to have the sickle cell trait. HbC, another mutant β-globin, is fairly common. HbC has a greater tendency to aggregate with HbS than does HbA, and those with HbS and HbC (called HbSC disease) are symptomatic. Conversely, HbF interacts more weakly with HbS, and therefore newborns with sickle cell anemia do not manifest the disease until they are 5 to 6 months old, when the HbF falls to adult levels.

2. The concentration of HbS in the cell. RBCs dehydration, which increases the HbS concentration, greatly facilitates sickling and can trigger occlusion of small blood vessels. Conversely, the coexistence of α-thalassemia (described later) reduces the HbS concentration and therefore the severity of sickling. The relatively low concentration of HbS also contributes to the lack of sickling in heterozygotes with sickle cell trait.

3. Duration of low oxygen tension. Sickling is confined to microvascular beds where blood flow is sluggish. This is normally the case in the spleen and the bone marrow, which are prominently affected by sickle cell disease. In other vascular beds, it has been suggested that particularly important pathogenic roles are played by two factors: inflammation and increased red cell adhesion.

Consequences of sickling

Two major consequences of RBCs sickling (Fig. 3-5)

1. Repeated episodes of deoxygenation cause membrane damage and dehydration of red cells, which become rigid and irreversibly sickled. These dysfunctional red cells are recognized and removed by mononuclear phagocyte cells, producing a chronic extravascular hemolytic anemia. Overall, the mean life span of red cells in sickle cell anemia patients averages only 20 days (one-sixth of normal).

2. The sickling of red cells produces widespread microvascular obstructions, which result in ischemic tissue damage and pain crises. Such occlusions do not correlate with the number of irreversibly sickled cells and therefore appears to result from factors, such as infection, inflammation, dehydration, and acidosis that trigger the sickling of reversibly sickled cells.

Pathologic features

- The anatomic alterations in sickle cell anemia result from
  1. Severe chronic hemolytic anemia
  2. Increased breakdown of heme pigments, which are processed into bilirubin
3. Microvascular obstruction, which provokes tissue ischemia and infarction.

- In peripheral smears, bizarre elongated, spindled, or boat-shaped irreversibly sickled red cells are evident (Fig. 3-4).
- Both the anemia and the vascular stasis lead to fatty changes in the heart, liver, and renal tubules.
- There is a compensatory hyperplasia of erythroid progenitors in the marrow. The rapidly increasing marrow often causes bone resorption and secondary new bone formation, resulting in prominent cheekbones and changes in the skull resembling a "crew-cut" in roentgenograms.
- Extramedullary hematopoiesis can also appear in the spleen and liver.
- In children there is moderate splenomegaly (splenic weight as great as 500 gm) caused by congestion of the red pulp, which is stuffed with sickled red cells. However, the chronic splenic erythrostasis results in progressive hypoxic tissue damage, which eventually reduces the spleen to a functionally useless nubbin of fibrous tissue. This process, referred to as autosplenectomy, is complete by adulthood.
- Vascular congestion, thrombosis, and infarction can affect any organ, including bones, liver, kidney, retina, brain, lung, and skin. The bone marrow is particularly prone to ischemia, because of its relatively sluggish blood flow and high rate of metabolism. Priapism, another common problem, can lead to penile fibrosis and eventual erectile dysfunction.
- As with the other hemolytic anemias, hemosiderosis and gallstones are common.

Course

Homozygous sickle cell disease usually becomes apparent after the sixth month of life, since HbF is gradually replaced by HbS. There is severe anemia; most patients have hematocrit values of 18% to 30% (normal range, 35%-45%). The chronic hemolysis is associated with marked reticulocytosis and hyperbilirubinemia. From the time of onset, the process runs an unremitting course, punctuated by sudden crises. The most serious of these are the vaso-occlusive, or pain, crises. Pain crises can involve many sites but are most common in the bone marrow, where they often progress to infarction and necrosis. A feared complication is the acute chest syndrome, which can be triggered by pulmonary infections or fat emboli from necrotic marrow that secondarily involve the lung. The blood flow in the inflamed, ischemic lung becomes sluggish and "spleenlike," leading to sickling within hypoxic pulmonary beds. This exacerbates the underlying pulmonary dysfunction, creating a vicious cycle of worsening pulmonary and systemic hypoxemia, sickling, and vaso-occlusion. Another major complication is central nervous system stroke, which sometimes occurs in the setting of the acute chest syndrome. The acute chest syndrome and stroke are the two leading causes of ischemia-related death.

A second acute event, the aplastic crisis, represents a sudden but usually temporary cessation of erythropoiesis. As in hereditary spherocytosis, these are usually triggered by parvovirus infection of erythroblasts, and, while severe, are self-limited.

Patients with sickle cell disease are also prone to infections. Both children and adults with sickle cell disease are practically without a functioning spleen. This making them susceptible to infections by encapsulated bacteria, such as pneumococci. For reasons that are not entirely clear, patients with sickle cell disease are particularly predisposed to Salmonella osteomyelitis.

Diagnosis

- In full-blown sickle cell disease, at least some irreversibly sickled red cells can be seen on an ordinary peripheral blood smear.
- In sickle cell trait, sickling can be induced in vitro by exposing cells to marked hypoxia.
- The ultimate diagnosis depends on the electrophoretic demonstration of HbS.
- Prenatal diagnosis of sickle cell anemia can be performed by analyzing the DNA in fetal cells obtained by amniocentesis or biopsy of chorionic villi.

3. Thalassemia

The thalassemias are "a heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of α- or β-globin chains". As a consequence there is a deficiency of hemoglobin, with additional secondary red cell abnormalities caused by the relative excess of the other unaffected globin chain.

Molecular Pathogenesis
A diverse collection of molecular defects underlies the thalassemias, which are inherited as autosomal codominant conditions. The adult hemoglobin, or HbA, is a tetramer composed of two α chains and two β chains. The α chains are encoded by two α-globin genes, while the β chains are encoded by a single β-globin gene. The mutations that cause thalassemia are particularly common among Mediterranean, African, and Asian populations. The clinical features vary widely depending on the specific combination of alleles that are inherited by the patient.

**β-Thalassemia**

The β-globin mutations associated with β-thalassemia fall into two categories:
1. β⁰, in which no β-globin chains are produced; and
2. β⁺, in which there is reduced (but detectable) β-globin synthesis.

The majority of mutations consist of single-base changes. Individuals inheriting one abnormal allele have thalassemia minor or thalassemia trait, which is asymptomatic or mildly symptomatic. Most individuals inheriting any two β⁰ and β⁺ alleles have beta-thalassemia major.

**Two conditions contribute to the pathogenesis of the anemia in β-thalassemia**
1. The reduced synthesis of β-globin leads to inadequate HbA formation, so that the MCHC is low, and the cells appear hypochromic and microcytic.
2. Red cell hemolysis is even more important is, which results from the unbalanced rates of β-globin and α-globin chain synthesis. Unpaired α chains form insoluble aggregates that precipitate within the red cells and cause membrane damage that is severe enough to provoke extravascular hemolysis (Fig. 3-6). Erythroblasts in the bone marrow are also susceptible to damage through the same mechanism, which in severe β-thalassemia results in the destruction of the majority of erythroid progenitors before their maturation into red cells. This intramedullary destruction of erythroid precursors (ineffective erythropoiesis) is also associated with an inappropriate increase in the absorption of dietary iron, which often leads to iron overload.

**α-Thalassemia**

The molecular basis of α-thalassemia is quite different from that of β-thalassemia. Most of the α-thalassemias are caused by deletions that remove one or more of the α-globin gene loci. The severity of the disease that results from these lesions is directly proportional to the number of α-globin genes that are missing. For example, the loss of a single α-globin gene is associated with a silent-carrier state, whereas the deletion of all four α-globin genes is associated with fetal death in utero, because the blood has virtually no oxygen-delivering capacity. With loss of three α-globin genes there is a relative excess of β-globin or chains other than α-globin. Excess β-globin (or γ-globin chains early in life) forms relatively stable β4 and γ4 tetramers known as HbH and Hb Bart, respectively, that cause less membrane damage than do free α-globin chains. Therefore, the hemolytic anemia and ineffective erythropoiesis tend be less severe in α-thalassemia than in β-thalassemia. Unfortunately, both HbH and Hb Bart have an abnormally high affinity for oxygen, which renders them ineffective at delivering oxygen to the tissues.

**Pathological features**

- In β-thalassemia minor the abnormalities are confined to the peripheral blood. In smears the red cells appear small (microcytic), pale (hypochromic), and regular in shape. Target cells are often seen, a feature that results from the relatively large surface area-to-volume ratio, which leads Hb to collect in a central, dark-red “puddle.”
- In smears from patients with β-thalassemia major the microcytosis and hypochromia are much more pronounced, and there is marked poikilocytosis, anisocytosis, and reticulocytosis. Nucleated red cells (normoblasts) are also seen, which reflect the underlying erythropoietic force.
- The anatomic changes in β-thalassemia major are similar to those seen in other hemolytic anemias but extreme in degree.
  - The combination of ineffective erythropoiesis and hemolysis results in a striking hyperplasia of erythroid progenitors, with a shift toward early forms. The expanded erythropoietic marrow may completely fill the intramedullary space of the skeleton, invade the bony cortex, impair bone growth, and produce skeletal deformities.
The extramedullary hematopoiesis and the hyperplasia of the mononuclear phagocytes result in prominent splenomegaly, hepatomegaly, and lymphadenopathy.

The ineffective erythropoietic precursors consume nutrients and produce growth retardation and a degree of cachexia.

Unless steps are taken to prevent iron overload, over the span of years severe hemosiderosis develops.

**Clinical Course**

- β-thalassemia major manifests itself postnatally as HbF synthesis diminishes.
- Affected children fail to develop normally, and their growth is retarded from shortly after birth. They are sustained only by repeated blood transfusions.
- With transfusions alone survival into the second or third decade is possible, but gradually systemic iron overload develops.
- The combination of iron present in transfused red cells and the increased uptake of dietary iron from the gut lead inevitably to iron overload. The latter stems from inappropriately low levels of plasma hepcidin, a negative regulator of iron uptake that is "underexpressed" in conditions (such as β-thalassemia major) that are associated with ineffective erythropoiesis.
- Unless patients are treated aggressively with iron chelators, cardiac failure from secondary hemochromatosis commonly occurs and often causes death in the second or third decade of life.
- In β-thalassemia minor there is usually only a mild microcytic hypochromic anemia; generally, these patients have a normal life expectancy. Iron deficiency anemia is associated with a similar red cell appearance and must be excluded by appropriate laboratory tests.

**Diagnosis**

- The diagnosis of β-thalassemia minor is made by Hb electrophoresis. In addition to reduced amounts of HbA (α2β2), the level of HbA2 (α2δ2) is increased.
- The diagnosis of β-thalassemia major can generally be made on clinical grounds. The peripheral blood shows a severe microcytic hypochromic anemia, with marked variation in cell shapes (poikilocytosis). The reticulocyte count is increased. Hb electrophoresis shows profound reduction or absence of HbA and increased levels of HbF. The HbA2 level may be normal or increased.
- Prenatal diagnosis of both forms of thalassemia can be made by DNA analysis.

4. **Glucose-6-Phosphate Dehydrogenase Deficiency (G6PDD)**

The red cell is vulnerable to injury by endogenous and exogenous oxidants, which are normally inactivated by reduced glutathione (GSH). Abnormalities affecting the enzymes that are required for GSH production reduce the ability of red cells to protect themselves from oxidative injury and lead to hemolytic anemias. The prototype (and most prevalent) of these anemias is that associated with a deficiency of glucose-6-phosphate dehydrogenase (G6PD). The G6PD gene is on the X chromosome. G6PD deficiency produces no symptoms until the patient is exposed to an environmental factor (most commonly infectious agents or drugs) that results in increased oxidant stress. The drugs incriminated include antimalarials (e.g., primaquine), sulfonamides,nitrofurantoin, phenacetin, aspirin (in large doses), and vitamin K derivatives. More commonly, episodes of hemolysis are triggered by infections, which induced phagocytes to produce free radicals as part of the normal host response. These offending agents produce oxidants such as hydrogen peroxide that are sopped up by GSH, which is converted to oxidized glutathione in the process. Because regeneration of GSH is impaired in G6PD-deficient cells, hydrogen peroxide is free to "attack" other red cell components, including globin chains, which have sulfhydryl groups that are susceptible to oxidation. Oxidized Hb denatures and precipitates, forming intracellular inclusions called Heinz bodies, which can damage the cell membrane sufficiently to cause intravascular hemolysis. Other cells that are less severely damaged nevertheless suffer from a loss of deformability, and their cell membranes are further damaged when splenic phagocytes attempt to "pluck out" the Heinz bodies, creating so-called bite cells (Fig. 3-7). All of these changes predispose the red cells to becoming trapped in the splenic sinusoids and destroyed by the phagocytes (extravascular hemolysis). Drug-induced hemolysis is acute and of variable clinical severity. Typically, patients develop evidence of hemolysis after a lag period of 2 or 3 days. Because the G6PD gene is on the X chromosome, all the red
cells of affected males are affected. Most carrier females are asymptomatic. In a variant known G6PD Mediterranean, found mainly in the Middle East, the enzyme deficiency and the hemolysis that occur upon exposure to oxidants are more severe.

5. Paroxysmal Nocturnal Hemoglobinuria (PNH) is rare disorder of unknown etiology. It is the only form of hemolytic anemia that results from an acquired membrane defect secondary to a mutation that affects myeloid stem cells. It is believed that the hemolysis is nocturnal because the blood becomes acidic during sleep (because of CO\(_2\) retention) and an acid pH may promote hemolysis. It is not known why red cell destruction is paroxysmal. Other proteins are deficient from the membranes of granulocytes and platelets, possibly explaining the striking susceptibility of these patients to infections and intravascular thromboses.

6. Immunohemolytic Anemias
Antibodies that recognize determinants on red cell membranes cause these uncommon forms of hemolytic anemia. The antibodies may arise spontaneously or be induced by exogenous agents such as drugs or chemicals. Immunohemolytic anemias are classified into

a. Warm Antibody Type
   - Primary (idiopathic)
   - Secondary: B-cell lymphoid neoplasms (e.g., chronic lymphocytic leukemia), autoimmune disorders (e.g., systemic lupus erythematosus), drugs (e.g., α-methyldopa, penicillin, quinidine)

b. Cold Antibody Type
   - Acute: Mycoplasma infection, infectious mononucleosis
   - Chronic: idiopathic, B-cell lymphoid neoplasms (e.g., lymphoplasmacytic lymphoma)

Whatever the cause of antibody formation, the diagnosis of immunohemolytic anemias depends on the detection of antibodies and/or complement on patient red cells. This is done using the direct Coombs antiglobulin test, which measures the capacity of antibodies raised in animals against human immunoglobulins or complement to agglutinate red cells from the patient. The indirect Coombs test, in which patient serum is tested for the ability to agglutinate defined red cells, can then be used to characterize the target of the autoantibody.

7. Traumatic hemolytic anemia
Red cells are disrupted by physical trauma in a variety of circumstances. Clinically important hemolytic anemias are sometimes caused by cardiac valve prostheses or by the narrowing and partial obstruction of the vasculature. Microangiopathic hemolytic anemia is observed in a variety of pathologic states in which small vessels become partially obstructed. The latter include

a. disseminated intravascular coagulation (DIC), which is the most frequent of these conditions. The narrowing is caused by the intravascular deposition of fibrin
b. malignant hypertension,
c. SLE
d. thrombotic thrombocytopenic purpura,
e. hemolytic-uremic syndrome
f. disseminated cancer

All of the above produce vascular lesions that predispose the circulating red cells to mechanical injury. The morphologic alterations in the injured red cells (schistocytes) are striking and quite characteristic; "burr cells," "helmet cells," and "triangle cells" may be seen (Fig. 3-8). While the recognition of microangiopathic hemolysis often provides an important diagnostic clue, in and of itself it is not usually a major clinical problem.

8. Malaria
It has been estimated that 200 million persons suffer from this infectious disease, which is one of the most widespread afflictions of humans. Malaria is endemic in Asia and Africa, but with widespread jet travel,
cases now occur all over the world. Malaria is caused by one of four types of protozoa. Of these, the most important is *Plasmodium falciparum*, a serious disorder with a high fatality rate. The other three species (*P. malariae*, *P. vivax*, and *P. ovale*) cause relatively benign disease. Showers of new merozoites are released from the red cells at intervals of approximately 48 hours for *P. vivax*, *P. ovale*, and *P. falciparum*, and 72 hours for *P. malariae*. The clinical spikes of shaking, chills, and fever coincide with this release. The parasites destroy large numbers of red cells and thus cause hemolytic anemia. A characteristic brown malarial pigment, probably a derivative of Hb that is identical to hematin, is released from the ruptured red cells along with the merozoites, discoloring principally the spleen, but also the liver, lymph nodes, and bone marrow. Activation of the phagocytic defense mechanisms of the host leads to marked hyperplasia of the mononuclear phagocyte system throughout the body, reflected in massive splenomegaly. Less frequently, the liver may also be enlarged. *Fatal falciparum malaria often involves the brain, a complication known as cerebral malaria.* Normally, red cells bear negatively charged surfaces that interact poorly with endothelial cells. Infection of red cells with *P. falciparum* induces the appearance of positively charged surface knobs containing parasite-encoded proteins, which bind to adhesion molecules expressed on activated endothelium. In the brain this process gives rise to engorged cerebral vessels that are full of parasitized red cells and often occluded by microthrombi. Cerebral malaria is rapidly progressive; convulsions, coma, and death usually occur within days to weeks. Fortunately, falciparum malaria more commonly pursues a more chronic course that may be punctuated at any time by a dramatic complication known as blackwater fever. The trigger for this uncommon complication is obscure, but it is associated with massive hemolysis, leading to jaundice, hemoglobinemia, and hemoglobinuria.

**ANEMIAS OF DIMINISHED ERYTHROPOIESIS**

This category includes anemias that are caused by an inadequate dietary supply of substances that are needed for hematopoiesis, particularly iron, folic acid, and vitamin B₁₂. Other disorders that suppress erythropoiesis include those associated with bone marrow failure (aplastic anemia) or the replacement of the bone marrow by tumor or inflammatory cells (myelophthisic anemia).

**Iron Deficiency Anemia**

It is estimated that anemia affects about 10% of the population in developed countries and 25% to 50% in developing countries. In both settings the most common cause of anemia is iron deficiency, which is the most common form of nutritional deficiency.

Total body iron content is about 2 gm for women and 6 gm for men. Approximately 80% of functional body iron is found in hemoglobin, with the remainder being found in myoglobin and iron-containing enzymes (e.g., catalase and cytochromes). The iron storage pool, represented by hemosiderin and ferritin-bound iron, contains on average 15% to 20% of total body iron. Stored iron is found mainly in the liver, spleen, bone marrow, and skeletal muscle. Because *serum ferritin* is largely derived from the storage pool of iron, its concentration is a good indicator of the adequacy of body iron stores. *Assessment of bone marrow iron stores* is another reliable method for estimating body iron. Iron is transported in the plasma by an iron-binding protein called *transferrin*. In normal persons, transferrin is about 33% saturated with iron, yielding serum iron levels that average 120 µg/dL in men and 100 µg/dL in women. There is no regulated pathway for iron excretion, which is limited to the 1 to 2 mg/day that is lost by the shedding of mucosal and skin epithelial cells. Iron balance therefore is maintained largely by regulating the absorption of dietary iron. Iron is absorbed in the duodenum. Only a fraction of the iron that enters the enterocytes is delivered to plasma transferrin. The remainder is lost through the exfoliation of mucosal cells. When the body is replete with iron, most of the iron that enters duodenal cells is bound to ferritin and never transferred to transferrin; in iron deficiency, or when there is ineffective erythropoiesis, transfer to plasma transferrin is enhanced. This balance is regulated by hepcidin, a small hepatic peptide that is synthesized and secreted in an iron-dependent fashion. When hepcidin concentrations are high less iron is transferred out of the enterocytes to transferrin. Conversely, when hepcidin levels are low, as occurs in hemochromatosis, transport of iron from the enterocytes to plasma is increased, resulting eventually in systemic iron overload. **Iron deficiency anemia can result from a variety of causes:**
1. Low intake and poor availability from predominantly vegetarian diets are an important cause of iron deficiency.
2. Malabsorption can occur with sprue and celiac disease or after gastrectomy.
3. Increased demands not met by normal dietary intake occur around the world during pregnancy and infancy.
4. Chronic blood loss is one of the most important causes of iron deficiency anemia. This loss may occur from the gastrointestinal tract (e.g., peptic ulcers, colonic cancer, hemorrhoids, hookworm disease) or the female genital tract (e.g., menorrhagia, metrorrhagia, cancers).

Regardless of the cause, iron deficiency develops insidiously. At first iron stores are depleted, leading to a decline in serum ferritin and the absence of stainable iron in the bone marrow. This is followed by a decrease in serum iron and a rise in the serum iron-binding capacity. Ultimately the capacity to synthesize hemoglobin is diminished, leading to anemia and even reduced immunocompetence.

**Pathologic features**
- Iron deficiency anemia is usually relatively mild.
- The red cells are *microcytic and hypochromic*, reflecting the reductions in MCV and MCHC ([Fig. 3-9](#)).
- For unclear reasons, iron deficiency is often accompanied by an increase in the platelet count.
- Although erythropoietin levels are increased, the marrow response is blunted by the iron deficiency, and thus the marrow cellularity is usually only slightly increased.

**Diagnostic criteria include**
- anemia, hypochromic and microcytic red cell indices,
- low serum ferritin and serum iron levels,
- low transferrin saturation,
- increased total iron-binding capacity.

Persons frequently die *with* this form of anemia but rarely *of* it. It is important to remember that in reasonably well-nourished persons, microcytic hypochromic anemia is not a disease but rather a symptom of some underlying disorder.

**Anemia of Chronic Disease**
This is the most common form of anemia in hospitalized patients. *It superficially resembles the anemia of iron deficiency, but it stems from inflammation-induced sequestration of iron within the cells of the mononuclear phagocyte (reticuloendothelial) system.* It occurs in a variety of chronic inflammatory disorders, including the following:
1. Chronic microbial infections, such as osteomyelitis, bacterial endocarditis, and lung abscess
2. Chronic immune disorders, such as rheumatoid arthritis and regional enteritis
3. Neoplasms, such as Hodgkin lymphoma and carcinomas of the lung and breast

The serum iron levels are usually low, and the red cells can be normocytic and normochromic, or, as in anemia of iron deficiency, hypochromic and microcytic. However, the anemia of chronic disease is associated with increased storage iron in the bone marrow, a high serum ferritin concentration, and a reduced total iron-binding capacity, all of which readily rule out iron deficiency. This combination of findings is attributable to high concentrations of circulating hepcidin, which inhibits ferroportin and thereby block the transfer of iron from the mononuclear phagocyte storage pool to the erythroid precursors.

**Megaloblastic Anemias**
There are two principal causes of megaloblastic anemia: folate deficiency and vitamin B_{12} deficiency. Both vitamins are required for DNA synthesis, and, hence, the effects of their deficiency on hematopoiesis are quite similar. However, the causes and consequences of folate and vitamin B_{12} deficiency differ in important ways.

**Pathogenesis**
The morphologic hallmark of megaloblastic anemias is an enlargement of erythroid precursors (*megaloblasts*), which gives rise to abnormally large red cells (macrocytes). The other myeloid lineages are also affected. Most notably, granulocyte precursors are enlarged (*giant metamyelocytes*) and yield highly characteristic...
hypersegmented neutrophils. Underlying the cellular gigantism is an impairment of DNA synthesis, which results in a delay in nuclear maturation and cell division. Because the synthesis of RNA and cytoplasmic elements proceeds at a normal rate and thus outpaces that of the nucleus, the hematopoietic precursors show nuclear-cytoplasmic asynchrony. This maturational derangement contributes to anemia in several ways

1. Some megaloblasts are so defective in DNA synthesis that they undergo apoptosis in the marrow (ineffective hematopoiesis).
2. Others succeed in maturing into red cells but do so after fewer cell divisions; as a result, the total output from these precursors is diminished.

Granulocyte and platelet precursors are similarly affected. As a result, most patients with megaloblastic anemia develop pancytopenia (anemia, thrombocytopenia, and granulocytopenia).

Pathologic features

- The bone marrow is markedly hypercellular, as a result of increased numbers of megaloblasts.
- These cells are larger than normoblasts and have a delicate, finely reticulated nuclear chromatin (suggestive of nuclear immaturity) and an abundant, strikingly basophilic cytoplasm (Fig. 3-10).
- As the megaloblasts differentiate and begin to acquire hemoglobin, the nucleus retains its finely distributed chromatin and fails to undergo the chromatin clumping typical of an orthochromatic normoblast.
- The granulocytic precursors also demonstrate nuclear-cytoplasmic asynchrony, yielding giant metamyelocytes.
- Megakaryocytes, too, may be abnormally large and have bizarre multilobed nuclei.
- In the peripheral blood the earliest change is usually the appearance of hypersegmented neutrophils, which appear even before the onset of anemia. Normally, neutrophils have three or four nuclear lobes, but in megaloblastic anemias neutrophils often have five or more. The red cells typically include large, egg-shaped macro-ovalocytes; the MCV is often greater than 110 fL (normal, 82-92 fL). Although macrocytes appear hyperchromic, in reality the MCHC is normal. Large, misshapen platelets may also be seen.
- Morphologic changes in other systems, especially the gastrointestinal tract, also occur, giving rise to some of the clinical features.

Folate (folic acid) Deficiency Anemia

The risk of clinically significant folate deficiency is high in those

1. With a poor diet (the economically deprived, the indigent, and the elderly) or
2. With increased metabolic needs (pregnant women and patients with chronic hemolytic anemias).
3. On Phenytoint (antiepileptic drug) and a few other drugs inhibit folate absorption, while others, such as methotrexate, inhibit folate metabolism.
4. With malabsorptive disorders that affect the principal site of intestinal absorption (the upper third of the small intestine) such as celiac disease and tropical sprue.

After absorption, folate is transported in the blood mainly as a monoglutamate. Within cells its conversion from dihydrofolate to tetrahydrofolate by the enzyme dihydrofolate reductase is particularly important. Tetrahydrofolate acts as an acceptor and donor of one-carbon units in a variety of steps involved in the synthesis of DNA, and its deficiency accounts for the inadequate DNA synthesis that is characteristic of megaloblastic anemia.

Unlike in vitamin B12 deficiency, neurologic abnormalities do not occur in folate deficiency anemia. The diagnosis of a megaloblastic anemia is readily made from examination of a smear of peripheral blood and bone marrow. The anemia of folate deficiency is best distinguished from that of vitamin B12 deficiency by measuring serum and red cell folate and vitamin B12 levels.

Vitamin B12 (Cobalamin) Deficiency Anemia (Pernicious Anemia)

Inadequate levels of vitamin B12, or cobalamin, result in a megaloblastic macrocytic anemia similar to that caused by folate deficiency. However, vitamin B12 deficiency can also cause a demyelinating disorder involving the peripheral nerves and, ultimately and most importantly, the spinal cord.

Etiology & Causes of vitamin B12 deficiency
Inadequate gastric production or defective function of intrinsic factor is the prime cause of the deficiency. Intrinsic factor plays a critical role in the absorption of vitamin B\(_{12}\), a complex multistep process that proceeds as follows:

- Peptic digestion releases dietary vitamin B\(_{12}\), which then binds to salivary B\(_{12}\)-binding proteins called cobalophilins, or R binder.
- R-B\(_{12}\) complexes are transported to the duodenum and processed by pancreatic proteases; this releases B\(_{12}\), which attaches to intrinsic factor secreted from the parietal cells of the gastric fundic mucosa.
- The intrinsic factor-B\(_{12}\) complex passes to the distal ileum and attaches to the epithelial intrinsic factor receptors, which leads to absorption of vitamin B\(_{12}\).
- The absorbed B\(_{12}\) is bound to transport proteins called transcobalamin, which then deliver it to the liver and other cells of the body.

**Causes of the deficiency include**

Vitamin B\(_{12}\) is abundant in all animal foods, including eggs and dairy products, and is resistant to cooking and boiling (unlike folic acid). Even bacterial contamination of water and nonanimal foods can provide adequate amounts. As a result, deficiencies due to diet are rare and are virtually confined to strict vegans. Once vitamin B\(_{12}\) is absorbed, the body handles it very efficiently. It is stored in the liver, which normally contains reserves that are sufficient to support bodily needs for 5 to 20 years.

**Long-standing malabsorption of Vit. B\(_{12}\) is the most common and important cause.**

A. Until proved otherwise, a deficiency of vitamin B\(_{12}\) is caused by pernicious anemia. This disease results from an autoimmune reaction against parietal cells and intrinsic factor itself, which produces gastric mucosal atrophy (autoimmune chronic gastritis). Several associations favor an autoimmune basis:

1. Autoantibodies are present in the serum and gastric juice of most patients with pernicious anemia. Three types of antibodies have been found: parietal canalicular antibodies, which bind to the mucosal parietal cells; blocking antibodies, which block the binding of vitamin B\(_{12}\) to intrinsic factor; and binding antibodies that react with intrinsic factor-B\(_{12}\) complex and prevent it from binding to the ileal receptor.
2. An occurrence of pernicious anemia with other autoimmune diseases such as Hashimoto thyroiditis, Addison disease, and type I diabetes mellitus is well documented.
3. The frequency of serum antibodies to intrinsic factor is increased in patients with other autoimmune diseases.

B. Following gastrectomy (which leads to loss of cells producing intrinsic factor)

C. Following resection of ileum (which prevents absorption of intrinsic factor-B\(_{12}\) complex),

D. disorders that involve the distal ileum (such as Crohn disease, tropical sprue, and Whipple disease).

E. In individuals older than 70 years of age, gastric atrophy and achlorhydria can interfere with the production of acid and pepsin, which are needed to release the vitamin from its bound form in the diet. The metabolic defects that are responsible for the anemia are entangled with folate metabolism. Vitamin B\(_{12}\) is required for recycling of tetrahydrofolate, and hence its deficiency reduces the availability of the form of folate that is required for DNA synthesis. Thus the anemia of vitamin B\(_{12}\) deficiency improves with administration of folates. In contrast, the biochemical basis of the neuropathy in vitamin B\(_{12}\) deficiency is unclear, and administration of folate may actually exacerbate the neurologic disease. The principal neurologic lesions associated with vitamin B\(_{12}\) deficiency are demyelination of the posterior and lateral columns of the spinal cord, (Combined degeneration of the spinal cord). The severity of neurologic manifestations is not related to the degree of anemia; the neurologic disease can occur in the absence of overt megaloblastic anemia.

**Clinical Features**

As with any other anemia, there is pallor, easy fatigability, and, in severe cases, dyspnea and even congestive heart failure. The increased destruction of erythroid progenitors may give rise to mild jaundice. The spinal cord disease begins with symmetric numbness, tingling, and burning in feet or hands, followed by unsteadiness of gait and loss of position sense, particularly in the toes. Although the anemia responds dramatically to parenteral vitamin B\(_{12}\), the neurologic manifestations often fail to resolve. Patients with pernicious anemia have an increased risk of gastric carcinoma.
The diagnostic features of pernicious anemia include:
1. Low serum vitamin B₁₂ levels
2. Normal or elevated serum folate levels
3. Serum antibodies to intrinsic factor
4. Moderate to severe megaloblastic anemia
5. Leukopenia with hypersegmented granulocytes
6. A dramatic reticulocytic response (within 2-3 days) to parenteral administration of vitamin B₁₂.

APLASTIC ANEMIA (AA)
Aplastic anemia is “a disorder in which multipotent bone marrow stem cells are suppressed, leading to marrow failure and pancytopenia.”

Etiology and Pathogenesis
• AA is divided etiologically into:
  1. Primary (idiopathic) (50% of cases)
  2. Secondary to damaging agent to the BM
     a. Known toxic agent to the BM
        - Predictable damage, which is dose related, and usually reversible. Included in this category are antineoplastic drugs, benzene, and chloramphenicol.
        - Unpredictable (“idiiosyncratic” or hypersensitivity) damage to small doses of known myelotoxic drugs (e.g., chloramphenicol) or to drugs such as sulfonamides, which are not myelotoxic in other persons.
     b. After certain viral infections, most often community-acquired viral hepatitis. Marrow aplasia develops several months after recovery from the hepatitis and follows a relentless course.
• Autoreactive T cells may play an important role in marrow failure. This is supported by the observation that in 70% to 80% of cases aplastic anemia responds to immunosuppressive therapy aimed at T cells. Perhaps viral antigens, drug-derived haptons, and/or genetic damage create neoantigens within stem cells that serve as targets for the T cells.
• A small fraction of patients with "acquired" aplastic anemia have inherited defects in DNA telomerase, which is needed for the maintenance and stability of chromosomes. In these settings, the outcome is direct damage to and senescence of hematopoietic stem cells.

Pathological features
• The bone marrow is markedly hypocellular, with greater than 90% of the intertrabecular spaces occupied by fat.
• The limited cellularity often consists of only lymphocytes and plasma cells. These changes are better appreciated in bone marrow biopsy specimens than in marrow aspirates, which often yield a "dry tap."
• Thrombocytopenia and granulocytopenia may result in hemorrhages and bacterial infections, respectively.
• Secondary changes include anemia-induced fatty change in the liver
• Transfusions may eventually cause hemosiderosis.

It is important to distinguish aplastic anemia from anemias caused by
1. Marrow infiltration (myelophthisic anemia).
2. Aleukemic leukemia
3. Granulomatous diseases affecting the BM.

Because pancytopenia is common to these conditions, their clinical manifestations may be indistinguishable, but they are easily distinguished by examination of the bone marrow. Splenomegaly is characteristically absent in aplastic anemia; if it is present, the diagnosis of aplastic anemia should be seriously questioned. Typically, the red cells are normocytic and normochromic & reticulocytes are reduced in number.

The prognosis of marrow aplasia is quite unpredictable. As mentioned earlier, withdrawal of toxic drugs may lead to recovery in some cases. The idiopathic form has a poor prognosis if left untreated. Bone marrow transplantation is an extremely effective form of therapy. Alternatively, poor transplant candidates may benefit from immunosuppressive therapy.
MYELOPHTHISIC ANEMIA
This form of anemia is caused by the extensive replacement of the marrow by cancers or other lesions. Causes include
1. Metastatic carcinoma to the BM most commonly from breast, lung, or prostate primaries.
2. Advanced tuberculosis,
3. Lipid storage disorders
4. Osteosclerosis
The principal manifestations of marrow infiltration include anemia and thrombocytopenia; in general, the white cell series is less affected. Characteristically, misshapen red cells, some resembling teardrops, are seen in the peripheral blood. Immature granulocytic and erythroid precursors may also be seen (leukerythroblastic blood picture), along with a slightly elevated white cell count.

LABORATORY DIAGNOSIS OF ANEMIAS
The diagnosis is established by
- Decrease in the Hb and the hematocrit (PCV) to levels that are below normal.
- The red cell hemoglobin content and size of the RBCs are discriminatory in that the results can place the anemia into one of three major subgroups: normocytic normochromic, microcytic hypochromic, and macrocytic.
- The presence of red cells with a particular morphology, such as spherocytes, sickled cells, and fragmented cells, provide additional etiologic clues.
- Specialized tests are particularly important in establishing the diagnosis of certain classes of anemia; these include
  - Gel electrophoresis: used to detect abnormal hemoglobins, such as HbS
  - Coombs test: used to diagnose immunohemolytic anemias
  - Reticulocyte counts: used to distinguish between anemias caused by red cell destruction (hemolysis) and depressed production (marrow failure)
  - Iron indices (serum iron, serum iron-binding capacity, transferrin saturation, and serum ferritin concentrations): used to distinguish between hypochromic microcytic anemias caused by iron deficiency, anemia of chronic disease, and thalassemia minor
  - Serum and red cell folate and vitamin B<sub>12</sub> concentrations: used to identify the cause of megaloblastic anemia
  - Plasma unconjugated bilirubin and haptoglobin concentrations: used to support the diagnosis of hemolytic anemia

In isolated anemia, tests performed on the peripheral blood are usually sufficient to establish a cause. In contrast, when anemia occurs in combination with thrombocytopenia and/or granulocytopenia, it is much more likely to be associated with marrow aplasia or infiltration; in these instances, BM aspiration & biopsy are often important for diagnosis.

POLYCYTHEMIA (Erythrocytosis)
This term signifies an increase in the blood concentration of red cells, which usually correlates with an increase in the hemoglobin concentration. Polycythemia are of two types
1. Relative polycythemia that is associated with hemoconcentration caused by dehydration, such as with water deprivation, prolonged vomiting, diarrhea, or the excessive use of diuretics.
2. Absolute polycythemia, when there is an increase in the total red cell mass. Absolute polycythemia is either
   - Primary when the increase in red cell mass results from an autonomous proliferation of the myeloid stem cells
   - Secondary when the red cell progenitors are proliferating in response to an increase in erythropoietin.
Primary polycythemia (polycythemia vera [PCV]) is a clonal, neoplastic proliferation of myeloid progenitors, which will be discussed under the heading of myeloproliferative disorders. The increases in erythropoietin that are seen in secondary polycythemias have a variety of causes
1. **Appropriate**: lung disease, high-altitude living, cyanotic heart disease
2. **Inappropriate**: erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatoma, cerebellar hemangioblastoma).

**WHITE CELL DISORDERS**

Disorders of white cells include deficiencies (leukopenias) and proliferations, which may be reactive or neoplastic. Reactive proliferation in response to an underlying primary, often microbial, disease is fairly common. Neoplastic disorders, though less common, are more ominous; they cause approximately 9% of all cancer deaths in adults and a staggering 40% in children younger than 15 years.

**NON-NEOPLASTIC DISORDERS OF WHITE CELLS**

**Leukopenia** is most commonly the result of a decrease in granulocytes (the most prevalent circulating white cells). **Lymphopenias** are associated with
1. congenital immunodeficiency diseases
2. acquired in association with
   - advanced HIV infection or
   - treatment with corticosteroids

**Neutropenia/Agranulocytosis**

Neutropenia signifies a reduction below normal of the number of granulocytes in peripheral blood; when severe, it is referred to as *agranulocytosis*. In the latter condition characteristically, the total white cell count is reduced to 1000 cells/µL and, in some instances, to as few as 200 cells/µL. Affected persons are extremely susceptible to bacterial and fungal infections, which can be severe enough to cause death.

**Etiology and Pathogenesis**

The mechanisms that cause neutropenia can be broadly divided into two categories

1. **Inadequate or ineffective granulopoiesis**, which is a manifestation of
   A. **generalized marrow failure** as in
   - Aplastic anemia
   - megaloblastic anemia
   - A variety of leukemias
   - Cancer chemotherapy through inducing transient marrow aplasia.
   
   B. **Isolated neutropenia** i.e. there is involvement of granulocytic precursors only as is seen with
   - Certain drugs
   - Neoplastic proliferations of cytotoxic T cells and natural killer (NK) cells.

2. **Accelerated removal or destruction of neutrophils**, which can be encountered with
   - Idiopathic
   - immune-mediated injury to neutrophils (triggered in some cases by drugs)
   - Increased peripheral utilization of neutrophils can occur in
     - overwhelming bacterial, fungal, or rickettsial infections
     - Splenomegaly that leads to sequestration and accelerated removal of neutrophils

**Pathologic features**

- The changes in the bone marrow depend on the underlying mechanism.
- **Marrow hypercellularity** is seen when the neutropenia results from excessive destruction of the mature neutrophils or from ineffective granulopoiesis, such as occurs in megaloblastic anemia.
- In contrast, agents such as drugs that suppress granulocytopenias are associated with a marked decrease in maturing granulocytic precursors in the marrow.
- Erythropoiesis and megakaryopoiesis can be normal if the responsible agent specifically affects the granulocytes, but with most myelotoxic drugs all marrow elements are affected.
The main problem is infections. They commonly take the form of ulcerating, necrotizing lesions of the mouth, pharynx, or other sites within the oral cavity (agranulocytic angina). These lesions often show a massive growth of microorganisms, due to the inability to mount a leukocyte response.

**Reactive Leukocytosis**

An increase in the number of white cells is common in a variety of reactive inflammatory states caused by microbial and nonmicrobial stimuli. Leukocytoses are relatively nonspecific and can be classified on the basis of the particular white cell series affected.

- **Neutrophilic Leukocytosis**
  - Acute bacterial infections, especially pyogenic
  - sterile inflammation caused by tissue necrosis (myocardial infarction, burns)

- **Eosinophilic Leukocytosis (Eosinophilia)**
  - Allergic disorders such as asthma, hay fever, allergic skin diseases (e.g., pemphigus, dermatitis herpetiformis)
  - parasitic infestations
  - drug reactions
  - certain malignancies (e.g., Hodgkin disease and some non-Hodgkin lymphomas)
  - collagen vascular disorders
  - some vasculitides
  - atheroembolic disease (transient)

- **Basophilic Leukocytosis (Basophilia):** this is rare, often indicative of a myeloproliferative disease (e.g., chronic myelogenous leukemia)

- **Monocytosis**
  - Chronic infections (e.g., tuberculosis)
  - bacterial endocarditis
  - rickettsiosis
  - malaria
  - collagen vascular diseases (e.g., systemic lupus erythematosus)
  - inflammatory bowel diseases (e.g., ulcerative colitis)

- **Lymphocytosis**
  - Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis)
  - viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus)
  - **Bordetella pertussis** infection

In some cases reactive leukocytosis may mimic leukemia. Such *leukemoid reactions* must be distinguished from true malignancies of the white cells.

**NEOPLASTIC PROLIFERATIONS OF WHITE CELLS**

Neoplastic disorders represent the most important of the white cell disorders. They can be divided into three broad categories based on the origin of the neoplastic cells:

- **A. Lymphoid neoplasms**, which include non-Hodgkin lymphomas (NHLs), Hodgkin lymphomas (discussed in chapter 4), lymphocytic leukemias, and plasma cell dyscrasias and related disorders. In many instances these tumors are composed of cells that resemble normal stages of lymphocyte differentiation, a feature that serves as one of the bases for their classification.

- **B. Myeloid neoplasms** arise from stem cells that normally give rise to the formed elements of the blood: granulocytes, red cells, and platelets. The myeloid neoplasms fall into three fairly distinct subcategories:
  1. **acute myelogenous leukemias**, in which immature progenitor cells accumulate in the bone marrow
  2. **chronic myeloproliferative disorders**, in which inappropriately increased production of formed blood elements leads to elevated blood cell counts
3. **myelodysplastic syndromes**, which are characteristically associated with ineffective hematopoiesis and cytopenias.

C. **Histiocytic neoplasms** represent proliferative lesions of histiocytes. Of special interest is a spectrum of proliferations comprising Langerhans cells (the *Langerhans cell histiocytoses*).

**ACUTE LEUKEMIAS (AL)**

There are two major types of AL; acute lymphoblastic (ALL) & acute myelogenous (AML). The pathophysiology, laboratory findings, and clinical features of one closely resemble those of the other. Thus, it is convenient to analyze the features common to both before discussing those that are specific to each.

**Acute leukemia (AL)** by definition is “usually an aggressive clonal malignant transformation involving the hemopoietic stem cells and characterized by uncontrolled proliferation of blasts in the BM with spillage into the peripheral blood & variable infiltration of other organs.”

**Etiology of AL**

Several factors have been linked to the occurrence of AL including

I. **Environmental Agents**

A. **Ionizing Radiation**

Exposure to atomic bomb explosions is associated with increased incidence of AL; at particularly high risk are those who are closer to the hypocenter. The predominant type is AML though ALL is reported in younger individuals. Exposure to diagnostic X-rays or radioisotopes at diagnostic levels (low dose) does not increase the risk. Infants whose mothers were exposed to X-rays during pregnancy are at higher risk.

B. **Chemicals**

Exposure to the following has been noted to be associated with a higher incidence

- **Benzene**
  - Benzene and other petroleum derivatives
  - Shoe makers and plastic glues
  - Handling buses and trucks

- **Alkylating agents**: (cytotoxic drugs used in the treatment of certain malignancies)

II. **Host susceptibility to AL is determined by**

A. **Genetic factors**

- If one identical twin is affected, the other twin has a 20% chance of developing ALL.
- Those with Down's syndrome have 10-30 fold increase risk (> 3y; lymphoid, < 3y; myeloid).
- Patients with Blooms syndrome, Fanconi anemia & Ataxia telangiectasia are known to be associated with increased risk.

B. **Acquired factors; their role is supported by the observations that AL show increased incidence in association with the following**

- Myelodysplasia (myelodysplastic syndrome; MDS).
- after chemotherapy ± radiotherapy (Secondary AML)
- Chronic myeloproliferative disorders (CML, PRV, and MF).
- Aplastic anemia.
- Paroxysmal nocturnal hemoglobinuria.

III. **Oncogenic viruses:** there is no good evidence except for HTLV-1, which may cause adult T-cell leukemia/lymphoma.

IV. **Others:** there is a significant correlation between infants with AL and

- Alcohol intake, smoking, & exposure to benzene and petroleum derivatives of their mothers during pregnancy.
- Infants whose mothers have had a history of at least two previous abortions. This may increase the relative risk of AL 25 × times.
Pathophysiology of Acute Leukemias

- In acute leukemia there is a block in differentiation. This leads to the accumulation of immature leukemic blasts in the bone marrow, which suppress the function of normal hematopoietic stem cells by physical displacement and other poorly understood mechanisms.
- Eventually bone marrow failure results, which accounts for the major clinical manifestations of acute leukemia.

The acute leukemias have the following clinical characteristics:

- Variable age of onset: ALs can occur at any age, however, childhood AL (age <15 years) is usually lymphoblastic (80%) whereas adult AL (age >15 years) is usually myeloblastic (80%).
- Abrupt stormy onset especially in children
- Symptoms related to depression of normal marrow function. These include
  - fatigue (due mainly to anemia)
  - fever (reflecting infections resulting from the absence of mature leukocytes)
  - bleeding (petechiae, ecchymoses, epistaxis, gum bleeding) secondary to thrombocytopenia.
- Bone pain and tenderness the result from marrow expansion and infiltration of the subperiosteum.
- Arthralgia, testicular involvement (more common in ALL), gum infiltration (more common in AML). (Fig. 3-11)
- Generalized lymphadenopathy, splenomegaly, and hepatomegaly. These reflect dissemination of the leukemic cells, and are more pronounced in ALL than in AML.
- Central nervous system manifestations. These include headache, vomiting, and nerve palsy's resulting from meningeal spread; these features are more common in children than in adults and are more common in ALL than AML.

Laboratory diagnosis of Acute Leukemias

- The diagnosis of acute leukemia rests on the identification of blast forms in the peripheral blood and the bone marrow.
- It is based on the presence of ≥ 20 % blasts in the BM and/or peripheral blood. However; it can be diagnosed with even < 20 % blasts if specific leukemia-associated cytogenetic or molecular genetic abnormalities are present.
- Because of different responses to therapy, it is of great practical importance to distinguish ALL from AML. The nuclei of lymphoblasts in Wright-Giemsa-stained preparations have somewhat coarse and clumped chromatin and one or two nucleoli; myeloblasts tend to have finer chromatin and more cytoplasm, which may contain granules (Fig. 3-12). The cytoplasm of lymphoblasts often contains large aggregates of periodic acid-Schiff-positive material, whereas myeloblasts are often peroxidase positive. ALL: is negative for Myeloperoxidase, Sudan Black B, and Non-specific esterases. But positive in many cases with Periodic acid schiff is (PAS). Conversely, AML is positive for Myeloperoxidase, Sudan Black B, and Non-specific esterases. PAS is positive only in AML-M6.
- Blood film:
  - may show high WBC count (due to spillage of blasts) or low count (blasts may be present or absent). The white cell count is variable; it is sometimes elevated to more than 100,000 cells/µL, but in about 50% of patients it is less than 10,000 cells/µL.
  - Uncommonly the peripheral blood examination shows pancytopenia but no blasts (aleukemic leukemia); here, the diagnosis can only be established by examining the bone marrow.
  - Anemia is almost always present, and the platelet count is usually below 100,000 platelets/µL.
  - Neutropenia is also a common finding in the peripheral blood. Bone marrow aspirate is necessary to confirm the diagnosis (especially when low counts).
- Bone marrow trephine biopsy is only essential when:
  1. BM aspirate is inadequate; this is commonly, due to increased reticulin fibers.
  2. To distinguish whether a poor aspirate is due to hypocellularity or persistent leukemia.

Investigations
Hematological: see above

Biochemical tests may reveal increased S. uric acid, S. LDH, and hypercalcemia.

Liver & Renal Function Tests are performed as a baseline before treatment begins.

Radiological Examination may reveal,
- Lytic bone lesions.
- Mediastinal widening caused by enlargement of the thymus &/or mediastinal lymphadenopathy.

CSF examination may show blast cells, indicating CNS involvement.
Cytology is useful if the leukemia is not obviously myeloid.
Immunophenotyping is indicated in all patients in whom the leukemia is not obviously myeloid.
Cytogenetic analysis is essential in all patients, best performed on bone marrow aspirate.

Classification of acute leukemia

This is based on
1. Morphology of blasts
2. Cytochemistry through the use of special stains like; SBB, PAS, MPO, Estrases…etc
3. Immunophenotyping (cell surface marker analysis by flow cytometry).
4. Cytogenetic analysis
5. Molecular genetic analysis

Morphological classification
I. French American British (FAB) classification (1976)
A. Acute Lymphoid Leukemia (ALL) is classified into three subtypes depending on the morphology of the constituent blasts. L1, L2 & L3 (Fig. 3-13):
B. Acute Myeloid Leukemia (AML) is classified into eight subtypes:
   - M0: AML with minimal evidence of myeloid differentiation
   - M1: AML without maturation (Fig. 3-14)
   - M2: AML with maturation
   - M3: Acute promyelocytic leukemia
   - M4: Acute myelomonocytic leukemia
   - M5: Acute monoblastic M5a/monocytic M5b leukemia
   - M6: Acute erythroleukemia
   - M7: Acute megakaryoblastic leukemia

II. WHO classification (2000 & 2002)
There was a consensus that FAB L1, L2, L3 of ALL are no longer relevant, since L1 & L2 morphology do not predict immunophenotype, genetic abnormalities, or clinical behavior. ALL- L3 is generally equivalent to Burkitt lymphoma in leukemic phase and should be diagnosed as such.

The WHO Classification of AML (2002): had reduced the blast threshold for diagnosis from 30% (in FAB classification) to 20% in the peripheral blood and /or BM. In addition, patients with certain clonal, recurrent cytogenetic abnormalities should be considered to have AML regardless the blast percentage.

Immunophenotyping AL
This is very useful in subtyping ALL and distinguishing them from AML. Terminal deoxytransferase (TdT) is an enzyme specifically expressed in pre-B and pre-T cells. Further subtyping of ALL into pre-B- and pre-T-cell types relies on lineage-specific markers, such as CD19 (B cell) and CD3 (T cell). The most specific myeloid marker is anti-MPO followed by CD117.

Karyotyping of AL
ALL: the most common karyotypic abnormalities in pre-B-cell tumors is hyperploidy (>50 chromosomes/cell), which is associated with t(12: 21) chromosomal translocation involving the TEL1 and AML1 genes. The
presence of these aberrations correlates with a good outcome. Poor outcomes are observed with pre-B-cell tumors that have translocations involving the MLL gene on chromosome 11q23 or the Philadelphia (Ph) chromosome.


**Course & Prognosis of AL**
If untreated, patients will only survive for few months, and they will usually die either of severe infection or bleeding due to progressive and relentless marrow replacement by blast cells. Factors affecting prognosis in acute leukemia are shown in

Treatment of lymphoblastic tumors of childhood represents one of the great success stories in oncology. Children 2 to 10 years of age have the best prognosis; most can be cured. Other groups of patients do less well.

**THE CHRONIC LYMPHOID LEUKEMIA**
A number of disorders are included in this group characterized by accumulation in the blood of mature lymphocytes of either B- or T- cell type. In general the diseases are incurable but tend to run a chronic and fluctuating course.

**Diagnosis**
This group is characterized by a chronic persistent lymphocytosis. Subtypes are distinguished by:

1. Morphology.
2. Immunophenotype.
3. Cytogenetics
4. DNA analysis may be useful in showing a monoclonal rearrangement of either Ig or TCR genes.

**Chronic Lymphocytic Leukemia (CLL)**
CLL is a low grade clonal lymphoproliferative disorder characterized by progressive accumulation of usually well-differentiated CD5+ lymphocytes in the marrow with an accompanying peripheral lymphocytosis. Arbitrarily, if the peripheral blood lymphocytosis exceeds 4000-5000 cells/mm³, the patient is diagnosed with chronic lymphocytic leukemia (CLL); if not, a diagnosis of small lymphocytic lymphoma (SLL) is made. Involvement of LN, spleen and liver invariably occurs sometimes during the disease course. The etiology is unknown. There is seven-fold increased risk of CLL in the close relatives of the patient. CLL is the most common leukemia of adults in the western world. For unclear reasons, both CLL and SLL are much less common in Asia.

**Clinical features of CLL**
1. The majority of patients are over 50 years (peak 60-80). The M: F ratio is about 2:1.
2. Most cases are diagnosed when routine blood test is performed.
3. Lymphadenopathy: Symmetrical enlargement of cervical, axillary or inguinal LNs is usually discrete and non-tender.
4. Features of anemia & thrombocytopenia may be present.
5. Splenomegaly and less commonly hepatomegaly are common in later stages.
6. Immunosuppression is a significant problem resulting from:
   a. Hypogammaglobulinemia and
   b. Cellular immune dysfunction.
   Early bacterial infections predominate but with advanced disease viral and fungal infections such as herpes zoster are also seen.

**Laboratory findings**
- **Lymphocytosis**: the absolute lymphocyte count is > 5 × 10⁹/L (up to 300 × 10⁹/L or more). The predominant cells are compact, small, resting lymphocytes with dark-staining round nuclei, scanty cytoplasm, and little variation in size (Fig. 3-15). The neoplastic lymphocytes are fragile and are frequently disrupted during the preparation of smears, which produces characteristic *smudge cells*. Variable numbers of larger activated lymphocytes are also usually present in the blood smear.
- **Anemia** is seen in later stages due to BM failure, or hypersplenism. AIHA and nutritional deficiencies may also occur.
- **Thrombocytopenia** seen in later stages due to BM failure, hypersplenism or autoimmune process.
• **BM examination** shows lymphocyte infiltration >30 % of all nucleated marrow cells. BM biopsy pattern of involvement reveals interstitial, nodular, mixed (nodular & interstitial) and diffuse.

• **Serum Ig reduction** becomes more marked with advanced disease.

**Immunophenotype, Karyotype, and Molecular Features**

CLL/SLL is a neoplasm of mature B cells expressing the pan-B-cell markers CD19, CD20, and CD23 and surface immunoglobulin heavy and light chains. The tumor cells also express CD5. Approximately 50% of patients have karyotypic abnormalities, the most common of which are trisomy 12 and deletions of chromosomes 11 and 12. Unlike other lymphoid neoplasms, chromosomal translocations are rare.

**Staging of CLL**

It is useful to stage patients at presentation both for prognosis and for deciding on therapy. The stage is determined by several variables such as peripheral lymphocyte count, presence or absence of lymphadenopathy, hepatosplenomegaly, anemia & thrombocytopenia.

**Course & prognosis**

- Many patients never need therapy.
- CLL may transform to:
  - Prolymphocytic leukemia that are resistant to treatment.
  - Richter's transformation (Immunoblastic lymphoma, localized high grade NHL)

**Prolymphocytic leukemia**

The prolymphocyte is around twice the size of a CLL lymphocyte and has a larger central nucleolus. It typically presents with splenomegaly without lymphadenopathy and with a high and rapidly rising lymphocyte count. Anemia is a poor prognostic feature. Response to treatment is poor.

**Hairy cell leukemia**

This B-cell neoplasm has a peak incidence at 40-60 years with M: F ratio of about 4:1. Patients typically present with infections, anemia or splenomegaly. Lymphadenopathy is very uncommon. The peripheral blood shows pancytopenia with monocytopenia. The latter is a distinctive feature. Lymphocyte count is rarely > 20 × 10⁹/L. The blood film reveals a variable number of unusually large lymphocytes with villous cytoplasmic projections (Fig. 3-16). BM biopsy; shows a characteristic appearance of mild fibrosis and a loose diffuse cellular infiltrate.

**CLASSIC CHRONIC MYELOPROLIFERATIVE NEOPLASMS (MPN)**

This term covers a group of clonal disorders of the hematopoietic stem cells that lead to effective proliferation of one or more hemopoietic component in the BM, and in many cases, in the liver and spleen leading to an elevated blood levels of one or more cell lines (i.e., erythrocytosis, leukocytosis, and thrombocytosis). Come under this heading are

1. Chronic myeloid leukemia (CML - Ph+ve)
2. Polycythemia vera (PV)
3. Essential thrombocytemia (ET)
4. Primary myelofibrosis (MF)

These disorders are closely related to each other and transitional forms and evolution from one entity into another occurs during the course of the disease.

**Karyotype, and Molecular Features**

- The vast majority of CML (90-95%) show t(9;22) (Philadelphia chromosome) & M-BCR-ABL p210 (99%).
- Nearly all PV patients, and about 50% of ET and MF cases show a single acquired mutation of cytoplasmic Janus-Associated Kinase 2 (JAK2) that occurs in the BM and in the peripheral blood granulocytes. This mutation is not found in secondary polycythemia, or reactive thrombocytosis. JAK2 plays a major role in normal myeloid development. It does not appear to be the initiating mutation.

**Polycythemia**
Polycythemia (erythrocytosis): is an increase in the Hb concentration above the upper limit of normal for the patient's age and sex in specific population. It is classified according to its pathophysiology

A. Absolute
1. Primary
   - Polycythemia (rubra) vera
   - Familial (congenital) Polycythemia.
2. Secondary
   Caused by compensatory erythropoietin increase in:
   - High altitudes
   - Pulmonary disease and alveolar hypoventilation (sleep apnoea)
   - Cardiovascular disease, especially congenital with cyanosis.
   - Increased affinity hemoglobin (familial Polycythemia).
   - Heavy cigarette smoking
   Caused by inappropriate erythropoietin increase in:
   - Renal diseases (e.g. hydronephrosis, vascular impairment, cysts, carcinoma)
   - Tumors (such as uterine leimmoma, renal cell ca., hepatocellular carcinoma, cerebellar hemangiochroma).

B. Relative
Stress or pseudopolycythemia:
   - Cigarette smoking
   - Dehydration: water deprivation, vomiting.
   - Plasma loss: burns, enteropathy.

Polycythemia rubra vera (PV) is an insidious clonal MPN characterized by generalized hyperplasia of all marrow elements, but dominated by expansion of the red blood cell mass. Although the diagnostic finding is the increase in red cell volume, in many patients there is also an over production of granulocytes and platelets. The disease is of older subjects with equal sex incidence. The clinical features are the result of hyperviscosity, hypervolemia or hypermetabolism; these include headache, dyspnea, blurred vision, pruritis, characteristically after hot bath, plethoric appearance (Fig. 3-17). Splenomegaly occurs in 75% of patients. Hypertension occurs in one-third of patients. The course may be complicated by hemorrhage, thrombosis, gout (Fig. 3-18) & peptic ulceration. Typically, the prognosis is good with a median survival of 10-16 years. Thrombosis and hemorrhage are the major clinical problems. Transition from PV to MF and AL may occur.

Essential thrombocytopenia (ET) is characterized by a sustained increase in platelet count, because of megakaryocytic proliferation and overproduction of platelets. There is endogenous megakaryocyte and possibly erythroid colony growth independent of thrombopoietin or erythropoietin. Myelopoiesis is polyclonal in many cases of ET.

A persisting platelet count > 400 × 10^9/L is the central diagnostic feature but other causes of raised platelet count need to be fully excluded before the diagnosis can be made. Many cases are symptomless and diagnosed on routine blood counts. Thrombosis may occur in venous or arterial systems & is a risk in about 25% of the patients (Fig. 3-19). Hemorrhage as a result of abnormal platelet function, may cause either chronic or acute bleeding. Up to 40% of patients will have palpable splenomegaly, whereas in others there may be splenic atrophy because of infarction. Often the disease is stationary for 10-20 years or more but eventually transforms to MF, AL and PV.

Myelofibrosis (Idiopathic Myelofibrosis) (IMF)
MF is a clonal MPN of the pluripotent hemopoietic stem cell, characterized by proliferation of multiple cell lineages and accompanied by progressive BM fibrosis, with development of hemopoiesis in the spleen and liver. The onset is insidious with symptoms of anemia. One-third or more of the patients have previous history of PV. Massive splenomegaly is the main physical sign.

Laboratory findings
1. Anemia is usual (but a normal or increased Hb level may be found in some patients).
2. The WBC and platelet counts are frequently high at presentation but later in the course of the disease, leucopenia and thrombocytopenia are common.
3. A leukoerythroblastic blood film is found. The red cells show characteristic 'tear-drop' poikilocytes (Fig. 3-20).
4. BM is usually unobtainable by aspiration (dry tap). Trephine biopsy shows hypercellular marrow with extensive marrow fibrosis. Increased megakaryocytes are frequently seen (Fig. 3-21).
5. In 10% of cases there is increased bone formation with increased bone density on X-ray.
6. Neutrophil alkaline phosphotase (NAP) score is usually increased.
7. High serum uric acid and LDH levels.

Course & prognosis
MF has the poorest prognosis of the MPNs; the median survival is 3-5 years (range 1-15 years). Causes of death include: heart failure, infection and in 10-20% of cases transformation to AML.

Chronic myeloid leukemia (CML) (Chronic Myelogenous Leukemia)
CML is a clonal acquired genetic change in a pluripotential hemopoietic stem cell, which proliferates and generates a population of differentiated cells that gradually replaces normal hemopoiesis and leads to a greatly expanded total myeloid mass. CML represents about 15% of leukemias. In the study of CML Philadelphia (Ph) chromosome was discovered (in 1960), which is found in about 90-95% of patients. Ph chromosome is a minute chromosome 22 from which the long arms are deleted (22q-). It is part of reciprocal translocation between chromosome 9 & 22 t(9;22) in which part of 22 is clearly visible on 9 but the part of 9 on 22 is too small to be distinguished cytogenetically. The next discovery (in 1986) was the characterization of the BCR-ABL chimeric gene (found in 99% of patients).

CML usually passes into 3 phases during its course:
A. Chronic Phase (CP),
B. Accelerated Phase (AP),
C. Blastic Phase (BP).
The Chronic phase usually lasts 2-7 years and in 50% of cases it is transformed to blastic phase directly. The peak incidence is usually between 40-60 years. In up to 50% of cases the diagnosis is made incidentally from a routine blood count (asymptomatic). There may be features of anemia (pallor, dyspnoea, and tachycardia) & of abnormal platelet function (bruising, epistaxis, menorrhagia, etc). Splenomegaly is nearly always present and is frequently massive. Gout & renal impairment (caused by hyperuricemia) may occur.

Lab findings
- Anemia; usually normochromic normocytic.
- Leukocytosis; usually in the range of 20-200 ×10^9/l, occasional patients may present with leukocytosis of 200-800 ×10^9/l, causing features of hyperviscosity.
- Blood film shows a full spectrum of granulocytic cells, ranging from blast forms (usually 2-10%) to mature neutrophils, with intermediate myelocytes & neutrophils predominating (Fig. 3-22).
- The percentages of eosinophils & basophils are usually increased.
- Platelet numbers are usually increased in the range of 300-600 ×10^9/l, but may be normal or decreased.
- Ph chromosome is positive.

BM Aspirate:
- Markedly hypercellular marrow
- Blast cells < 12% of ANC.
- Eosinophils & basophils are usually prominent.
- Megakaryocytes are small, hypolobed and increased in numbers.

BM Biopsy:
- Shows complete loss of fat spaces due to dense hypercellularity

The clinical features is quite variable
- Asymptomatic; the diagnosis is based entirely on blood and marrow findings.
- Patients may develop fever, excessive sweating, anorexia and weight loss or bone pain.
• Occasionally, patients present with generalized lymphadenopathy; LN biopsy shows nodal infiltration with blast cells that may be myeloid or lymphoid.
• Localized skin infiltrates may be seen. Discrete masses of immature leukemia cells may develop at almost any site; these are sometimes referred to as "Chloromas" or "Granulocytic Sarcomas".

Course & prognosis
• Patients with CML-CP usually show an excellent response with prolonged survival by imatinib. Responders to imatinib may never relapse.
• Transformation to acute leukemia.
• Death usually occurs from terminal blastic transformation or intercurrent hemorrhage or infection.

MYELODYSPLASTIC SYNDROME (MDS)
MDS is a group of clonal disorders of multipotent hemopoietic stem cells which are characterized by increasing BM failure with quantitative and qualitative abnormalities of megakaryocytes, erythroid and myeloid cells.

MDS is either primary or secondary to chemotherapy ± radiotherapy.

Pathogenesis
MDS is presumed to start following genetic damage to multipotent hemopoietic progenitor cell, leading to increased stem cell proliferation but ineffective differentiation and maturation, resulting in a hypercellular BM with peripheral blood pancytopenia; this is the hallmark of the disease.

Clinically over half of patients are >70 years with slight male predominance. The evolution is often slow. The patients may present with anemia (transfusion-dependent), recurrent infections (neutrophils and monocytes are often functionally impaired) & easy bruising or bleeding (platelets are often functionally impaired). The spleen is not usually enlarged.

Lab. findings
A. Peripheral Blood:
• Pancytopenia is frequent
• Anemia; is usually macrocytic or dimorphic but occasionally hypochromic.
• Granulocytes are often decreased in number and frequently lack granulation
• Pelger abnormality (neutrophil with single or bilobed nucleus) is often present.
• Platelets may be improperly large or small and are usually decreased in number.
• Myeloblasts in variable numbers are present in poor prognosis cases.

B. Bone Marrow:
• Usually hypercellular but is hypocellular in 10-20% of cases. Marked fibrosis occurs in <10%.
• Multinucleate normoblasts and other dyserythropoietic features are seen.
• Ring sideroblasts may be seen.
• Granulocyte precursors show defective granulation.
• Megakaryocytes are abnormal (micronuclear, small binuclear or polynuclear).

At least 10% of the cells in a lineage should be dysplastic in order to consider the diagnosis of MDS.

MDS is classified into
1. Refractory anemia (RA): the dysplasia is present solely in RC.
2. Refractory cytopenias with multilineage dysplasia (RCMD): Bi- or pan-cytopenia, dysplasia is present in ≥ 2 myeloid lineages.
3. Refractory anemia with ringed-sideroblasts (RARS): RA with > 15% ringed sideroblasts in BM.
4. RCMD & ringed sideroblasts: combines the above two categories.
5. RA with excess blasts (RAEB) : (poor prognosis)
6. MDS-Unclassified: PB: Cytopenias; no blasts or Auer rods; the BM shows myeloid or megakaryocytic dysplasia; Blasts <5%.
7. MDS associated with isolated del (5q) (good prognosis)
The patients are also divided into low & high risk groups that require different management. The low-risk group is those with < 5% blasts in BM, only one cytopenia and favorable cytogenetics. The high-risk group shows ≥ 5% BM blasts and often unfavorable cytogenetics and pancytopenia.

**PLASMA CELL DYSCRASIAS**

These originate from a clone of B cells that differentiates into plasma cells and secretes a single complete or partial immunoglobulin. In these conditions the serum usually contains excessive amounts of immunoglobulins; these disorders are also called monoclonal gammopathies, and the associated immunoglobulin is referred to as an M protein. It should be noted, however, the presence of an M component is not necessarily an indication of an overt B-cell malignancy; M components are fairly common in otherwise normal elderly persons & in a condition called monoclonal gammopathy of undetermined significance.

Plasma cell dyscrasias are most common in middle-aged and elderly persons.

*The plasma cell dyscrasias can be divided into six major variants:*

1. multiple myeloma
2. localized plasmacytoma (solitary myeloma)
3. lymphoplasmacytic lymphoma
4. heavy-chain disease
5. primary or immunocyte-associated amyloidosis, and
6. monoclonal gammopathy of undetermined significance.

In all forms, the immunoglobulin genes are somatically hypermutated, consistent with an origin from a post-follicular center B cell.

**Multiple Myeloma (MM)** is the most common of the malignant plasma cell dyscrasias. It is a clonal proliferation of neoplastic plasma cells in the bone marrow that is usually associated with *multifocal lytic lesions throughout the skeletal system.* Many myelomas have chromosomal translocations involving the IgH locus on chromosome 14. The identified fusion partners include the cyclin D1, fibroblast growth factor receptor 3, and cyclin D3 genes. Dysregulation of D cyclins seems to be of general importance in multiple myeloma. The most common M component is IgG (60%), followed by IgA (20% to 25%). In the remaining 15% to 20% of cases, the plasma cells produce only κ or λ light chains. Because of their low molecular weight, the free light chains are rapidly excreted in the urine, where they are termed *Bence-Jones proteins.* Even more commonly, malignant plasma cells secrete complete immunoglobulin molecules and free light chains and thus produce both serum M components and Bence-Jones proteins. The excess light chains have adverse effects on renal function.

**Localized Plasmacytomas** are solitary lesions involving the skeleton or the soft tissues. Extrasosseous lesions occur mainly in the upper respiratory tract (sinuses, nasopharynx, larynx). Most of those with solitary skeletal plasmacytomas develop full-blown multiple myeloma over a period of 5 to 10 years.

**Lymphoplasmacytic Lymphoma** is composed of a mixed proliferation of B cells that range from small round lymphocytes to plasmacytic lymphocytes to plasma cells. It behaves like an *indolent B-cell lymphoma* and commonly involves multiple lymph nodes, the bone marrow, and the spleen at the time of presentation. It is included in the plasma cell dyscrasias because the tumor produces an M component, but, unlike multiple myeloma, it consists in most cases of IgM. Often, the large amount of IgM causes the blood to become viscous, producing a syndrome called *Waldenström macroglobulinemia.*

**Heavy-Chain Disease** is not a specific entity but a group of proliferations in which only heavy chains are produced, most commonly IgA. IgA heavy-chain disease shows a predilection for the lymphoid tissues where IgA is normally produced, such as the small intestine and respiratory tract.

**Primary or Immunocyte-Associated Amyloidosis** is due to monoclonal proliferation of plasma cells that secrete free light chains. The amyloid deposits (of AL type) consist of partially degraded light chains.

**Monoclonal Gammopathy of Undetermined Significance (MGUS)** refers to monoclonal gammopathies that are detected in asymptomatic individuals. M proteins are found in the serum of 1% to 3% of asymptomatic healthy persons older than age 50 years, making this the most common plasma cell dyscrasia. Despite the name, it appears that *MGUS is a precursor lesion that should be considered a form of neoplasia.* Patients with MGUS develop a well-defined plasma cell dyscrasia (myeloma, lymphoplasmacytic lymphoma, or amyloidosis) at a rate of 1% per year. Moreover, MGUS cells often contain the same chromosomal translocations that are found...
in full-blown multiple myeloma. Thus, the diagnosis of MGUS should be made with caution and only after careful exclusion of all other forms of monoclonal gammopathies, particularly multiple myeloma.

**Gross features**

- Multiple myeloma presents most often as multifocal destructive bone lesions throughout the skeletal system. The following bones are affected in descending order of frequency:
  - vertebral column 65%
  - ribs, 45%
  - skull, 40%
  - pelvis, 30%
  - femur, 25%

- These focal lesions generally begin in the medullary cavity, erode the cancellous bone, and progressively destroy the cortical bone. The bone resorption results from the secretion of certain cytokines (e.g., IL-1β, tumor necrosis factor, IL-6) by myeloma cells. These cytokines stimulate production of another cytokine called RANK-ligand, which promotes the differentiation and activation of osteoclasts. There are often **pathologic fractures**, which occur most frequently in the vertebral column. The bone lesions usually appear radiographically as **punched-out defects** of 1 to 4 cm in diameter (Fig. 3-23), but in some cases diffuse skeletal demineralization is evident.

**Microscopic features**

- BM examination reveals an increased number of plasma cells, which constitute 10% to 90% of the cellularity.
- The neoplastic cells can resemble normal mature plasma cells, but they more often show abnormal features, such as prominent nucleoli or abnormal cytoplasmic inclusions containing immunoglobulin (Fig. 3-24).
- With progressive disease, plasma cell infiltrations of soft tissues can be encountered in the spleen, liver, kidneys, lungs, and lymph nodes.
- Terminally, a leukemic picture may emerge.

**Myeloma nephrosis** refers to **renal** involvement; it is a distinctive feature of multiple myeloma.

- Proteinaceous casts are prominent in the distal convoluted tubules and collecting ducts. Most of these casts are made up of Bence-Jones proteins.
- Some casts have tinctorial properties of amyloid.
- Multinucleate giant cells created by the fusion of infiltrating macrophages usually surround the casts.
- Very often the epithelial cells lining the cast-filled tubules become necrotic or atrophic because of the toxic actions of the Bence-Jones proteins.
- Pyelonephritis can also occur as a result of the increased susceptibility to bacterial infections. Less commonly, interstitial infiltrates of abnormal plasma cells are seen.

**Metastatic calcification** stemming from bone resorption and hypercalcemia may be encountered. The clinical manifestations of the plasma cell dyscrasias result from

1. The destructive effect of the infiltrating neoplastic cells in various tissues and
2. The abnormal immunoglobulins secreted by the tumors.

In multiple myeloma the destructive effects of plasma cell tumors predominate, whereas in lymphoplasmacytic lymphoma most of the signs and symptoms result from the IgM macroglobulins in the serum.

**Bone pain**, resulting from infiltration by neoplastic plasma cells, is extremely common.

**Pathologic fractures and hypercalcemia** occur, with focal bone destruction and diffuse resorption. Hypercalcemia can cause neurologic manifestations such as confusion and lethargy; it also contributes to renal disease. Generalized osteoporosis occurs in 20%.

**Anemia** results from marrow replacement as well as from inhibition of hematopoiesis by tumor cells.

**Recurrent infections** with bacteria are serious clinical problems. They result from severe suppression of normal immunoglobulin secretion.

**Hyperviscosity syndrome** may occur due to excessive production and aggregation of myeloma proteins, but this is much more characteristic of lymphoplasmacytic lymphoma.
• **Renal insufficiency** occurs in as many as 50% of patients. It results from multiple conditions, such as recurrent bacterial infections and hypercalcemia, but most importantly from the toxic effects of Bence-Jones proteins on cells lining the tubules.

• **Amyloidosis** develops in 5% to 10% of patients.

• There is usually high **ESR** and C-reactive protein.

**Diagnosis of multiple myeloma** depends on three principal findings:
1. Monoclonal protein in serum and/or urine.
2. Increased plasma cells in the bone marrow.
3. Complications related to organ or tissue infiltrations such as bone disease, renal impairment, anemia, hypercalcemia, hyperviscosity, amyloidosis or recurrent infection.

• The diagnosis is strongly suspected when the characteristic focal, punched-out radiologic defects in the bone are present—especially when located in the vertebrae or calvarium.

• Electrophoresis of the serum and urine is an important diagnostic tool. In 99% of cases a monoclonal spike of complete immunoglobulin or immunoglobulin light chain (IgG in 60%, IgA in 20% and light chain only in the rest) can be detected in the serum, in the urine, or in both.

• Examination of the bone marrow is used to confirm the presence of a plasma cell proliferation. Bone marrow shows increased plasma cells (usually > 20%) often with abnormal forms (**Fig. 3-25**).

• Other features
  - Abnormal plasma cells appear in the blood film in 15% of cases.
  - Anemia is usually normochromic normocytic or macrocytic. Rouleaux formation is marked (**Fig. 3-26**).

**Prognosis**
Multiple myeloma is a progressive disease; with median survival without intensive chemotherapy of 3 - 4 years. Although aggressive therapies are being tried the disease is presently curable.

**BLEEDING DISORDERS:** (HEMORRHAGIC DIATESES)

*Excessive bleeding can result from:*
1. Increased fragility of vessels
2. Platelet deficiency or dysfunction
3. Derangement of coagulation
4. Combinations of these

*Tests used to evaluate different aspects of hemostasis include*
- **Bleeding time**: this measures the time taken for a standardized skin puncture to stop bleeding and provides an in vivo assessment of platelet response to limited vascular injury. The reference range depends on the actual method employed and varies from 2 to 9 minutes. Prolongation generally indicates a reduced platelet count (thrombocytopenia) or dysfunction.

- **Platelet counts**: these are obtained from anticoagulated blood using an electronic particle counter. The reference range is 150 to 300 × 10^3/µL.

- **Prothrombin time (PT)**: this assesses the extrinsic and common coagulation pathways. A prolonged PT can result from deficiency or dysfunction of factor V, factor VII, factor X, prothrombin, or fibrinogen.

- **Partial thromboplastin time (PTT)**: this assesses the intrinsic and common clotting pathways. Prolongation of the PTT can be due to deficiency or dysfunction of factor V, VIII, IX, X, XI, or XII, prothrombin, or fibrinogen.

**BLEEDING DISORDERS CAUSED BY VESSEL WALL ABNORMALITIES**

Disorders within this category, sometimes called *nonthrombocytopenic purpuras*, are relatively common but do not usually cause serious bleeding problems. Most often, they induce small hemorrhages (petechiae and purpura) in the skin or mucous membranes, (particularly the gingivae). The platelet count, bleeding time, and results of the coagulation tests (PT, PTT) are usually normal. (Fig. 3-27)

**Conditions in which hemorrhages can be related to abnormalities in the vessel wall include the following:**

1. **Infections**: many infections induce petechial and purpuric hemorrhages, but especially implicated are
   - a. meningococcemia
   - b. other forms of septicemia
   - c. infective endocarditis
   - d. several of the rickettsioses.

   The involved mechanism is presumably microbial damage to the microvasculature (vasculitis) or disseminated intravascular coagulation (DIC).

2. **Drug reactions** sometimes induce cutaneous petechiae and purpura without causing thrombocytopenia. In many instances, the vascular injury is mediated by drug-induced antibodies and deposition of immune complexes in the vessel walls, leading to hypersensitivity (leukocytoclastic) vasculitis.

3. **Scurvy and Cushing syndrome** are both associated with microvascular bleeding resulting from impaired formation of collagens needed for the support of blood vessel wall.

4. **Henoch-Schönlein purpura** is a systemic hypersensitivity disease of unknown cause characterized by a purpuric rash, colicky abdominal pain (presumably due to focal hemorrhages into the gastrointestinal tract), polyarthralgia, and acute glomerulonephritis. All these changes result from the deposition of circulating immune complexes within vessels throughout the body and within the glomerular mesangial regions.

5. **Hereditary hemorrhagic telangiectasia** is an autosomal dominant disorder characterized by dilated, tortuous blood vessels with thin walls that bleed readily. (Fig. 3-28)

**BLEEDING RELATED TO REDUCED PLATELET NUMBER (THROMBOCYTOPENIA)**

A count below 100,000/µL is generally considered to constitute thrombocytopenia.

Bleeding resulting from thrombocytopenia alone is associated with a prolonged bleeding time and normal PT and PTT. Platelet counts in the range of 20,000 to 50,000 cells/µL are associated with an increased risk of post-traumatic bleeding, and spontaneous bleeding becomes evident when counts fall below 20,000 cells/µL. Most bleeding tends to occur from small, superficial blood vessels and produces petechiae or large ecchymoses in the skin, the mucous membranes of the gastrointestinal and urinary tracts, and other sites. Larger hemorrhages into the central nervous system are a major hazard in patients with markedly depressed platelet counts.

**Thrombocytopenia can be due to one of the following four major categories:**

1. **Decreased production of platelets**: this can accompany generalized diseases of bone marrow such as aplastic anemia and leukemias or result from diseases that affect the megakaryocytes somewhat selectively. In vitamin B12 or folic acid deficiency, there is poor development and accelerated destruction of megakaryocytes within the bone marrow (ineffective megakaryopoiesis) because DNA synthesis is impaired.
2. **Decreased platelet survival:** this is an important cause of thrombocytopenia & can have an immunologic or nonimmunologic etiology.

   a. **Immune thrombocytopenia:** the platelet destruction is caused by circulating antiplatelet antibodies or, less often, immune complexes. The antiplatelet antibodies can be directed against a self-antigen on the platelets (autoantibodies) or against platelet antigens that differ among different individuals (alloantibodies). *Alloimmune thrombocytopenias* arise when an individual is exposed to platelets of another person, as may occur after blood transfusion or during pregnancy. In the latter case, neonatal, sometimes fetal, thrombocytopenia occurs by a mechanism analogous to erythroblastosis fetalis.

   b. **Nonimmunologic thrombocytopenia:** the destruction of platelets may be caused by mechanical injury, in a manner analogous to red cell destruction in microangiopathic hemolytic anemia. The underlying conditions are also similar, including prosthetic heart valves and diffuse narrowing of the microvessels (e.g., in malignant hypertension).

3. **Sequestration of platelets:** thrombocytopenia, usually moderate in severity, may develop in any patient with marked splenomegaly, a condition sometimes referred to as *hypersplenic thrombocytopenia*. The spleen normally sequesters 30% to 40% of the body's platelets, which remain in equilibrium with the circulating pool. When necessary, this condition can be ameliorated by splenectomy.

4. **Dilutional thrombocytopenia:** massive transfusions can produce a dilutional thrombocytopenia. Blood stored for longer than 24 hours contains virtually no viable platelets; thus, plasma volume and red cell mass are reconstituted by transfusion, but the number of circulating platelets is relatively reduced.

**Immune Thrombocytopenic Purpura (ITP)**

ITP can occur in:
- The setting of a variety of conditions and exposures (secondary ITP) or
- In the absence of any known risk factors (primary or idiopathic ITP).

There are two clinical subtypes of primary ITP: acute and chronic; both are autoimmune disorders in which platelet destruction results from the formation of antiplatelet autoantibodies.

**Chronic ITP:**

Chronic ITP is caused by the formation of autoantibodies against platelet membrane glycoproteins. Antibodies reactive with these membrane glycoproteins can be demonstrated in the plasma as well as bound to the platelet surface (platelet-associated immunoglobulins) in approximately 80% of patients. In the overwhelming majority of cases, the antiplatelet antibodies are of the IgG class. The mechanism of platelet destruction is as follows:
- Opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system.
- About 75% to 80% of patients are remarkably improved after splenectomy, indicating that the spleen is the major site of removal of sensitized platelets. Since it is also an important site of autoantibody synthesis, the beneficial effects of splenectomy may in part derive from removal of the source of autoantibodies.

**Acute ITP:**

Like chronic ITP, this condition is caused by antiplatelet autoantibodies, but its clinical features and course are distinct. Acute ITP is a disease of childhood occurring with equal frequency in both sexes.

**BLEEDING DISORDERS RELATED TO DEFECTIVE PLATELET FUNCTIONS**

Qualitative defects of platelet function can be congenital or acquired. Several congenital disorders characterized by prolonged bleeding time and normal platelet count have been described.

**HEMORRHAGIC DIATHESSES RELATED TO ABNORMALITIES IN CLOTTING FACTORS**

A deficiency of any of the clotting factor has been reported to be the cause of bleeding with the exception of factor XII deficiency. The bleeding associated with such deficiency states differs from that of platelet deficiency in that spontaneous petechiae or purpura are uncommon. Rather, the bleeding is manifested by large post-traumatic ecchymoses or hematomas, or prolonged bleeding after trauma such as lacerations or surgery. Bleeding into the gastrointestinal and urinary tracts, and particularly into weight-bearing joints, is common. (Fig. 3-29)
Hereditary deficiencies have been identified for each of the clotting factors. Deficiencies of factor VIII (hemophilia A) and of factor IX (Christmas disease, or hemophilia B) are transmitted as sex-linked recessive disorders. Most others follow autosomal patterns of transmission. These hereditary disorders typically involve a single clotting factor.

Deficiencies of Factor VIII-vWF Complex (Hemophilia A and von Willebrand disease), two of the most common inherited disorders of bleeding, are caused by qualitative or quantitative defects involving the factor VIII-vWF complex. (Fig. 3-30) Plasma factor VIII-vWF is a complex made up of two separate proteins (factor VIII and vWF). Factor VIII, an intrinsic pathway component required for activation of factor X. Deficiency of factor VIII gives rise to hemophilia A. Circulating factor VIII is noncovalently associated with very large vWF multimers. The most important function of vWF in vivo is to promote the adhesion of platelets to subendothelial matrix.

The two components of the factor VIII-vWF complex are encoded by separate genes and synthesized in different cells. vWF is produced by endothelial cells and megakaryocytes and can be demonstrated in platelet α-granules. Endothelial cells are the major source of subendothelial and plasma vWF. vWF gene is located on chromosome 12.

Factor VIII is made in several tissues; sinusoidal endothelial cells and Kupffer cells in the liver and glomerular and tubular epithelial cells in the kidney appear to be particularly important sites of synthesis. Factor VIII gene is located on X chromosome.

**Von Willebrand Disease**

This has an estimated frequency of 1% & is believed to be one of the most common inherited disorders of bleeding in humans. Clinically, it is characterized by spontaneous bleeding from mucous membranes, excessive bleeding from wounds, or menorrhagia.

Patients with von Willebrand disease typically have:

- A prolonged bleeding time.
- A normal platelet count.
- The plasma level of active vWF is reduced.
- Because vWF stabilizes factor VIII by binding to it, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. This may be reflected by a prolongation of the PTT in von Willebrand disease types 1 and 3.

In most cases, it is transmitted as an autosomal dominant disorder, but several rare autosomal recessive variants have been identified.

Because a severe deficiency of vWF has a marked affect on the stability of factor VIII, some of the bleeding characteristics resemble those seen in hemophilia.

**Hemophilia A (Factor VIII Deficiency)**

Hemophilia A is the most common hereditary disease associated with serious bleeding. It is caused by a reduction in the amount or activity of factor VIII. Hemophilia A is inherited as an X-linked recessive trait, and thus occurs in males and in homozygous females. However, excessive bleeding has been described in heterozygous females, presumably due to extremely unfavorable lyonization (inactivation of the normal X chromosome in most of the cells). Approximately 30% of patients have no family history; their disease is presumably caused by new mutations. Hemophilia A exhibits a wide range of clinical severity that correlates well with the level of factor VIII activity.

- Those with less than 1% of normal activity develop severe disease.
- Levels between 2% and 5% of normal are associated with moderate disease.
- Patients with 6% to 50% of activity develop mild disease.

The variable degrees of factor VIII deficiency are largely explained by heterogeneity in the causative mutations. Several genetic lesions (deletions, nonsense mutations that create stop codons, splicing errors) have been documented.

Patients with hemophilia A typically have:

- A normal bleeding time.
- A normal platelet count and a normal PT.
- A prolonged PTT.
These tests point to an abnormality of the intrinsic coagulation pathway. Factor VIII-specific assays are required to establish the diagnosis.

**Hemophilia B (Christmas disease, Factor IX Deficiency)**

Severe factor IX deficiency produces a disorder clinically indistinguishable from factor VIII deficiency (hemophilia A). This should not be surprising, given that factor VIII and IX function together to activate factor X. Wide spectrums of mutations involving the factor IX gene are found in hemophilia B. Like hemophilia A, it is inherited as an X-linked recessive trait and shows variable clinical severity. In about 14% of these patients, factor IX is present but nonfunctional.

**Patients with hemophilia B typically have:**
- A normal bleeding time
- A normal platelet count, and a normal PT
- A prolonged PTT

Factor IX-specific assays are required to establish the diagnosis.

**DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**

DIC is an acute, subacute, or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases. It is characterized by activation of the coagulation sequence that leads to the formation of microthrombi throughout the microcirculation of the body, often in an uneven distribution. Sometimes the coagulopathy is localized to a specific organ or tissue. As a consequence of the thrombotic diathesis, there is consumption of platelets, fibrin, and coagulation factors and, secondarily, activation of fibrinolytic mechanisms.

Thus, **DIC can present with signs and symptoms relating to:**
- Tissue hypoxia and infarction caused by the countless microthrombi or
- Depletion of the elements required for hemostasis (hence, the term "consumption coagulopathy" is sometimes used to describe DIC). Activation of the fibrinolytic mechanism aggravates the hemorrhagic diathesis.

**Etiology and Pathogenesis**

At the outset, it must be emphasized that DIC is not a primary disease. It is a coagulopathy that occurs in the course of a variety of clinical conditions.

**Two major mechanisms trigger DIC:**

1. **Release of tissue factor or thromboplastic substances into the circulation:** Tissue thromboplastic substances can be derived from a variety of sources, such as the **placenta** in obstetric complications and the granules of **leukemic cells** in acute promyelocytic leukemia & **mucus** released from certain adenocarcinomas can also act as a thromboplastic substance by directly activating factor X, independent of factor VII. In gram-negative sepsis (an important cause of DIC), **bacterial endotoxins** cause activated monocytes to release interleukin-1 and TNF, both of which increase the expression of tissue factor on endothelial cell membranes and simultaneously decrease the expression of thrombomodulin. The net result is a shift in balance toward procoagulation.

2. **Widespread injury to the endothelial cells** is the other major trigger that can initiate DIC by causing release of tissue factor, promoting platelet aggregation, and activating the intrinsic coagulation pathway. TNF is an extremely important mediator of endothelial cell inflammation and injury in septic shock. Even subtle endothelial injury can unleash procoagulant activity by enhancing membrane expression of tissue factor. Widespread endothelial injury may be produced by deposition of antigen-antibody complexes (e.g., systemic lupus erythematosus), temperature extremes (e.g., heat stroke, burns), or microorganisms (e.g., meningococci, rickettsiae).

The initiating factors in these conditions are often multiple and interrelated.

**The consequences of DIC are twofold:**
- There is widespread deposition of fibrin within the microcirculation. This can lead to
  A. **Ischemia** of the more severely affected or more vulnerable organs
  B. A **hemolytic anemia** resulting from fragmentation of red cells as they squeeze through the narrowed microvasculature (microangiopathic hemolytic anemia).
A hemorrhagic diathesis can dominate the clinical picture. This results from consumption of platelets and clotting factors as well as activation of plasminogen. Plasmin can not only cleave fibrin, but also digest factors V and VIII, thereby reducing their concentration further.

Pathologic features
- In general, fibrin microthrombi are found principally in the arterioles and capillaries of the following sites in decreasing order of frequency: brain, heart, lungs, kidneys, adrenals, spleen, and liver. However, no tissue is spared, and thrombi are occasionally found in only one or several organs without affecting others.
- The glomeruli contain small fibrin thrombi. The microvascular occlusions lead to small infarcts in the renal cortex. In severe cases, the ischemia can destroy the entire cortex and cause bilateral renal cortical necrosis.
- Involvement of the adrenal glands can produce the Waterhouse-Friderichsen syndrome.
- Microinfarcts are also commonly encountered in the brain. These can give rise to bizarre neurologic signs.
- It has been suggested that DIC contributes to Sheehan postpartum pituitary necrosis.
- When the underlying disorder is toxemia of pregnancy, the placenta is the site of capillary thromboses.
- The bleeding tendency associated with DIC is manifested not only by larger than expected hemorrhages near foci of infarction but also by diffuse petechiae and ecchymoses, which can be found on the skin & serosal coverings & mucosal lining of internal organs.

Depending on the balance between clotting and bleeding tendencies, the range of possible clinical manifestations is quite wide. In general, acute DIC (e.g., that associated with obstetric complications) is dominated by a bleeding diathesis, whereas chronic DIC (e.g., as occurs in an individual with cancer) tends to present with symptoms related to thrombosis. The manifestations may be minimal, or there may be shock, with acute renal failure, dyspnea, cyanosis, convulsions, and coma. Most often, attention is called to the presence of DIC by prolonged postpartum bleeding or by the presence of petechiae and ecchymoses on the skin. These may be the only manifestations, or there may be severe hemorrhage into the gut or urinary tract.

Laboratory evaluation reveals thrombocytopenia and prolongation of PT and PTT (resulting from depletion of platelets, clotting factors, and fibrinogen). Fibrin split products are increased in the plasma.

ACQUIRED DISORDERS
these are usually characterized by multiple clotting abnormalities.
- Vitamin K deficiency: Results in impaired synthesis of factors II, VII, IX, and X and protein C. Since the liver makes virtually all the clotting factors:
  - Severe parenchymal liver disease: Can be associated with a hemorrhagic diathesis.
  - Disseminated intravascular coagulation: Produces a deficiency of multiple coagulation factors.
TRANSFUSION MEDICINE

Blood transfusion refers to transfer of blood or blood components from a donor to a recipient.

**PRINCIPLES**
- Blood donation should always be voluntary.
- Never give transfusion unnecessarily.
- Blood transfusion should follow components policy.

**BLOOD DONATION**
- Donor must be fit & healthy.
- It should not harm the donor.
- It should not transmit any disease to the recipient.

**Before blood donation the donor should be subjected to**
1. Detailed Medical history (Questionnaire Form)
2. Limited physical examination

**Questionnaire form**

1. Name of the donor
2. Sex
3. Age 18-65 year
4. Weight > 50 Kg
5. Occupation X Pilot, Fire fighter
6. Last donation Not less than 2 months
7. Frequency of donation 2-3 times/y (Max 3 times/yr for females and 4times/yr for males
8. History of blood transfusion defer 6 months
9. Major surgery defer 6 months
10. History of heart disease, active pulmonary disease (active T.B), diabetics, hypertension, hyperthyroidism. Those with one of the above diseases are generally deferred from donation.
11. History of blood diseases such as leukemia, lymphoma, thalassaemia major, sickle cell anemia and polycythemia should be deferred from donation.
12. History of abnormal bleeding tendency should also be deferred
13. History of epilepsy is generally a cause of deferral
14. History of infectious diseases
15. AIDS patients, AIDS contacts, homosexuals, drug abusers, those with multiple partners, hemophiliacs receiving products of human origin all should be indefinitely deferred.

16. Hepatitis: history of jaundice or viral hepatitis A: deferred one year. Hepatitis B (HBs Ag +) or C is deferred permanently.

17. Malaria: those infected are not accepted as blood donors.

18. Brucellosis: deferred for 2 years from last febrile episode.

19. EBV infected patients are deferred for 2 years

20. Syphilis: patients with this disease are considered as permanent deferral

21. Drugs: patient on certain drugs (anticoagulants, anti hypertensive, insulin) are not accepted

22. Pregnancy: not allowed. Accepted 3-6 ms postpartum

23. Donor consent:: written consent

**Physical Examination**

*This should be simple & brief and include*

1. **General appearance**

2. **Temp:** Not more than 37°C

3. **Pulse:** 50-100 beats/ min

4. **Blood pressure:** systolic 90-180-Diastolic 50-100

5. **Weight:** At least 50 Kg

6. **Hb level:** more than 13.5 g/dl for males & 12.5 g/dl for females

**Anticoagulants**

*ACD (Acid citrate dextrose)*

- Shelf life of blood: 21 days
- Now used only in automated plasmapheresis.

*CPD (Citrate phosphate dextrose)*

- Shelf life of blood: 28 days

*CPD-A (Plus Adenine)*

- Shelf life of blood: 35 days (used now)

Blood donation is taken by an aseptic technique in to plastic bags designed to hold 450 ml +/- 45 ml of blood, mixed with 63 ml of anticoagulant. The ratio of anticoagulant to blood must be maintained at the optimal level of 1:7.

The citrate anticoagulates the blood by combining with the blood calcium.
Mandatory tests on blood units
1. ABO &Rh grouping
2. Test for HIV Ab
3. Test for HBs Ag
4. Test for HCV
5. Test for syphilis
6. Screening for atypical antibodies.

BLOOD TRANSFUSION
Before giving blood to the patient we should do

Compatibility testing
This include
1. ABO & RH typing of the donor and the recipient blood
2. Screening of the donor & the recipient sera for unexpected antibodies
3. Cross matching the donor & the recipient blood by cross matching the donor cells & the recipient serum.

Objectives of cross matching are
1. Assurance of the ABO compatibility
2. Recognition of clinically significant antibodies

Standard routine cross matching is done by

Saline tube
Mixing donor cells & recipient serum, leave the tube at room temp (18-25 C)

Albumin tube
by adding albumin to the mixture of the donor cells & recipient serum at 37 C to detect worm reacting antibodies

Indirect antiglobulin test
at 37 C to detect antibodies in the recipient serum that coat or cause sensitization of the donor red cells

Complications of blood transfusion
Incidence of transfusion reaction is about 2-5%. It is mostly of mild degree.

Fatal complications are uncommon
Complications can be divided broadly into
1. Immunological complications
2. Nonimmunological complications

Immunological complications

1. Sensitization to red cells antigens
Because the ABO & Rh D antigens are the only Ags matched between donor & recipient, there is a possibility of sensitization to other red cells Ags.

In clinical practice this sensitization could lead to
A. Hemolytic disease of the newborn if the recipient is a female
B. Difficulties in compatibility testing if the recipient required further transfusion
C. Hemolytic transfusion reaction

2. Hemolytic transfusion reaction
Most of the cases are due to clerical or administrative error, rarely due to laboratory error
This reaction is caused by premature destruction, almost always of the donor cells by antibodies present in the recipient

The hemolytic transfusion reaction could be
- Immediate or
- Delayed

Immediate Transfusion reaction:
- This is the most dangerous type
- Usually caused by ABO incompatibility

The antibodies are IgM in type that bind to the red cells and cause complement activation leading to intravascular lysis of the red cells with production of the anaphylatoxins the C3a & C5a liberated during complement activation. The C3a & C5a will cause smooth muscle contraction, platelets aggregation, increased capillary permeability, release of vasoactive amines and hydrolases from mast cells and granulocytes

Sign & Symptoms
- Occur within minutes to 1 hour from the start of transfusion
- Heat in the vein
- Throbbing headache
- Flushing of the face
- Chest tightness
- Nausea
- Lumber pain
- Hypotension & tachycardia
- DIC, hemoglobin-urea (passing red urine), acute renal failure, collapse & death in severe cases.

Less commonly the haemolysis is extra-vascular caused by removal of C3b & IgG coated red cells by the macrophages in the liver and spleen. Symptoms are usually less rapid in onset occur usually after 1 hour with fever, jaundice and unexplained decrease in Hb. Renal failure is rare.

Management of Transfusion reaction
- Stop transfusion immediately. Keep the IV line
- Maintain the Circulating blood volume, restore the blood pressure and urinary flow
- Collect blood sample from site a way from the site of infusion in 3 tubes
  1. EDTA sample – for CBP.
  2. Citrated sample-for coagulation studies
  3. Clotted sample -for serological studies (Blood grouping, Coombs test, repeat antibodies screening for the recipient, repeat the compatibility testing)
- Collect the next urine sample & 24 hr urine post transfusion check for Hb-urea
- Check the label & the number on the blood unit &check the cross match form for any error.
Tests to be done in the lab

• Check the ABO & Rh group of the recipient & the donor samples again
• Examine the post transfusion sample for haemolysis & check the donor unit for haemolysis
• Do Coombs test on recipient post transfusion sample
• Repeat cross match with both pre & post transfusion samples
• Screen pre & post transfusion samples and donor plasma for antibodies
• Check the Hb
• Coagulation screening test for the possibility of DIC
• Bacteriological evaluation: inspect the donor unit haemolysis or clot. Blood from the giving set and the blood unit should be cultured
• Biochemical studies: test for hemoglobinemia and for bilirubin
• Check the urine for hemoglobinurea.

Delayed Transfusion reaction
This is manifested usually 7-10 days after transfusion and is caused by antibodies, which are present in low titer & are not detected at time of cross matching. So this reaction is neither predictable nor preventable. The antibodies are caused by sensitization due to previous pregnancy or transfusion.

S&S: fever, jaundice and lowering of Hb.

3. Febrile reaction due to WBC & platelets Ags
• Most common immunological reaction
• Seen in patients having multiple blood transfusion or pregnancy
• Caused by Ab to HLA Ags, WBC & platelets specific Ags (Usually WBC)
• The onset of the reaction is delayed 30-90 min after start of transfusion
• The main symptom is fever

Management
• Slow the transfusion
• Give antipyretic
• No need to terminate the transfusion
• If symptom recur in patients require repeated transfusions we should check the patient for WBC or Platelets Abs & if these are present we should use WBC depleted blood (by using WBC filter).

4. Reaction to platelets Ag (Post-transfusion Purpura)
• Seen in women with history of multiple pregnancies or in those with history of multiple transfusion
• Caused by Abs to platelets Ag (PI)
• The reaction occurs 7-10 days after transfusion
• The main feature is purpura due to thrombocytopenia (caused by destruction of the platelets by the Abs)
• It is usually self limiting

5. Reaction due to plasma protein antibodies
• Majority are due to Anti IgA antibodies
• Main symptom is urticaria
• Treatment is by antihistamine
• Rarely more severe anaphylactic reaction occur which should be treated urgently with adrenaline and any next transfusion should be IgA deficient blood

Nonimmunological complications
1. Reaction due to bacterial pyrogens or bacteria
   Although rare complication, it has very high mortality rate characterized by sudden onset of high fever, shock & bleeding due to DIC. Blood may be contaminated by cold-growing organisms (pseudomonas or colon-aerogenes group). These microorganisms utilize citrate as the primary source of carbon, which leads to citrate depletion and hence clotting of blood. Visual inspection of the blood units may reveal clots and indicate the presence of contamination.
   The infusion of large number of gram-negative microorganisms results in a serious reaction i.e. endotoxic shock. The latter is accompanied by fever, marked hypotension, pain, vomiting and the development of profound shock. The reaction may start with shaking chills following a latent period of 30 minutes or more. As little as 10 ml of blood may contain sufficient microorganisms to produce the reaction.
   Management
   • Do direct examination & culture of the blood from the patient & the blood unit
   • Give antibiotic IV
   This complication could be prevented by
   • Ensuring aseptic technique in the preparation of blood bags & anticoagulant
   • Aseptic condition in blood donation
   • Bags should not be opened for sampling and the unit should be transfused within 24 hr if any open method has been used
   • Blood should be kept in accurately controlled refrigerator at 2-6 C
   • Avoid leaving blood at room temp.
   • Inspect all blood units for signs of contamination as clotting or haemolysis.

2. Circulatory overload
   Transfusion generally increases blood volume except in those who are actively bleeding. This increase in blood volume may be dangerous in the elderly with a compromised cardiovascular function, pregnancy and in those with severe anemia
   Prevention
   • Blood should be given slowly over 4 hr.
   • Give diuretics at the start of transfusion-No more than 2 units should be given within 24 hr.
   • Blood should be given during the daytime and the patient should be followed carefully
If S&S of overload & pulmonary edema occur

- Transfusion should be stopped
- Patient propped upright
- Give diuretics IV

3. Thrombophlebitis; this is a complication of indwelling venous cannulae and is not specifically related to blood transfusion.

4. Air embolism; this is now a rare complication of transfusion therapy due to the introduction of plastic bags, which provide a closed system. Only large volumes of air, and not the entry of a few bubbles, result in a clinically significant air embolism. Symptoms include pain, cough, and sudden onset of dyspnoea. The treatment includes clumping off the administrating tube.

5. Haemosiderosis; each unit of blood contain approximately 200 mg of iron. Repeated transfusions over many years, in the absence of blood loss, cause deposition of iron initially in the reticulo-endothelial system. After 50 units in adults, and lesser amount in children, the liver, myocardium and endocrine glands are damaged. This is a major problem in thalassemia major and other severe chronic refractory anemias, and this could be prevented by giving chelating agent.

6. Complications of massive transfusion
These tend to occur in cases of replacement the total blood volume within 24 hr (For adult about 10-units/24 hr)

This could lead to

1. Dilution of platelets. As blood stored more than 48 hr has no functional platelets. Transfusion of 8-10 units of blood to an adult will lead to thrombocytopenia (low platelets). It follows that any patient receiving many blood units should be monitored through platelets count & judged on his clinical condition. Some give one platelets unit for every 4 blood units. Others give platelets transfusion if platelets count becomes less than 100,000 /cmm if there is bleeding or surgical intervention

2. Dilution of coagulation factors
This occurs if blood stored more than 14 days is given. Blood stored less than 14 days has adequate level of most of the coagulation factors except factor V & VIII, as they are the most labile factors.

3. Metabolic changes
a. Citrate toxicity. This is not a problem except in a very rapid transfusion (unit every 5 minutes).

b. Hyperkalaemia & hypocalcaemia. These are usually transient & rapidly corrected.

7. Transmission of Infection
Diseases transmitted by blood could be classified as follows

1. Bacterial
   - Syphilis
   - Brucellosis

2. Protozoal
   - Malaria
   - Toxoplasmosis

3. Viral
   - Hepatitis viruses
   - HIV, HTLV I, HTLV II
   - EBV

Bacterial diseases

Syphilis
- **The agent** is Treponema Pallidum
- **Donor is infective** during the early spirochetemia phase i.e. before the development of the antibodies
- **Blood products implicated**: fresh blood & components
• **Viability in blood:** the bacteria are unlikely to survive more than 3 days at 4-6 C, so transmission of syphilis by blood is a rare complication.
• It is more likely to be transmitted by platelets concentrate because of its storage at room temp and its short shelf life.
• If blood is taken from seropositive donor (Showing positive serological tests for syphilis) this cause passive transmission of the antibodies to the recipient and the recipient become seropositive for 4-10 days

**Prevention**
• Mandatory screening of all donor units by VDRL or TPHA
• Exclusion of high-risk group.

**Brucellosis**
• The **agent** is Brucella abortus
• **Viability** in stored blood: months
• **Incubation period:** 6 days- 4 months
• Reports of transfusion related brucellosis: mainly in children, splenctomized or immunocompromized.
• **Prevention:** defer infected patient for 2 years after cure

**Protozoal diseases**

**Malaria**
• **The gent** is Plasmodia Species (vivax, ovale, malariae, falciparum
• **Viability:** viable in stored blood at 4 C at least 1 week; in case of P. falciparum up to 2 weeks
• **Blood product implicated:** products containing red cells
• **Incubation period:** vivax & falciparum 1 week- 1 month; malariae: months
• **Prevention**
  In endemic areas: prophylactic treatment of donors with chloroquine 48 h before donation or single doze of chloroquine to the recipient 24 before transfusion.

**Viral disease**

**AIDS (Acquired immune deficiency syndrome)**
• **The agent** is Human immunodeficiency virus HIV type I & II
• **Blood product implicated:** whole blood (cellular& plasma blood components)
• Incubation period: mean incubation period is 4.5 yr
• **Prevention**
  1. Education through the media
  2. Self –exclusion of high risk group
  3. Screening all donors for HIV antibodies

**Hepatitis Viruses**

**Post transfusion hepatitis** could be caused by the following viruses

1. *Hepatitis viruses* (A, B, C,)
2. *Cytomegalovirus* (CMV)
3. Epstein-Bar virus (EBV)

**Prevention**
Tests to screen for Hepatitis B (HB s AG)
Tests to screen for HCV
Exclusion of high risk group
CHAPTER FIVE
PATHOLOGY OF THE GIT
Dr, Sahera, Dr Bayan, Dr Abdulkareem

THE ORAL CAVITY & OROPHARYNX

Many pathological processes can affect the constituents of the oral cavity. The more important and frequent conditions will covered in this lecture. Diseases involving the teeth and related structures will not be discussed.

Gingivitis

Gingivitis refers to "inflammation of soft tissues surrounding the teeth (gum)." It is primarily due to lack of proper oral hygiene that leads to accumulation of dental plaques. The latter consist of normal flora, proteins of saliva, and desquamated epithelial cells. Plaques are converted to calculi through mineralization. Continuous and persistent irritation by these calculi leads to chronic gingivitis. The condition manifests as redness, edema, and bleeding. Eventually there is loss of soft tissue adaptation to the teeth (loose tooth). (Fig. 5-1)

PROLIFERATIVE LESIONS

The most common proliferative lesions of the oral cavity are
1. Irritation Fibroma and Ossifying fibroma
2. Ossifying fibroma
3. Pyogenic granuloma
4. Peripheral giant cell granuloma

Irritation fibroma is a nodular mass of fibrous tissue that occurs mainly in the buccal mucosa along the bite line & gingivo-dental margin. (Fig. 5-2)

Ossifying fibroma is a common growth of the gingiva. Some may be due to maturation of a long-standing pyogenic granuloma.

Pyogenic granuloma (granuloma pyogenicum) is a highly vascular lesion that is usually seen in the gingiva of children, young adults, and pregnant women (pregnancy tumor). The lesion is typically ulcerated and bright red in color (due to rich vascularity) (Fig. 5-3). Microscopically there is vascular proliferation similar to that of granulation tissue. (Fig. 5-3) They lesion either regresses (particularly after pregnancy), or undergoes fibrous maturation and may develop into ossifying fibroma.

Peripheral giant cell granuloma (giant cell epulis) is a relatively common lesion that characteristically protrudes from the gingiva at sites of chronic inflammation. It is so named because microscopically there are aggregates of multinucleate giant cells separated by a fibro-vascular stroma. (Fig. 5-4)

INFLAMMATORY CONDITIONS

Inflammatory ulcerations
The most common inflammatory ulcerations of the oral cavity are
1. Traumatic
2. Aphthous
3. Herpetic

Traumatic ulcers, usually the result of trauma (e.g. fist fighting) or licking a jagged tooth.

Aphthous ulcers are extremely common, single or multiple, painful, recurrent, superficial, ulcerations of the oral mucosa. The ulcer is covered by a thin yellow exudate and rimmed by a narrow zone of erythema. (Fig. 5-5)

Herpetic ulcers (see under herpes simplex infection)

Glossitis
This is inflammation of the tongue, but sometimes it is also applied to the beefy-red tongue that occurs in certain deficiency states. The latter is the result of atrophy of the papillae and thinning of the mucosa, thus exposing the underlying vasculature. (Fig. 5-6) However, in some instances, the atrophy leads to inflammation (and even shallow ulcerations). Examples of such deficiency states that include
1. B12 (pernicious anemia),
2. Riboflavin
3. Niacin
4. Pyridoxine
5. Iron-deficiency anemia
**Plummer-Vinson syndrome** is a combination of
1. Iron-deficiency anemia  
2. Glossitis 
3. Esophageal dysphagia (due to esophageal webs) 

Glossitis (with ulcerations) may also be seen with
- Jagged carious teeth 
- Ill-fitting dentures 
- Exposure to hot fluids or corrosive chemicals 
- Inhalation of burn fumes including excessive smoking 
- Syphilis 

**INFECTIONS**

1. **Herpes simplex infections**

Most of these are caused by herpes simplex virus (HSV) type 1 & sometimes 2. Primary HSV infection typically occurs in children aged 2 to 4 years; is often asymptomatic, but sometime presents as **acute herpetic gingivostomatitis**, characterized by vesicles and ulcerations throughout the oral cavity. The great majority of affected adults harbor latent HSV-1 (the virus migrates along the regional nerves and eventually becomes dormant in the local ganglia e.g., the trigeminal). In some individuals, usually young adults, the virus becomes reactivated to produce the common but usually mild **cold sore**. (Fig. 5-7)

Factors activating the virus include
1. Trauma 
2. Allergies 
3. Exposure to ultraviolet light (sunlight) 
4. Upper respiratory tract infections

The viral infection is associated with intracellular and intercellular edema, yielding clefts that may become transformed into vesicles. The vesicles range from a few millimeters to large ones that eventually rupture to yield extremely painful, red-rimmed, shallow ulcerations.

2. **Other Viral Infections**

These include
- Herpes zoster 
- EBV (infectious mononucleosis) 
- Enterovirus 
- Measles 
- CMV 

3. **Oral Candidiasis (thrush)**

This is the most common fungal infection of the oral cavity. The thrush is a grayish white, superficial, inflammatory psudomembrane composed of the fungus enmeshed in a fibrino-suppurative exudates. (Fig. 5-8)

This can be readily scraped off to reveal an underlying red inflammatory base. The fungus is a normal oral flora but causes troubles only
1. In the setting of immunosuppression (e.g. diabetes mellitus, organ or bone marrow transplant recipients, neutropenia, cancer chemotherapy, or AIDS) or
2. When broad-spectrum antibiotics are taken; these eliminate or alter the normal bacterial flora of the mouth.
3. In infants, where the condition is relatively common, presumably due to immaturity of the immune system in them.

4. **Deep Fungal Infections**

Some fungal infections may extends deeply to involve the muscles & bones in relation to oral cavity. These include, among others, histoplasmosis, blastomycosis, and aspergillosis. The incidence of such infections has been increasing due to increasing number of patients with AIDS, therapies for cancer, & organ transplantation

5. **Diphtheria**: characterized grossly by dirty white, fibrino-suppurative, tough, inflammatory pseudomembrane over tonsils & posterior pharynx. (Fig. 5-9)

**ORAL MANIFESTATIONS OF SYSTEMIC DISEASE**

Many systemic diseases are associated with oral lesions & it is not uncommon for oral lesions to be the first manifestation of some underlying systemic condition.

1. **Scarlet fever**: strawberry tongue: white coated tongue with hyperemic papillae projecting (Fig. 5-10)
2. **Measles**: Koplik spots: small whitish ulcerations (spots) on a reddened base, about Stensen duct (Fig. 5-11)

3. **Diphtheria**: dirty white, fibrinosuppurative, tough pseudomembrane over the tonsils and retropharynx

4. **AIDS**
   a. opportunistic oral infections: herpesvirus, Candida, other fungi
   b. Kaposi sarcoma (Fig. 5-12)
   c. hairy leukoplakia

5. **AML** (especially monocytic leukemia): enlargement of the gingivae + periodontitis (Fig. 5-13)

6. **Melanotic pigmentation** (Fig. 5-14)
   a. Addison disease
   b. hemochromatosis
   c. fibrous dysplasia of bone
   d. Peutz-Jegher syndrome

7. **Pregnancy**: pyogenic granuloma ("pregnancy tumor")

**Hairy Leukoplakia**
Approximately 80% of patients with hairy leukoplakia have been infected with HIV; the remaining 20% are seen in association with other immunodeficiency states. The condition presents as a white fluffy ("hairy") patches that are situated on the lateral border of the tongue. (Fig. 5-15) **EBV is now accepted as the cause of the condition.** When hairy leukoplakia precedes HIV infection, manifestations of AIDS generally appear within 2 or 3 years.

**TUMORS AND PRECANCEROUS LESIONS**
Many of the oral cavity tumors (e.g., papillomas, hemangiomas, lymphomas) are not different from their homologous tumors elsewhere in the body. Here we will consider only oral squamous cell carcinoma and its associated precancerous lesions.

**Leukoplakia** and **Erythroplakia** are considered premalignant lesions of squamous cell carcinoma.

**Leukoplakia** (Fig. 5-16) is a white patch that cannot be scraped off and cannot be attributed clinically or microscopically to any other disease i.e. if a white lesion in the oral cavity can be given a specific diagnosis it is not a leukoplakia. As such, white patches caused by entities such as candidiasis are not leukoplakias. **All leukoplakias must be considered precancerous (have the potential to progress to squamous cell carcinoma) until proved otherwise through histologic evaluation.**

**Erythroplakias** (Fig. 5-17) are red velvety patches that are much less common, yet much more serious than leukoplakias. The incidence of dysplasia and thus the risk of complicating squamous cell carcinoma is much more frequent in erythroplakia compared to leukoplakias.

Both leukoplakia and erythroplakia are usually found between ages of 40 and 70 years, and are much more common in males than females. The use of tobacco (cigarettes, pipes, cigars, and chewing tobacco) is the most common incriminated factor.

**Squamous cell carcinoma**
The vast majority (95%) of cancers of the head and neck are squamous cell carcinomas; these arise most commonly in the oral cavity. The 5-year survival rate of early-stage oral cancer is approximately 80%, but this drops to about 20% for late-stage disease. These figures highlight the importance of early diagnosis & treatment, optimally of the precancerous lesions.

**The pathogenesis of squamous cell carcinoma is multifactorial.**
1. Chronic smoking and alcohol consumption
2. Oncogenic variants of human papilloma virus (HPV). It is now known that at least 50% of oropharyngeal cancers, particularly those of the tonsils and the base of tongue, harbor oncogenic variants of HPV.
3. Inheritance of genomic instability; a family history of head and neck cancer is a risk factor.
4. Exposure to actinic radiation (sunlight) & pipe smoking are known predisposing factors for cancer of the lower lip.

**Gross features** (Fig. 5-18 A)
Squamous cell carcinoma may arise anywhere in the oral cavity, but the favored locations are
1. The tongue
2. Floor of mouth
3. Soft palate
4. Gingiva
3. Lower lip
In the early stages, cancers of the oral cavity appear as roughened areas of the mucosa. As the lesion enlarges, it typically appears as either an ulcer or a protruding mass (fungating).

**Microscopic features** (Fig. 5-18 B)
- Early there is full-thickness dysplasia (carcinoma in situ) followed by invasion of the underlying connective tissue stroma.
- The grade varies from well-differentiated keratinizing to poorly differentiated.

As a group, these tumors tend to infiltrate and extend locally before they eventually metastasize to cervical lymph nodes and more remotely. The most common sites of distant metastasis are mediastinal lymph nodes, lung, liver and bones.

**SALIVARY GLANDS**
There are three major salivary glands—parotid, submandibular, and sublingual. Additionally, there are numerous minor salivary glands distributed throughout the mucosa of the oral cavity.

**Xerostomia** refers to dry mouth due to a lack of salivary secretion; the causes include
1. **Sjögren syndrome**: an autoimmune disorder, that is usually also accompanied by involvement of the lacrimal glands that produces dry eyes (keratoconjunctivitis sicca).

2. **Radiation therapy**
**Inflammation (Sialadenitis)**
Sialadenitis refers to inflammation of a salivary gland; it may be
- 1. Traumatic
- 2. Infectious: viral, bacterial
- 3. Autoimmune

The most common form of viral sialadenitis is **mumps**, which usually affects the parotids. The pancreas and testes may also be involved.

**Bacterial sialadenitis is seen as a complication of**
1. **Stones** obstructing ducts of a major salivary gland (*Sialolithiasis*), particularly the submandibular. (Fig. 5-19)
2. **Dehydration** with decreased secretory function as is sometimes occurs in
   a. patients on long-term phenothiazines that suppress salivary secretion.
   b. elderly patients with a recent major thoracic or abdominal surgery.

Unilateral involvement of a single gland is the rule and the inflammation may be **suppurative**. The inflammatory involvement causes painful enlargement and sometimes a purulent ductal discharge.

**Sjögren syndrome** causes an immunologically mediated sialadenitis i.e. inflammatory damage of the salivary tissues.

**Mucocele**
This is common salivary lesion results from interruption of salivary outflow due to blockage or rupture of a salivary gland duct. This leads to seepage of saliva into the surrounding tissues. The lower lip is the most common location due to exposure of this site to trauma (fist fighting, falling etc.). It presents as fluctuant swelling. Microscopically, there is accumulation of mucin with inflammatory cells. (Fig. 5-20)

**Ranula** is a mucocele of the sublingual gland; it may become extremely large.

**NEOPLASMS OF SALIVARY GLANDS**
Neoplasms of the salivary glands (benign and malignant) are generally uncommon, constituting less than 2% of human tumors. We will restrict our discussion on the more common examples.

The relative frequency distributions of these tumors in relation to various salivary glands are as follows

<table>
<thead>
<tr>
<th>Salivary gland</th>
<th>Relative frequency of tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid gland</td>
<td>80%</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>10%</td>
</tr>
<tr>
<td>Minor salivary and sublingual glands</td>
<td>10%</td>
</tr>
</tbody>
</table>

The incidence of malignant tumors within the glands is, however, different from the above

<table>
<thead>
<tr>
<th>Salivary gland affected</th>
<th>Relative frequency of malignant tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual tumors</td>
<td>80%</td>
</tr>
<tr>
<td>Minor salivary glands</td>
<td>50%</td>
</tr>
<tr>
<td>Submandibular glands</td>
<td>40%</td>
</tr>
<tr>
<td>Parotid glands</td>
<td>25%</td>
</tr>
</tbody>
</table>
These tumors usually occur in adults, with a slight female predominance. Excluded from this rule is Warthin tumor, which occurs much more frequently in males than in females. The benign tumors occur most often around the age of 50 to 60 years; the malignant ones tend to appear in older age groups. Neoplasms of the parotid produce distinctive swellings in front of, or below the ear. Clinically, there are no reliable criteria to differentiate benign from the malignant tumors; therefore, pathological evaluation is necessary. (Fig. 5-21)

Plasmal Adenomas (Mixed Salivary Gland Tumors)
These benign tumors commonly occur within the parotid gland (constitute 60% of all parotid tumors).

Gross features (Fig. 5-22 A)
- Most tumors are rounded, encapsulated masses.
- The cut surface is gray-white with myxoid and light blue translucent areas of chondroid.

Microscopic features (Fig. 5-22 B)
- The main constituents are a mixture of ductal epithelial and myoepithelial cells, and it is believed that all the other elements, including mesenchymal, are derived from the above cells (hence the name adenoma).
- The epithelial/myoepithelial components of the neoplasm are arranged as glands, strands, or sheets. These various epithelial/myoepithelial elements are dispersed within a background of loose myxoid tissue that may contain islands of cartilage-like islands and, rarely bone.
- Sometimes, squamous differentiation is present.
- In some instances, the tumor capsule is focally deficient allowing the tumor to extend as tongue-like protrusions into the surrounding normal tissue.

Enucleation of the tumor is, therefore, not advisable because residual foci (the protrusions) may be left behind and act as a potential source of multifocal recurrences. (Fig. 5-23) The incidence of malignant transformation increases with the duration of the tumor.

Warthin Tumor is the second most common salivary gland neoplasm. It is benign, arises usually in the parotid gland and occurs more commonly in males than in females. About 10% are multifocal and 10% bilateral. Smokers have a higher risk than nonsmokers for developing these tumors. Grossly, it is round to oval, encapsulated mass & on section display gray tissue with narrow cystic or cleft-like spaces filled with secretion.

Microscopically, these spaces are lined by a double layer of neoplastic epithelial cells resting on a dense lymphoid stroma, sometimes with germinal centers. This lympho-epithelial lining frequently project into the spaces. The epithelial cells are oncocyes as evidenced by their eosinophilic granular cytoplasm (stuffed with mitochondria). (Fig. 5-24)

Mucocoeploderm Carcinoma
As the name indicates, these neoplasms are composed of variable mixtures of mucus-secreting cells (muc), and squamous cells (epidermoid). They are the most common form of primary malignant tumor of the salivary glands. They occur mainly in the parotids. Low-grade tumors may invade locally but do not metastasize. By contrast, high-grade neoplasms metastasize to distant sites in 30% of cases. Grossly, mucocoeploderm carcinomas are gray-white, infiltrative tumors that frequently show small, mucin-containing cysts.

Microscopically, there are cords, sheets, and cysts of squamous and mucous-secreting cells. (Fig. 5-25)

Other Salivary Gland Tumors
Two less common neoplasms worth brief description:
Adenoid cystic carcinoma: half of the cases are found in the minor salivary glands (in particular the palate). Although slow growing, they have a tendency to invade perineural spaces and to recur. Eventually, 50% or more disseminate widely to distant sites such as bone, liver, and brain. Microscopically, they are composed of small cells having dark, compact nuclei and scant cytoplasm. These cells tend to be disposed in sieve-like (cribriform) patterns. The spaces between the tumor cells are often filled with a hyaline material thought to represent excess basement membrane. (Fig. 5-26)

Acinic cell tumor is composed of cells resembling the normal acinar cells (hence the name). Most arise in the parotids; the small remainder arises in the submandibular glands. On histologic examination, they reveal a variable architecture and cell morphology. Most characteristically, the cells have clear cytoplasm & are disposed in sheets, microcysts, glands, or papillae. About 10% to 15% of these neoplasms metastasize to lymph nodes. (Fig. 5-27)
ESOPHAGUS
The main functions of the esophagus are to 1. Conduct food and fluids from the pharynx to the stomach 2. Prevent reflux of gastric contents into the esophagus. These functions require motor activity coordinated with swallowing, i.e. wave of peristalsis, associated with relaxation of the LES in anticipation of the peristaltic wave. This is followed by closure of the LES after the swallowing reflex. Maintenance of sphincter tone (positive pressure relative to the rest of esophagus) is necessary to prevent reflux of gastric contents.

CONGENITAL ANOMALIES
Several congenital anomalies affect the esophagus including the presence of ectopic gastric mucosa & pancreatic tissues within the esophageal wall, congenital cysts & congenital herniation of the esophageal wall into the thorax. The latter is due to impaired formation of the diaphragm. Atresia and fistulas are uncommon but must be recognized & corrected early because they cause immediate regurgitation, suffocation & aspiration pneumonitis when feeding is attempted. In atresia, a segment of the esophagus is represented by only a noncanalized cord, with the upper pouch connected to the bronchus or the trachea and a lower pouch leading to the stomach. (Fig. 5-28)

Webs, rings, and stenosis (Fig. 5-29)
Mucosal webs are shelf-like, eccentric protrusions of the mucosa into the esophageal lumen. These are most common in the upper esophagus. The triad of upper esophageal web, iron-deficiency anemia, and glossitis is referred to as Plummer-Vinson syndrome. This condition is associated with an increased risk for postcricoid esophageal carcinoma.

Esophageal rings unlike webs are concentric plates of tissue protruding into the lumen of the distal esophagus. Esophageal webs and rings are encountered most frequently in women over age 40. Episodic dysphagia is the main symptom.

Stenosis consists of fibrous thickening of the esophageal wall. Although it may be congenital, it is more frequently the result of severe esophageal injury with inflammatory scarring, as from gastroesophageal reflux disease (GERD), radiation, scleroderma and caustic injury. Stenosis usually manifests as progressive dysphagia, at first to solid foods but eventually to fluids as well.

LESIONS ASSOCIATED WITH MOTOR DYSFUNCTION (Fig. 5-30)
Coordinated motor activity is important for proper function of the esophagus. The major entities that are caused by motor dysfunction of the esophagus are
1. Achalasia
2. Hiatal hernia
3. Diverticula
4. Mallory-Weiss tear

Achalasia
Achalasia means "failure to relax." It is characterized by three major abnormalities:
1. Aperistalsis (failure of peristalsis)
2. Increased resting tone of the LES
3. Incomplete relaxation of the LES in response to swallowing
In most instances, achalasia is an idiopathic disorder. In this condition there is progressive dilation of the esophagus above the persistently contracted LES. The wall of the esophagus may be of normal thickness, thinner than normal owing to hypertrophy of the muscular wall, or markedly thinned by dilation (when dilatation overruns hypertrophy). The mucosa just above the LES may show inflammation and ulceration. Young adults are usually affected and present with progressive dysphagia. (Fig. 5-31)

Complications of achalasia are
1. Aspiration pneumonitis of undigested food
2. Monilial esophagitis
3. Esophageal squamous cell carcinoma (about 5% of patients)
4. Lower esophageal diverticula

Hiatal Hernia (Fig. 5-32)
Hiatal hernia is characterized by separation of the diaphragmatic crura leading to widening of the space around the esophageal wall. Two types of hiatal hernia are recognized:

1. **The sliding type (95%)**
2. **The paraesophageal type**

In the sliding hernia the stomach skates up through the patent hiatus above the diaphragm creating a bell-shaped dilation. In paraesophageal hernias, a separate portion of the stomach, usually along the greater curvature, enters the thorax through the widened foramen. The cause of hiatal hernia is unknown. It is not clear whether it is a congenital malformation or is acquired during life. Only about 10% of adults with a sliding hernia suffer from heartburn or regurgitation of gastric juices into the mouth. These are due to incompetence of the LES and are accentuated by positions favoring reflux (bending forward, lying supine) and obesity.

**Complications of hiatal hernias include**
1. Ulceration, bleeding and perforation (both types)
2. Reflux esophagitis (frequent with sliding hernias)
3. Strangulation of paraesophageal hernias

**Diverticula (Fig. 5-33)**

By definition a diverticulum is a "focal out pouching of the alimentary tract wall that contains all or some of its constituents"; they are divided into

1. **False diverticulum** is an out pouching of the mucosa and submucosa through weak points in the muscular wall.
2. **True diverticulum** consists of all the layers of the wall and is thought to be due to motor dysfunction of the esophagus. They may develop in three regions of the esophagus
   a. Zenker diverticulum, located immediately above the UES
   b. Traction diverticulum near the midpoint of the esophagus
   c. Epiphrenic diverticulum immediately above the LES.

**Lacerations (Mallory-Weiss Syndrome)**

These refer to longitudinal tears at the GEJ or gastric cardia and are the consequence of severe retching or vomiting. They are encountered most commonly in alcoholics, since they are susceptible to episodes of excessive vomiting, but have been reported in persons with no history of vomiting or alcoholism. During episodes of prolonged vomiting, reflex relaxation of LES fails to occur. The refluxing gastric contents suddenly overcome the contracted musculature leading to forced, massive dilation of the lower esophagus with tearing of the stretched wall.

**Pathological features**

The linear irregular lacerations, which are usually found astride the GEJ or in the gastric cardia, are oriented along the axis of the esophageal lumen. The tears may involve only the mucosa or may penetrate deeply to perforate the wall. (Fig. 5-34) Infection of the mucosal defect may lead to inflammatory ulcer or to mediastinitis. Usually the bleeding is not profuse and stops without surgical intervention. Healing is the usual outcome. Rarely esophageal rupture occurs.

**Esophageal Varices**

**Portal hypertension** when sufficiently prolonged or severe induces the formation of collateral bypass veins wherever the portal and caval venous systems communicate. Esophageal varices refer to the prominent plexus of deep mucosal and submucosal venous collaterals of the lower esophagus subsequent to the diversion of portal blood through them through the coronary veins of the stomach. From the varices the blood is diverted into the azygos veins, and eventually into the systemic veins. Varices develop in 90% of cirrhotic patients. Worldwide, after alcoholic cirrhosis, hepatic schistosomiasis is the second most common cause of variceal bleeding.

**Pathological features** (Fig. 5-35)

The increased pressure in the esophageal plexus produces dilated tortuous vessels that are liable to rupture.

- Varices appear as tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach.
- The net effect is irregular protrusion of the overlying mucosa into the lumen. The mucosa is often eroded because of its exposed position.
- Variceal rupture produces massive hemorrhage into the lumen. In this instance, the overlying mucosa appears ulcerated and necrotic.
Rupture of esophageal varices usually produces massive hematemesis. Among patients with advanced liver cirrhosis, such a rupture is responsible for 50% of the deaths. Some patients die as a direct consequence of the hemorrhage (hypovolemic shock); others of hepatic coma triggered by the hemorrhage.

**Esophagitis**

This term refers to inflammation of the esophageal mucosa. It may be caused by a variety of physical, chemical, or biologic agents. **Reflux Esophagitis (Gastroesophageal Reflux Disease or GERD)** is the most important cause of esophagitis and signifies esophagitis associated with reflux of gastric contents into the lower esophagus. Many causative factors are involved, the most important is decreased efficacy of esophageal antireflux mechanisms, particularly LES tone. In most instances, no cause is identified. However, the following may be contributary:

a. Central nervous system depressants including alcohol  
b. Smoking  
c. Pregnancy  
d. Nasogastric tube  
e. Sliding hiatal hernia  
f. Hypothyroidism  
g. Systemic sclerosis

Any one of the above mechanism may be the primary cause in an individual case, but more than one is likely to be involved in most instances. The action of gastric juices is vital to the development of esophageal mucosal injury.

**Gross (endoscopic) features** (Fig. 5-36 A)

- These depend on the causative agent and on the duration and severity of the exposure.  
- Mild esophagitis may appear grossly as simple hyperemia. In contrast, the mucosa in severe esophagitis shows confluent erosions or total ulceration into the submucosa.

**Microscopic features** (Fig. 5-36 B)

Three histologic features are characteristic:

1. Inflammatory cells including eosinophils within the squamous mucosa.  
2. Basal cells hyperplasia  
3. Extension of lamina propria papillae into the upper third of the mucosa.

The disease mostly affects those over the age of 40 years. The clinical manifestations consist of dysphagia, heartburn, regurgitation of a sour fluid into the mouth, hematemesis, or melena. Rarely, there are episodes of severe chest pain that may be mistaken for a "heart attack."

**The potential consequences of severe reflux esophagitis are**

1. Bleeding  
2. Ulceration  
3. Stricture formation  
4. Tendency to develop Barrett esophagus

**Barrett Esophagus (BE)**

10% of patients with long-standing GERD develop this complication. BE is the single most important risk factor for esophageal adenocarcinoma. BE refers to columnar metaplasia of the distal squamous mucosa; this occurs in response to prolonged injury induced by refluxing gastric contents. Two criteria are required for the diagnosis of Barrett esophagus:

1. Endoscopic evidence of columnar lining above the GEJ  
2. Histologic confirmation of the above in biopsy specimens.

The pathogenesis of Barrett esophagus appears to be due to a change in the differentiation program of stem cells of the esophageal mucosa. Since the most frequent metaplastic change is the presence of columnar cells admixed with goblet cells, the term "intestinal metaplasia" is used to describe the histological alteration.

**Gross features**
Barrett esophagus is recognized as a red, velvety mucosa located between the smooth, pale pink esophageal squamous mucosa and the light brown gastric mucosa.

It is displayed as tongues, patches or broad circumferential bands replacing the squamocolumnar junction several centimeters. (Fig. 5-37 A)

**Microscopic features**
- the esophageal squamous epithelium is replaced by metaplastic columnar epithelium, including interspersed goblet cells, & may show a villous pattern (as that of the small intestine hence the term intestinal metaplasia). (Fig. 5-37 B)
- Critical to the pathologic evaluation of patients with Barrett mucosa is the search for dysplasia within the metaplastic epithelium. This dysplastic change is the presumed precursor of malignancy (adenocarcinoma). Dysplasia is recognized by the presence of cytologic and architectural abnormalities in the columnar epithelium, consisting of enlarged, crowded, and stratified hyperchromatic nuclei with loss of intervening stroma between adjacent glandular structures. Depending on the severity of the changes, dysplasia is classified as low-grade or high-grade.
- **Approximately 50% of patients with high-grade dysplasia may already have adjacent adenocarcinoma.** Most patients with the first diagnosis of Barrett esophagus are between 40 and 60 years. Barrett esophagus is clinically significant due to
  1. The secondary complications of local peptic ulceration with bleeding and stricture.
  2. The development of adenocarcinoma, which in patients with long segment disease (over 3 cm of Barrett mucosa), occurs at a frequency that is 30- to 40 times greater than that of the general population.

**Other causes of esophagitis**
In addition to GERD (which is, in fact, a chemical injury), esophageal inflammation may have many origins. Examples include ingestion of mucosal irritants (such as alcohol, corrosive acids or alkalis as in suicide attempts), cytotoxic anticancer therapy, bacteremia or viremia (in immunosuppressed patients), fungal infection (in debilitated or immunosuppressed patients or during broad-spectrum antimicrobial therapy; candidiasis by far the most common), and uremia.

**TUMORS**

**Benign Tumors**
Leiomyomas are the most common benign tumors of the esophagus. (Fig. 5-38)

**Malignant Tumors**
Carcinomas of the esophagus (5% of all cancers of the GIT) have, generally, a poor prognosis because they are often discovered too late. Worldwide, squamous cell carcinomas constitute 90% of esophageal cancers, followed by adenocarcinoma.

Other tumors are rare.

**Squamous Cell Carcinoma (SCC)**
Most SCCs occur in adults over the age of 50. The disease is more common in males than females. The regions with high incidence include Iran & China. Blacks throughout the world are at higher risk than are whites.

**Etiology and Pathogenesis**
Factors Associated with the Development of Squamous Cell Carcinoma of the Esophagus are classified as

1. **Dietary**
   - Deficiency of vitamins (A, C, riboflavin, thiamine, and pyridoxine) & trace elements (zinc)
   - Fungal contamination of foodstuffs
   - High content of nitrates/nitrosamines
   - Betel chewing (betel: the leaf of a climbing evergreen shrub, of the pepper family, which is chewed in the East with a little lime.)
2. **Lifestyle**
   - Burning-hot food
   - Alcohol consumption
   - Tobacco abuse
3. Esophageal Disorders
   - Long-standing esophagitis
   - Achalasia
   - Plummer-Vinson syndrome

4. Genetic Predisposition
   - Long-standing celiac disease
   - Racial disposition

The marked geographical variations in the incidence of the disease strongly implicate dietary and environmental factors, with a contribution from genetic predisposition. The majority of cancers in Europe and the United States are attributable to alcohol and tobacco. Some alcoholic drinks contain significant amounts of such carcinogens as polycyclic hydrocarbons, nitrosamines, and other mutagenic compounds. Nutritional deficiencies associated with alcoholism may contribute to the process of carcinogenesis. Human papillomavirus DNA is found frequently in esophageal squamous cell carcinomas from high-incidence regions.

**Gross features** (Fig. 5-39 A)
- Like squamous cell carcinomas arising in other locations, those of the esophagus begin as in situ lesions.
- When they become overt, about 20% of these tumors are located in the upper third, 50% in the middle third, and 30% in the lower third of the esophagus.
- Early lesions appear as small, gray-white, plaque-like thickenings of the mucosa but with progression, three gross patterns are encountered:
  1. Fungating (polypoid) (60%) that protrudes into the lumen
  2. Flat (diffusely infiltrative) (15%) that tends to spread within the wall of the esophagus, causing thickening, rigidity, and narrowing of the lumen
  3. Excavated (ulcerated) (25%) that digs deeply into surrounding structures and may erode into the respiratory tree (with resultant fistula and pneumonia) or aorta (with catastrophic bleeding) or may permeate the mediastinum and pericardium.
- Local extension into adjacent mediastinal structures occurs early, possibly due to the absence of serosa for most of the esophagus. Tumors located in the upper third of the esophagus also metastasize to cervical lymph nodes; those in the middle third to the mediastinal, paratracheal, and tracheobronchial lymph nodes; and those in the lower third most often spread to the gastric and celiac groups of nodes.

**Microscopic features** (Fig. 5-39 B)
- Most squamous cell carcinomas are moderately to well-differentiated,
- They are invasive tumors that have infiltrated through the wall or beyond.

The rich lymphatic network in the submucosa promotes extensive circumferential and longitudinal spread. Esophageal carcinomas are usually quite large by the time of diagnosis, produces dysphagia and obstruction gradually. Cachexia is frequent. Hemorrhage and sepsis may accompany ulceration of the tumor. The five-year survival rate in patients with superficial esophageal carcinoma is about 75%, compared to 25% in patients who undergo "curative" surgery for more advanced disease. Local recurrence and distant metastasis following surgery are common. The presence of lymph node metastases at the time of resection significantly reduces survival.

**Adenocarcinoma**
With increasing recognition of Barrett mucosa, most adenocarcinomas in the lower third of the esophagus arise from the Barrett mucosa.

**Etiology and Pathogenesis**
These focus on Barrett esophagus. The lifetime risk for cancer development from Barrett esophagus is approximately 10%. Tobacco exposure and obesity are risk factors. Helicobacter pylori infection may be a contributing factor.

**Gross features**: (Fig. 5-40 A)
- adenocarcinomas arising in the setting of Barrett esophagus are usually located in the distal esophagus and may invade the adjacent gastric cardia.
As is the case with squamous cell carcinomas, adenocarcinomas initially appear as flat raised patches that may develop into large nodular fungating masses or may exhibit diffusely infiltrative or deeply ulcerative features.

**Microscopic features (Fig. 5-40 B)**

- Most tumors are mucin-producing glandular tumors exhibiting intestinal-type features.
- Multiple foci of dysplastic mucosa are frequently present adjacent to the tumor.

Adenocarcinomas arising in Barrett esophagus chiefly occur in patients over the age of 40 years and similar to Barrett esophagus, it is more common in men than in women, and in whites more than blacks (in contrast to squamous cell carcinomas). As in other forms of esophageal carcinoma, patients usually present because of difficulty swallowing, progressive weight loss, bleeding, and chest pain. The prognosis is as poor as that for other forms of esophageal cancer, with under 20% overall five-year survival. Identification and resection of early cancers with invasion limited to the mucosa or submucosa improves five-year survival to over 80%. Regression or surgical removal of Barrett esophagus has not yet been shown to eliminate the risk for adenocarcinoma.