ANEMIA

INTRODUCTION
Anemia is the blood disorder, characterized by the reduction in:
1. Red blood cell (RBC) count
2. Hemoglobin content
3. Packed cell volume (PVC).
Generally, reduction in RBC count, hemoglobin content and PCV occurs because of:
1. Decreased production of RBC
2. Increased destruction of RBC
3. Excess loss of blood from the body.
All these incidents are caused either by inherited disorders or environmental influences such as nutritional problem, infection and exposure to drugs or toxins.

CLASSIFICATION OF ANEMIA
Anemia is classified by two methods:
1. Morphological classification
2. Etiological classification.

1. MORPHOLOGICAL CLASSIFICATION
Morphological classification depends upon the size and color of RBC. Size of RBC is determined by mean corpuscular volume (MCV). Color is determined by mean corpuscular hemoglobin concentration (MCHC). By this method, the anemia is classified into four types (Table 14.1):

i). Normocytic Normochromic Anemia
Size (MCV) and color (MCHC) of RBCs are normal. But the number of RBC is less.

ii). Macrocytic Normochromic Anemia
RBCs are larger in size with normal color. RBC count is less.

iii). Macrocytic Hypochromic Anemia
RBCs are larger in size. MCHC is less, so the cells are pale (less colored).

iv). Microcytic Hypochromic Anemia
RBCs are smaller in size with less color.

2. ETIOLOGICAL CLASSIFICATION
On the basis of etiology (study of cause or origin), anemia is divided into five types (Table 14.2):

i.) Hemorrhagic anemia
ii.) Hemolytic anemia
iii.) Nutrition deficiency anemia
iv.) Aplastic anemia
v.) Anemia of chronic diseases.

<table>
<thead>
<tr>
<th>Type of anemia</th>
<th>Size of RBC (MCV)</th>
<th>Color of RBC (MCHC)</th>
</tr>
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<tbody>
<tr>
<td>Normocytic normochromic</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Normocytic hypochromic</td>
<td>Normal</td>
<td>Less</td>
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<tr>
<td>Macrocytic hypochromic</td>
<td>Large</td>
<td>Less</td>
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<tr>
<td>Microcytic hypochromic</td>
<td>Small</td>
<td>Less</td>
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</table>
i.) Hemorrhagic Anemia
Hemorrhage refers to excessive loss of blood. Anemia due to hemorrhage is known as hemorrhagic anemia. It occurs both in acute and chronic hemorrhagic conditions.

a) Acute hemorrhage
Acute hemorrhage refers to sudden loss of a large quantity of blood as in the case of accident. Within about 24 hours after the hemorrhage, the plasma portion of blood is replaced. However, the replacement of RBCs does not occur quickly and it takes at least 4 to 6 weeks. So, with less number of RBCs, hemodilution occurs. However, morphologically the RBCs are normocytic and normochromic. Decreased RBC count causes hypoxia, which stimulates the bone marrow to produce more number of RBCs. So, the condition is corrected within 4 to 6 weeks.

b) Chronic hemorrhage
It refers to loss of blood by internal or external bleeding, over a long period of time. It occurs in conditions like peptic ulcer, purpura, hemophilia and menorrhagia. Due to continuous loss of blood, lot of iron is lost from the body causing iron deficiency. This affects the synthesis of hemoglobin resulting in less hemoglobin content in the cells. The cells also become small. Hence, the RBCs are microcytic and hypochromic (Table 14.2).

### TABLE 1.2: Etiological classification of anemia

<table>
<thead>
<tr>
<th>Type of anemia</th>
<th>Causes</th>
<th>Morphology of RBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic anemia</td>
<td>Acute loss of blood</td>
<td>Normocytic, normochromic</td>
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<tr>
<td></td>
<td>Chronic loss of blood</td>
<td>Microcytic, hypochromic</td>
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<tr>
<td>Hemolytic anemia</td>
<td>Extrinsic hemolytic anemia:</td>
<td>Normocytic normochromic</td>
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<tr>
<td></td>
<td>i. Liver failure</td>
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<td></td>
<td>ii. Renal disorder</td>
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<td></td>
<td>iii. Hypersplenism</td>
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<td></td>
<td>iv. Burns</td>
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<td></td>
<td>v. Infections – hepatitis, malaria and</td>
<td></td>
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<tr>
<td></td>
<td>septicemia</td>
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<td></td>
<td>vi. Drugs – Penicillin, antimalarial drugs</td>
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<td></td>
<td>and sulfa drugs</td>
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<td></td>
<td>vii. Poisoning by lead, coal and tar</td>
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<td></td>
<td>viii. Presence of isoagglutinins like anti</td>
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<td></td>
<td>Rh</td>
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<td></td>
<td>xi. Autoimmune diseases – rheumatoid arthritis and ulcerative colitis</td>
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<tr>
<td></td>
<td>Intrinsic hemolytic anemia:</td>
<td>Sickle cell anemia: Sickled shape</td>
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<td></td>
<td>Hereditary disorders</td>
<td>Thalassemia: Small and irregular</td>
</tr>
<tr>
<td>Nutrition deficiency anemia</td>
<td>Iron deficiency</td>
<td>Microcytic, hypochromic</td>
</tr>
<tr>
<td></td>
<td>Protein deficiency</td>
<td>Macrocytic, hypochromic</td>
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<tr>
<td></td>
<td>Vitamin B12</td>
<td>Macrocytic, normochromic/hypochromic</td>
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</tbody>
</table>
ii.) **Hemolytic Anemia**

Hemolysis means destruction of RBCs. Anemia due to excessive hemolysis which is not compensated by increased RBC production is called hemolytic anemia. It is classified into two types:

A. Extrinsic hemolytic anemia.

B. Intrinsic hemolytic anemia.

a) **Extrinsic hemolytic anemia:**

It is the type of anemia caused by destruction of RBCs by external factors. Healthy RBCs are hemolized by factors outside the blood cells such as antibodies, chemicals and drugs. Extrinsic hemolytic anemia is also called **autoimmune hemolytic anemia.**

Common causes of external hemolytic anemia:

i. Liver failure

ii. Renal disorder

iii. Hypersplenism

iv. Burns

v. Infections like hepatitis, malaria and septicemia

vi. Drugs such as penicillin, antimalarial drugs and sulfa drugs

vii. Poisoning by chemical substances like lead, coal and tar

viii. Presence of isoagglutinins like antiRh

ix. Autoimmune diseases such as rheumatoid arthritis and ulcerative colitis.

b) **Intrinsic hemolytic anemia:**

It is the type of anemia caused by destruction of RBCs because of the defective RBCs. There is production of unhealthy RBCs, which are short lived and are destroyed soon. Intrinsic hemolytic anemia is often inherited and it includes **sickle cell anemia** and **thalassemia.**

i) **Sickle cell anemia**

Sickle cell anemia is an inherited blood disorder, characterized by sickle shaped red blood cells. It is also called **hemoglobin SS disease** or **sickle cell disease.** It is common in people of African origin. Sickle cell anemia is due to the abnormal hemoglobin called hemoglobin S (sickle cell hemoglobin). In this, αchains are normal and βchains are abnormal. The molecules of hemoglobin S polymerize into long chains and precipitate inside the cells. Because of this, the RBCs attain sickle (crescent) shape and become
more fragile leading to hemolysis. Sickle cell anemia occurs when a person inherits two abnormal genes (one from each parent).

II) **Thalassemia**

Thalassemia is an inherited disorder, characterized by abnormal hemoglobin. It is also known as Cooley’s anemia or Mediterranean anemia. It is more common in Thailand and to some extent in Mediterranean countries.

Thalassemia is of two types:

i. α-thalassemia

ii. β-thalassemia.

i. **α-Thalassemia**

α-thalassemia occurs in fetal life or infancy. In this α-chains are less, absent or abnormal. In adults, β-chains are in excess and in children, γ-chains are in excess. This leads to defective erythropoiesis and hemolysis. The infants may be stillborn or may die immediately after birth.

ii. **β-Thalassemia**

In β-thalassemia, β-chains are less in number, absent or abnormal with an excess of α-chains. The α-chains precipitate causing defective erythropoiesis and hemolysis.

3. **Nutrition Deficiency Anemia**

Anemia that occurs due to deficiency of a nutritive substance necessary for erythropoiesis is called nutrition deficiency anemia. The substances which are necessary for erythropoiesis are iron, proteins and vitamins like C, B12 and folic acid. The types of nutrition deficiency anemia are:

a) **Iron deficiency anemia**

Iron deficiency anemia is the most common type of anemia. It develops due to inadequate availability of iron for hemoglobin synthesis. RBCs are microcytic and hypochromic.

Causes of iron deficiency anemia:

i. Loss of blood

ii. Decreased intake of iron

iii. Poor absorption of iron from intestine

iv. Increased demand for iron in conditions like growth and pregnancy.

**Features of iron deficiency anemia:**

Features of iron deficiency anemia are brittle nails, spoon shaped nails (koilonychias), brittle hair, atrophy of papilla in tongue and dysphagia (difficulty in swallowing).

b) **Protein deficiency anemia**

Due to deficiency of proteins, the synthesis of hemoglobin is reduced. The RBCs are macrocytic and hypochromic.

c) **Pernicious anemia or Addison’s anemia**

Pernicious anemia is the anemia due to deficiency of vitamin B12. It is also called Addison’s anemia. It is due to atrophy of the gastric mucosa because of autoimmune destruction of parietal cells. The gastric atrophy results in decreased production of
intrinsic factor and poor absorption of vitamin B12, which is the maturation factor for RBCs. RBCs are larger and immature with almost normal or slightly low hemoglobin level. Synthesis of hemoglobin is almost normal in this type of anemia. So, cells are macrocytic and normochromic/hypochromic. Before knowing the cause of this anemia, it was very difficult to treat the patients and the disease was considered to be fatal. So, it was called pernicious anemia. Pernicious anemia is common in old age and it is more common in females than in males. It is associated with other autoimmune diseases like disorders of thyroid gland, Addison’s disease, etc. Characteristic features of this type of anemia are lemon yellow color of skin (due to anemic paleness and mild jaundice) and red sore tongue. Neurological disorders such as paresthesia (abnormal sensations like numbness, tingling, burning, etc.), progressive weakness and ataxia (muscular incoordination) are also observed in extreme conditions.

d) Megaloblastic anemia
Megaloblastic anemia is due to the deficiency of another maturation factor called folic acid. Here, the RBCs are not matured. The DNA synthesis is also defective, so the nucleus remains immature. The RBCs are megaloblastic and hypochromic. Features of pernicious anemia appear in megaloblastic anemia also. However, neurological disorders may not develop.

4. Aplastic Anemia
Aplastic anemia is due to the disorder of red bone marrow. Red bone marrow is reduced and replaced by fatty tissues. Bone marrow disorder occurs in the following conditions:
   i. Repeated exposure to X-ray or gamma ray radiation.
   ii. Presence of bacterial toxins, quinine, gold salts, benzene, radium, etc.
   iii. Tuberculosis.
iv. Viral infections like hepatitis and HIV infections.
In aplastic anemia, the RBCs are normocytic and normochromic.

5. Anemia of Chronic Diseases
Anemia of chronic diseases is the second common type of anemia (next to iron deficiency anemia). It is characterized by short lifespan of RBCs, caused by disturbance in iron metabolism or resistance to erythropoietin action. Anemia develops after few months of sustained disease. RBCs are normocytic and normochromic. Common causes anemia of chronic diseases:
   i.) Noninfectious inflammatory diseases such as rheumatoid arthritis (chronic inflammatory autoimmune disorder affecting joints).
   ii.) Chronic infections like tuberculosis (infection caused by Mycobacterium tuberculosis) and abscess (collection of pus in the infected tissue) in lungs.
   iii.) Chronic renal failure, in which the erythropoietin secretion decreases (since erythropoietin is necessary for the stimulation of bone marrow to produce RBCs, its deficiency causes anemia).
iv.) Neoplastic disorders (abnormal and disorganized growth in tissue or organ) such as Hodgkin’s disease (malignancy involving lymphocytes) and cancer of lung and breast. RBCs are generally normocytic and normochromic in this type of anemia. However, in progressive disease associated with iron deficiency the cells become microcytic and hypochromic.
HAEMOPHILIA

Haemophilia is a mostly inherited genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. This results in people bleeding for a longer time after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. Those with a mild case of the disease may have symptoms only after an accident or during surgery. Bleeding into a joint can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of consciousness.

There are two main types of haemophilia: haemophilia A, which occurs due to low amounts of clotting factor VIII, and haemophilia B, which occurs due to low levels of clotting factor IX. They are typically inherited from one's parents through an X chromosome carrying a nonfunctional gene. Rarely a new mutation may occur during early development or haemophilia may develop later in life due to antibodies forming against a clotting factor. Other types include haemophilia C, which occurs due to low levels of factor XI, and parahaemophilia, which occurs due to low levels of factor V. Acquired haemophilia is associated with cancers, autoimmune disorders, and pregnancy. Diagnosis is by testing the blood for its ability to clot and its levels of clotting factors.

The type of haemophilia known as parahaemophilia is a mild and rare form and is due to a deficiency in factor V. This type can be inherited or acquired.

A non-genetic form of haemophilia is caused by autoantibodies against factor VIII and so is known as acquired haemophilia A. Acquired haemophilia can be associated with cancers, autoimmune disorders and following childbirth.

Prevention may occur by removing an egg, fertilizing it, and testing the embryo before transferring it to the uterus. Treatment is by replacing the missing blood clotting factors. This may be done on a regular basis or during bleeding episodes. Replacement may take place at home or in hospital. The clotting factors are made either from human blood or by recombinant methods. Up to 20% of people develop antibodies to the clotting factors which makes treatment more difficult. The medication desmopressin may be used in those with mild haemophilia A. Studies of gene therapy are in early human trials.
There are several types of haemophilia: haemophilia A, haemophilia B, haemophilia C, parahaemophilia, acquired haemophilia A, and acquired haemophilia B.

Haemophilia A, is a recessive X-linked genetic disorder resulting in a deficiency of functional clotting Factor VIII. Haemophilia B, is also a recessive X-linked genetic disorder involving a lack of functional clotting Factor IX. Haemophilia C, is an autosomal genetic disorder involving a lack of functional clotting Factor XI. Haemophilia C is not completely recessive, as heterozygous individuals also show increased bleeding.

Characteristic symptoms vary with severity. In general symptoms are internal or external bleeding episodes, which are called "bleeds". People with more severe haemophilia suffer more severe and more frequent bleeds, while people with mild haemophilia usually suffer more minor symptoms except after surgery or serious trauma. In cases of moderate haemophilia symptoms are variable which manifest along a spectrum between severe and mild forms.

In both haemophilia A and B, there is spontaneous bleeding but a normal bleeding time, normal prothrombin time, normal thrombin time, but prolonged partial thromboplastin
Internal bleeding is common in people with severe haemophilia and some individuals with moderate haemophilia. The most characteristic type of internal bleed is a joint bleed where blood enters into the joint spaces.[16] This is most common with severe haemophiliacs and can occur spontaneously (without evident trauma). If not treated promptly, joint bleeds can lead to permanent joint damage and disfigurement.[16] Bleeding into soft tissues such as muscles and subcutaneous tissues is less severe but can lead to damage and requires treatment.

**COMPLICATIONS**

Severe complications are much more common in cases of severe and moderate haemophilia. Complications may arise from the disease itself or from its treatment:

- **Deep internal bleeding**, e.g. deep-muscle bleeding, leading to swelling, numbness or pain of a limb.
- **Joint damage** from haemarthrosis (haemophilic arthropathy), potentially with severe pain, disfigurement, and even destruction of the joint and development of debilitating arthritis.
- **Transfusion transmitted infection** from blood transfusions that are given as treatment.
- **Adverse reactions** to clotting factor treatment, including the development of an immune inhibitor which renders factor replacement less effective.
- **Intracranial haemorrhage** is a serious medical emergency caused by the buildup of pressure inside the skull. It can cause disorientation, nausea, loss of consciousness, brain damage, and death.

**TREATMENT**

replacement coagulation factor. Clotting factors are either given preventively or on-demand.

Desmopressin (DDAVP) may be used in those with mild haemophilia A. Tranexamic acid or epsilon aminocaproic acid may be given along with clotting factors to prevent breakdown of clots. Symptomatic treatment are also given.
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Easy and prolonged bleeding</th>
</tr>
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<tbody>
<tr>
<td>Usual onset</td>
<td>At birth</td>
</tr>
<tr>
<td>Causes</td>
<td>Usually genetic</td>
</tr>
<tr>
<td>Diagnostic method</td>
<td>Blood test</td>
</tr>
<tr>
<td>Prevention</td>
<td>Preimplantation screening</td>
</tr>
<tr>
<td>Treatment</td>
<td>Replace missing blood clotting factors</td>
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</table>

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JAIPUR COLLEGE OF PHARMACY, JAIPUR
HEBEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis is an abnormality of red blood cells, or erythrocytes. The disorder is caused by mutations in genes relating to membrane proteins that allow for the erythrocytes to change shape. The abnormal erythrocytes are sphere-shaped (spherocytosis) rather than the normal biconcave disk shaped. Dysfunctional membrane proteins interfere with the cell’s ability to be flexible to travel from the arteries to the smaller capillaries. This difference in shape also makes the red blood cells more prone to rupture. Cells with these dysfunctional proteins are degraded in the spleen. This shortage of erythrocytes results in hemolytic anemia.

It is the most common cause of inherited hemolysis in European and North American Caucasian populations, with an incidence of 1 in 5000 births. The clinical severity of HS varies from symptom-free carrier to severe hemolysis because the disorder exhibits incomplete penetrance in its expression.

Symptoms include anemia, jaundice, splenomegaly, and fatigue. Furthermore, the detritus of the broken-down blood cells – unconjugated or indirect bilirubin – accumulates in the gallbladder, and can cause pigmented gallstones to develop. In chronic patients, an infection or other illness can cause an increase in the destruction of red blood cells, resulting in the appearance of acute symptoms, a hemolytic crisis.

On a blood smear, Howell-Jolly bodies may be seen within red blood cells. Primary treatment for patients with symptomatic HS has been total splenectomy, which eliminates the hemolytic process, allowing normal hemoglobin, reticulocyte and bilirubin levels.

Acute cases can threaten to cause hypoxia through anemia and acute kernicterus through high blood levels of bilirubin, particularly in newborns. Most cases can be detected soon after birth. An adult with this disease should have their children tested, although the presence of the disease in children is usually noticed soon after birth. Occasionally, the disease will go unnoticed until the child is about 4 or 5 years of age. A person may also be a carrier of the disease and show no signs or symptoms of the disease. Other symptoms may include abdominal pain that could lead to the removal of the spleen and/or gallbladder.

Spherocytosis patients who are heterozygous for a hemochromatosis gene may suffer from iron overload, despite the hemochromatosis genes being recessive.
COMPLICATIONS

- Hemolytic crisis, with more pronounced jaundice due to accelerated hemolysis (may be precipitated by infection).

- Aplastic crisis with dramatic fall in hemoglobin level and (reticulocyte count)-decompensation, usually due to maturation arrest and often associated with megaloblastic changes; may be precipitated by infection, such as influenza, notably with parvovirus B19.

- Folate deficiency caused by increased bone marrow requirement.

- Pigmented gallstones occur in approximately half of untreated patients. Increased hemolysis of red blood cells leads to increased bilirubin levels, because bilirubin is a breakdown product of heme. The high levels of bilirubin must be excreted into the bile by the liver, which may cause the formation of a pigmented gallstone, which is composed of calcium bilirubinate. Since these stones contain high levels of calcium carbonates and phosphate, they are radiopaque and are visible on x-ray.

- Leg ulcer.

- Abnormally low hemoglobin A1C levels.[8] Hemoglobin A1C (glycated hemoglobin) is a test for determining the average blood glucose levels over an extended period of time, and is often used to evaluate glucose control in diabetics. The hemoglobin A1C levels are abnormally low because the life span of the red blood cells is decreased, providing less time for the non-enzymatic glycosylation of hemoglobin. Thus, even with high overall blood sugar, the A1C will be lower than expected.

PATHOPHYSIOLOGY

Hereditary spherocytosis can be an autosomal recessive or autosomal dominant trait. Hereditary spherocytosis is most commonly (though not exclusively) found in Northern European and Japanese families, although an estimated 25% of cases are due to spontaneous mutations. A patient has a 50% chance of passing the mutation onto each of his/her offspring.

Hereditary spherocytosis is caused by a variety of molecular defects in the genes that code for the red blood cell proteins spectrin(alpha and beta), ankyrin, band 3 protein, protein
4.2, and other red blood cell membrane proteins:
These proteins are necessary to maintain the normal shape of a red blood cell, which is a
biconcave disk. The integrating protein that is most commonly defective is spectrin which is
responsible for incorporation and binding of spectrin, thus in its dysfunction cytoskeletal
instabilities ensue.
The primary defect in hereditary spherocytosis is a deficiency of membrane surface area.
Decreased surface area may be produced by two different mechanisms: 1) Defects of
spectrin, ankyrin (most commonly), or protein 4.2 lead to reduced density of the membrane
skeleton, destabilizing the overlying lipid bilayer and releasing band 3-containing microvesicles. 2) Defects of band 3 lead to band 3 deficiency and loss of its lipid-stabilizing effect. This results in the loss of band 3-free microvesicles. Both pathways result
in membrane loss, decreased surface area, and formation of spherocytes with decreased
deformability.
As the spleen normally targets abnormally shaped red cells (which are typically older), it also
destroys spherocytes. In the spleen, the passage from the cords of Billroth into the sinusoids
may be seen as a bottleneck, where red blood cells need to be flexible in order to pass
through. In hereditary spherocytosis, red blood cells fail to pass through and get
phagocytosed, causing extravascular hemolysis.
**DIAGNOSIS**

In a peripheral blood smear, the red blood cells will appear abnormally small and lack the
central pale area that is present in normal red blood cells. These changes are also seen in non-
hereditary spherocytosis, but they are typically more pronounced in hereditary spherocytosis.
The number of immature red blood cells (reticulocyte count) will be elevated. An increase in
the mean corpuscular hemoglobin concentration is also consistent with hereditary
spherocytosis.
Other protein deficiencies cause hereditary elliptocytosis, pyropoikilocytosis or stomatocytosis.
In longstanding cases and in patients who have taken iron supplementation or received
numerous blood transfusions, iron overload may be a significant problem. This is a potential

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cause of heart muscle damage and liver disease. Measuring iron stores is therefore considered part of the diagnostic approach to hereditary spherocytosis. An osmotic fragility test can aid in the diagnosis. In this test, the spherocytes will rupture in liquid solutions less concentrated than the inside of the red blood cell. This is due to increased permeability of the spherocyte membrane to salt and water, which enters the concentrated inner environment of the RBC and leads to its rupture. Although the osmotic fragility test is widely considered the gold standard for diagnosing hereditary spherocytosis, it misses as many as 25% of cases. Flow cytometric analysis of eosin-5′-maleimide-labeled intact red blood cells and the acidified glycerol lysis test are two additional options to aid diagnosis.

**TREATMENT**

Although research is ongoing, at this point there is no cure for the genetic defect that causes hereditary spherocytosis. Current management focuses on interventions that limit the severity of the disease. Treatment options include:

- **Splenectomy**: As in non-hereditary spherocytosis, acute symptoms of anemia and hyperbilirubinemia indicate treatment with blood transfusions or exchanges and chronic symptoms of anemia and an enlarged spleen indicate dietary supplementation of folic acid and splenectomy, the surgical removal of the spleen. Splenectomy is indicated for moderate to severe cases, but not mild cases. To decrease the risk of sepsis, post-splenectomy spherocytosis patients require immunization against the influenza virus, encapsulated bacteria such as Streptococcus pneumoniae and meningococcus, and prophylactic antibiotic treatment. However, the use of prophylactic antibiotics, such as penicillin, remains controversial.

- **Partial splenectomy**: Since the spleen is important for protecting against encapsulated organisms, sepsis caused by encapsulated organisms is a possible complication of splenectomy. The option of partial splenectomy may be considered in the interest of preserving immune function. Research on outcomes is currently limited, but favorable. Surgical removal of the gallbladder may be necessary.
HEREDITARY STOMATOCYTOSIS

Hereditary stomatocytosis describes a number of inherited autosomal dominant human conditions which affect the red blood cell, in which the membrane or outer coating of the cell 'leaks' sodium and potassium ions.

CAUSES

The cause for these hereditary conditions is now understood to be various mutations in the erythrocyte membrane protein, band 3. It is this protein which mediates the cation leaks which are characteristic of this disease.

PATHOPHYSIOLOGY

Osmosis leads to the red blood cell having a constant tendency to swell and burst. This tendency is countered by manipulating the flow of sodium and potassium ions. A 'pump' forces sodium out of the cell and potassium in, and this action is balanced by a process called 'the passive leak'. In the hereditary stomatocytoses, the passive leak is increased and the cell becomes swamped with salt and water. The cell lyses and a haemolytic anaemia results. For as yet unknown reasons, the cells take on the shape of a cup, with a 'mouth-shaped' (stoma) area of central pallor. The two varieties of stomatocytosis classified with respect to hydration status are overhydrated (hydrocytosis) and dehydrated (xerocytosis).

TREATMENT

At present there is no specific treatment. Many patients with haemolytic anaemia take folic acid (vitamin B$_9$) since the greater turnover of cells consumes this vitamin. During crises transfusion may be required. Clotting problems can occur for which anticoagulation may be needed. Unlike hereditary spherocytosis, splenectomy is contraindicated.
1. THYROID DISEASE

**Thyroid disease** is a medical condition that affects the function of the thyroid gland. The thyroid gland is located at the front of the neck and produces thyroid hormones that travel through the blood to help regulate many other organs, meaning that it is an endocrine organ. These hormones normally act in the body to regulate energy use, infant development, and childhood development.

There are five general types of thyroid disease, each with their own symptoms. A person may have one or several different types at the same time. The five groups are:

1) Hypothyroidism (low function) caused by not having enough free thyroid hormones
2) Hyperthyroidism (high function) caused by having too much free thyroid hormones
3) Structural abnormalities, most commonly a goiter (enlargement of the thyroid gland)
4) Tumors which can be benign (not cancerous) or cancerous
5) Abnormal thyroid function tests without any clinical symptoms (subclinical hypothyroidism or subclinical hyperthyroidism).

In some types, such as subacute thyroiditis or postpartum thyroiditis, symptoms may go away after a few months and laboratory tests may return to normal. However most types of thyroid disease do not resolve on their own. Common hypothyroid symptoms include fatigue, low energy, weight gain, inability to tolerate the cold, slow heart rate, dry skin and constipation. Common hyperthyroid symptoms include irritability, anxiety, weight loss, fast heartbeat, inability to tolerate the heat, diarrhea, and enlargement of the thyroid. Structural abnormalities may not produce symptoms, however some people may have hyperthyroid or hypothyroid symptoms related to the structural abnormality or notice swelling of the neck. Rarely goiters can cause compression of the airway, compression of the vessels in the neck, or difficulty swallowing. Tumors, often called thyroid nodules, can also have many different symptoms ranging from hyperthyroidism to hypothyroidism to swelling in the neck and compression of the structures in the neck.

Diagnosis starts with a history and physical examination. Screening for thyroid disease in patients without symptoms is a debated topic although commonly practiced in the United States. If dysfunction of the thyroid is suspected, laboratory tests can help support or rule out thyroid disease. Initial blood tests often include thyroid-stimulating hormone (TSH) and free thyroxine (T4). Total and free triiodothyronine (T3) levels are less commonly used. If autoimmune disease of the thyroid is suspected, blood tests looking for Anti-thyroid autoantibodies can also be obtained. Procedures such as ultrasound, biopsy and a radioiodine scanning and uptake study may also be used to help with the diagnosis, particularly if a nodule is suspected.

Treatment of thyroid disease varies based on the disorder. Levothyroxine is the mainstay of treatment for people with hypothyroidism, while people with hyperthyroidism caused by Graves' disease can be managed with iodine therapy, antithyroid medication, or surgical removal of the thyroid gland. Thyroid surgery may also be performed to remove a thyroid nodule or to reduce the size of a goiter if it obstructs nearby structures or for cosmetic reasons.
SIGNS AND SYMPTOMS

Symptoms of the condition vary with type: hypo- vs. hyperthyroidism, which are further described below.

Possible symptoms of hypothyroidism are:

- Tiredness
- Unexplained weight gain
- Slow movement
- Muscle cramps
- Slow heart rate (bradycardia)
- Sensitivity to cold temperatures
- Constipation
- Depressed mood
- Memory difficulty

Possible symptoms of hyperthyroidism are:

- Difficulty sleeping (insomnia)
- Unexplained weight loss
- Tremors
- Fast heart rate (tachycardia) or palpitations
- Sensitivity to hot temperatures, excess sweating
- Diarrhea
- Anxiety, irritability

Note: certain symptoms and physical changes can be seen in both hypothyroidism and hyperthyroidism — fatigue, fine / thinning hair, menstrual cycle irregularities, muscle weakness / aches (myalgia), and different forms of myxedema.

DISEASES

1) Low function (Hypothyroidism)

Hypothyroidism is a state in which the body is not producing enough thyroid hormones, or is not able to respond to / utilize existing thyroid hormones properly. The main categories are:

- Thyroiditis: an inflammation of the thyroid gland
  - Hashimoto's thyroiditis / Hashimoto's disease
  - Ord's thyroiditis
  - Postpartum thyroiditis
  - Silent thyroiditis
  - Acute thyroiditis
  - Riedel's thyroiditis (the majority of cases do not affect thyroid function, but approximately 30% of cases lead to hypothyroidism)
- Iatrogenic hypothyroidism
  - Postoperative hypothyroidism
1) Medication- or radiation-induced hypothyroidism
- Thyroid hormone resistance
- Euthyroid sick syndrome
- Congenital hypothyroidism: a deficiency of thyroid hormone from birth, which untreated can lead to cretinism

2) High function (Hyperthyroidism)

**Figure: 1.1** Exophthalmos is the eye bulging that may be seen with Graves Disease, one of the major causes of hyperthyroidism

Hyperthyroidism is a state in which the body is producing too much thyroid hormone. The main hyperthyroid conditions are:

- Graves' disease
- Toxic thyroid nodule
- Thyroid storm
- Toxic nodular struma (Plummer's disease)
- Hashitoxicosis: *transient* hyperthyroidism that can occur in Hashimoto's thyroiditis

3) Structural abnormalities

**Figure: 1.2** Endemic goiter

- Goiter: an abnormal enlargement of the thyroid gland
4) Tumors

- Thyroid adenoma: benign / non-cancerous tumor
- Thyroid cancer
  - Papillary
  - Follicular
  - Medullary
  - Anaplastic
- Lingual thyroid
- Thyroglossal duct cyst

5) Medication side effects

Certain medications can have the unintended side effect of affecting thyroid function. While some medications can lead to significant hypothyroidism or hyperthyroidism and those at risk will need to be carefully monitored, some medications may affect thyroid hormone lab tests without causing any symptoms or clinical changes, and may not require treatment. The following medications have been linked to various forms of thyroid disease:

- Amiodarone (more commonly can lead to hypothyroidism, but can be associated with some types of hyperthyroidism)
- Lithium salts (hypothyroidism)
- Some types of interferon and IL-2 (thyroiditis)
- Glucocorticoids, dopamine agonists, and somatostatin analogs (block TSH, which can lead to hypothyroidism)

PATHOPHYSIOLOGY

Most thyroid disease in the United States stems from a condition where the body's immune system attacks itself. In other instances, thyroid disease comes from the body trying to adapt to environmental conditions like iodine deficiency or to new physiologic conditions like pregnancy.

i) Autoimmune Thyroid Disease

Autoimmune thyroid disease is a general category of disease that occurs due to the immune system targeting its own body. It is not fully understood why this occurs, but it is thought to be partially genetic as these diseases tend to run in families. In one of the most common types, Grave's Disease, the body produces antibodies against the TSH receptor on thyroid cells. This causes the receptor to activate even without TSH being present and causes the thyroid to produce and release excess thyroid hormone (hyperthyroidism). Another common form of autoimmune thyroid disease is Hashimoto thyroiditis where the body produces antibodies against different normal components of the thyroid gland, most commonly thyroglobulin, thyroid peroxidase, and the TSH receptor. These antibodies cause the immune system to attack the thyroid cells and cause inflammation (lymphocytic infiltration) and destruction (fibrosis) of the gland.
ii) Goiter

Goiter is the general enlargement of the thyroid that can be associated with many thyroid diseases. The main reason this happens is because of increased signaling to the thyroid by way of TSH receptors to try to make it produce more thyroid hormone. This causes increased vascularity and increase in size (hypertrophy) of the gland. In hypothyroid states or iodine deficiency, the body recognizes that it is not producing enough thyroid hormone and starts to produce more TSH to help stimulate the thyroid to produce more thyroid hormone. This stimulation causes the gland to increase in size to increase production of thyroid hormone. In hyperthyroidism caused by Grave’s Disease or toxic multinodular goiter, there is excess stimulation of the TSH receptor even when thyroid hormone levels are normal. In Grave’s Disease this is because of an autoantibodies (Thyroid Stimulating Immunoglobulins) which bind to and activate the TSH receptors in place of TSH while in toxic multinodular goiter this is often because of a mutation in the TSH receptor that causes it to activate without receiving a signal from TSH. In more rare cases, the thyroid may become enlarged because it becomes filled with thyroid hormone or thyroid hormone precursors that it is unable to release or because of congenital abnormalities or because of increased intake of iodine from supplementation or medication.

iii) Pregnancy

There are many changes to the body during pregnancy. One of the major changes to help with the development of the fetus is the production of human chorionic gonadotropin (hCG). This hormone, produced by the placenta, has similar structure to TSH and can bind to the maternal TSH receptor to produce thyroid hormone. During pregnancy, there is also an increase in estrogen which causes the mother to produce more thyroxine binding globulin, which is what carries most of the thyroid hormone in the blood. These normal hormonal changes often make pregnancy look like a hyperthyroid state but may be within the normal range for pregnancy, so it necessary to use trimester specific ranges for TSH and free T4. True hyperthyroidism in pregnancy is most often caused by an autoimmune mechanism from Grave’s Disease. New diagnosis of hypothyroidism in pregnancy is rare because hypothyroidism often makes it difficult to become pregnant in the first place. When hypothyroidism is seen in pregnancy, it is often because an individual already has hypothyroidism and needs to increase their levothyroxine dose to account for the increased thyroxine binding globulin present in pregnancy.

DIAGNOSIS

Diagnosis of thyroid disease depends on symptoms and whether or not a thyroid nodule is present. Most patients will receive a blood test. Others might need an ultrasound, biopsy or a radiiodine scanning and uptake study.

i) Blood tests

- CBC - Complete blood count

ii) Thyroid function test

There are several hormones that can be measured in the blood to determine how the thyroid gland is functioning. These include the thyroid hormones triiodothyronine (T3) and its precursor thyroxine (T4), which are produced by the thyroid gland. Thyroid-stimulating
hormone (TSH) is another important hormone that is secreted by the anterior pituitary cells in the brain. Its primary function is to increase the production of T3 and T4 by the thyroid gland.

The most useful marker of thyroid gland function is serum thyroid-stimulating hormone (TSH) levels. TSH levels are determined by a classic negative feedback system in which high levels of T3 and T4 suppress the production of TSH, and low levels of T3 and T4 increase the production of TSH. TSH levels are thus often used by doctors as a screening test, where the first approach is to determine whether TSH is elevated, suppressed, or normal.

- Elevated TSH levels can signify inadequate thyroid hormone production (hypothyroidism)
- Suppressed TSH levels can point to excessive thyroid hormone production (hyperthyroidism)

Because a single abnormal TSH level can be misleading, T3 and T4 levels must be measured in the blood to further confirm the diagnosis. When circulating in the body, T3 and T4 are bound to transport proteins. Only a small fraction of the circulating thyroid hormones are unbound or free, and thus biologically active. T3 and T4 levels can thus be measured as free T3 and T4, or total T3 and T4, which takes into consideration the free hormones in addition to the protein-bound hormones. Free T3 and T4 measurements are important because certain drugs and illnesses can affect the concentrations of transport proteins, resulting in differing total and free thyroid hormone levels. There are differing guidelines for T3 and T4 measurements.

- Free T4 levels should be measured in the evaluation of hypothyroidism, and low free T4 establishes the diagnosis. T3 levels are generally not measured in the evaluation of hypothyroidism.[9]
- Free T4 and total T3 can be measured when hyperthyroidism is of high suspicion as it will improve the accuracy of the diagnosis. Free T4, total T3 or both are elevated and serum TSH is below normal in hyperthyroidism. If the hyperthyroidism is mild, only serum T3 may be elevated and serum TSH can be low or may not be detected in the blood.
- Free T4 levels may also be tested in patients who have convincing symptoms of hyper- and hypothyroidism, despite a normal TSH.

iii) Antithyroid antibodies

Autoantibodies to the thyroid gland may be detected in various disease states. There are several anti-thyroid antibodies, including anti-thyroglobulin antibodies (TgAb), anti-microsomal/anti-thyroid peroxidase antibodies (TPOAb), and TSH receptor antibodies (TSHRAb).

- Elevated anti-thyroglobulin (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) can be found in patients with Hashimoto's thyroiditis, the most common autoimmune type of hypothyroidism. TPOAb levels have also been found to be elevated in patients who present with subclinical hypothyroidism (where TSH is elevated, but free T4 is normal), and can help predict progression to overt hypothyroidism. The American Association Thyroid Association thus recommends measuring TPOAb levels when evaluating subclinical hypothyroidism or when trying to identify whether nodular thyroid disease is due to autoimmune thyroid disease.
- When the etiology of hyperthyroidism is not clear after initial clinical and biochemical evaluation, measurement of TSH receptor antibodies (TSHRAb) can help make the
diagnosis. In Grave's disease, TSHRAb levels are elevated as they are responsible for activating the TSH receptor and causing increased thyroid hormone production.

**iv) Other markers**

- There are two markers for thyroid-derived cancers.
  - Thyroglobulin (TG) levels can be elevated in well-differentiated papillary or follicular adenocarcinoma. It is often used to provide information on residual, recurrent or metastatic disease in patients with differentiated thyroid cancer. However, serum TG levels can be elevated in most thyroid diseases. Routine measurement of serum TG for evaluation of thyroid nodules is thus currently not recommended by the American Thyroid Association.
  - Elevated calcitonin levels in the blood have been shown to be associated with the rare medullary thyroid cancer. However, the measurement of calcitonin levels as a diagnostic tool is currently controversial due to falsely high or low calcitonin levels in a variety of diseases other than medullary thyroid cancer.
- Very infrequently, TBG and transthyretin levels may be abnormal; these are not routinely tested.
- To differentiate between different types of hypothyroidism, a specific test may be used. Thyrotropin-releasing hormone (TRH) is injected into the body through a vein. This hormone is naturally secreted by the hypothalamus and stimulates the pituitary gland. The pituitary responds by releasing thyroid-stimulating hormone (TSH). Large amounts of externally administered TRH can suppress the subsequent release of TSH. This amount of release-suppression is exaggerated in primary hypothyroidism, major depression, cocaine dependence, amphetamine dependence and chronic phencyclidine abuse. There is a failure to suppress in the manic phase of bipolar disorder.

**v) Ultrasound**

Many people may develop a thyroid nodule at some point in their lives. Although many who experience this worry that it is thyroid cancer, there are many causes of nodules that are benign and not cancerous. If a possible nodule is present, a doctor may order thyroid function tests to determine if the thyroid gland's activity is being affected. If more information is needed after a clinical exam and lab tests, medical ultrasonography can help determine the nature of thyroid nodule(s). There are some notable differences in typical benign vs. cancerous thyroid nodules that can particularly be detected by the high-frequency sound waves in an ultrasound scan. The ultrasound may also locate nodules that are too small for a doctor to feel on a physical exam, and can demonstrate whether a nodule is primarily solid, liquid (cystic), or a mixture of both. It is an imaging process that can often be done in a doctor's office, is painless, and does not expose the individual to any radiation.
vi) Radioiodine scanning and uptake

![Radioiodine scanning and uptake diagram]

**Figure: 1.4** Five scintigrams taken from thyroids with different syndromes: A) normal thyroid, B) Graves disease, diffuse increased uptake in both thyroid lobes, C) Plummer's disease, D) Toxic adenoma, E) Thyroiditis.

Thyroid scintigraphy, in which the thyroid is imaged with the aid of radioactive iodine (usually iodine-123, which does not harm thyroid cells, or rarely, iodine-131), is performed in the nuclear medicine department of a hospital or clinic. Radioiodine collects in the thyroid gland before being excreted in the urine. While in the thyroid, the radioactive emissions can be detected by a camera, producing a rough image of the shape (a radioiodine scan) and tissue activity (a radioiodine uptake) of the thyroid gland.

vii) Biopsy

A medical biopsy refers to the obtaining of a tissue sample for examination under the microscope or other testing, usually to distinguish cancer from noncancerous conditions. Thyroid tissue may be obtained for biopsy by fine needle aspiration (FNA) or by surgery.

**TREATMENT**

i) Medication

Levothyroxine is a stereoisomer of thyroxine (T4) which is degraded much more slowly and can be administered once daily in patients with hypothyroidism. Natural thyroid hormone from pigs is sometimes also used, especially for people who cannot tolerate the synthetic version. Hyperthyroidism caused by Graves' disease may be treated with the thioamide drugs propylthiouracil, carbimazole or methimazole, or rarely with Lugol's solution. Additionally, hyperthyroidism and thyroid tumors may be treated with radioactive iodine. Ethanol injections for the treatment of recurrent thyroid cysts and metastatic thyroid cancer in lymph nodes can also be an alternative to surgery.

ii) Surgery

If it is not managed by medication, surgery is done according to the disease condition.
2. DIABETES

**Diabetes mellitus (DM)**, commonly known as **diabetes**, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. Symptoms often include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the nerves, damage to the eyes and cognitive impairment.

Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

- **Type 1 diabetes** results from the pancreas's failure to produce enough insulin due to loss of beta cells. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The loss of beta cells is caused by an autoimmune response. The cause of this autoimmune response is unknown.

- **Type 2 diabetes** begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses, a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is a combination of excessive body weight and insufficient exercise.

- **Gestational diabetes** is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot and eye care are important for people with the disease. Type 1 diabetes must be managed with insulin injections. Type 2 diabetes may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 diabetes. Gestational diabetes usually resolves after the birth of the baby.
SIGNS AND SYMPTOMS

Figure: 2.1 Overview of the most significant symptoms of diabetes

The classic symptoms of untreated diabetes are unintended weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes. Other symptoms of diabetes include weight loss and tiredness.

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurred vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Long-term vision loss can also be caused by diabetic retinopathy. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadies.

i) Diabetic emergencies

People (usually with type 1 diabetes) may also experience episodes of diabetic ketoacidosis (DKA), a metabolic disturbance characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and in severe cases a decreased level of consciousness. A rare but equally severe possibility is hyperosmolar hyperglycemic state (HHS), which is more common in type 2 diabetes and is mainly the result of dehydration.

Treatment-related low blood sugar (hypoglycemia) is common in people with type 1 and also type 2 diabetes depending on the medication being used. Most cases are mild and are not considered medical emergencies. Effects can range from feelings of unease, sweating, trembling,
and increased appetite in mild cases to more serious effects such as confusion, changes in behavior such as aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases. Rapid breathing, sweating, and cold, pale skin are characteristic of low blood sugar but not definitive. Mild to moderate cases are self-treated by eating or drinking something high in sugar. Severe cases can lead to unconsciousness and must be treated with intravenous glucose or injections with glucagon.

ii) Complications

![Figure: 2.2 Retinopathy, nephropathy, and neuropathy are potential complications of diabetes](image)

**Figure: 2.2** Retinopathy, nephropathy, and neuropathy are potential complications of diabetes

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20) but may be the first symptom in those who have otherwise not received a diagnosis before that time.

The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease and about 75% of deaths in people with diabetes are due to coronary artery disease. Other macrovascular diseases include stroke, and peripheral artery disease.

The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves. Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and eventual blindness. Diabetes also increases the risk of having glaucoma, cataracts, and other eye problems. It is recommended that people with diabetes visit an eye doctor once a year. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplantation. Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes. The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to the skin. Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle atrophy and weakness.

**CAUSES**

<table>
<thead>
<tr>
<th>Comparison of type 1 and 2 diabetes</th>
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<td><strong>Feature</strong></td>
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*Pathophysiology B.Pharmacy II semester*

**JAIPUR COLLEGE OF PHARMACY, JAIPUR**
Onset | Sudden | Gradual  
---|---|---
Age at onset | Mostly in children | Mostly in adults  
Body size | Thin or normal[^38] | Often obese  
Ketoacidosis | Common | Rare  
Autoantibodies | Usually present | Absent  
Endogenous insulin | Low or absent | Normal, decreased or increased

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Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types". The "other specific types" are a collection of a few dozen individual causes.

i) Type 1

Type 1 diabetes is characterized by loss of the insulin-producing beta cells of the pancreatic islets, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin.[^41] It causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Although it has been called "juvenile diabetes" due to the frequent onset in children, the majority of individuals living with type 1 diabetes are now adults.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used. Still, type 1 diabetes can be accompanied by irregular and unpredictable high blood sugar levels, and the potential for diabetic ketoacidosis or serious low blood sugar levels. Other complications include an impaired counterregulatory response to low blood sugar, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease). These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.
Figure: 2.3 Autoimmune attack in type 1 diabetes.

Type 1 diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors, such as a viral infection or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans. Among dietary factors, data suggest that gliadin (a protein present in gluten) may play a role in the development of type 1 diabetes, but the mechanism is not fully understood.

Type 1 diabetes can occur at any age, and a significant proportion is diagnosed during adulthood. Latent autoimmune diabetes of adults (LADA) is the diagnostic term applied when type 1 diabetes develops in adults; it has a slower onset than the same condition in children. Given this difference, some use the unofficial term "type 1.5 diabetes" for this condition. Adults with LADA are frequently initially misdiagnosed as having type 2 diabetes, based on age rather than cause.

ii) Type 2

Figure: 2.4 Reduced insulin secretion and absorption leads to high glucose content in the blood.

Type 2 diabetes is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type of diabetes mellitus. Many people with type 2 diabetes have evidence of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) before meeting the criteria for type 2 diabetes. The progression of prediabetes to overt type 2 diabetes can be slowed or reversed by lifestyle changes or medications that improve insulin sensitivity or reduce the liver's glucose production.

Type 2 diabetes is primarily due to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress,
and urbanization. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders. Even those who are not obese often have a high waist–hip ratio.

Dietary factors such as sugar-sweetened drinks is associated with an increased risk. The type of fats in the diet is also important, with saturated fat and trans fats increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk. Eating lots of white rice also may increase the risk of diabetes. A lack of physical activity is believed to cause 7% of cases. Substitution other whole grains or brown for white rice may lower the risk of diabetes, although results are mixed.

Adverse childhood experiences (ACEs), including abuse, neglect, and household difficulties, increase the likelihood of type 2 diabetes later in life by 32%, with neglect having the strongest effect.

iii) Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery. However, after pregnancy approximately 5–10% of women with GDM are found to have DM, most commonly type 2. GDM is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required.

Though it may be transient, untreated GDM can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and skeletal muscle malformations. Increased levels of insulin in a fetus's blood may inhibit fetal surfactant production and cause infant respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

iv) Other types

Maturity onset diabetes of the young (MODY) is a rare autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production. It is significantly less common than the three main types, constituting 1–2% of all cases. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the specific gene defect; thus there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion
of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells, whereas others increase insulin resistance (especially glucocorticoids which can provoke "steroid diabetes"). The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization (WHO) when the current taxonomy was introduced in 1999.

The following is a list of disorders that may increase the risk of diabetes:

- **Genetic defects of β-cell function**
  - Maturity onset diabetes of the young
  - Mitochondrial DNA mutations
- **Genetic defects in insulin processing or insulin action**
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- **Exocrine pancreatic defects**
  - Chronic pancreatitis
  - Pancreatectomy
  - Pancreatic neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
- **Endocrinopathies**
  - Growth hormone excess (acromegaly)
  - Cushing syndrome
  - Hyperthyroidism
  - Hypothyroidism
  - Pheochromocytoma
  - Glucagonoma
- **Infections**
  - Cytomegalovirus infection
  - Coxsackievirus B
- **Drugs**
  - Glucocorticoids
  - Thyroid hormone
  - β-adrenergic agonists
  - Statins \[64\]

The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich vs a starch-rich meal is highlighted.
Figure: 2.5 Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose.

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1. Therefore, deficiency of insulin or the insensitivity of its receptors play a central role in all forms of diabetes mellitus.

The body obtains glucose from three main sources: the intestinal absorption of food; the breakdown of glycogen (glycogenolysis), the storage form of glucose found in the liver; and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in regulating glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.

Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.

If the amount of insulin available is insufficient, or if cells respond poorly to the effects of insulin (insulin resistance), or if the insulin itself is defective, then glucose is not absorbed properly by the body cells that require it, and is not stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as metabolic acidosis in cases of complete insulin deficiency.

When glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume is replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). In addition, intracellular glucose deficiency stimulates appetite leading to excessive food intake (polyphagia).
DIAGNOSIS

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level $\geq$ 7.0 mmol/L (126 mg/dL)
- Plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL) two hours after a 75 gram oral glucose load as in a glucose tolerance test (OGTT)
- Symptoms of high blood sugar and casual plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL)
- Glycated hemoglobin (HbA$_{1C}$) $\geq$ 48 mmol/mol ($\geq$ 6.5 DCCT %).

7.0 mmol/L (126 mg/dL) is considered diagnostic for diabetes mellitus.

Per the WHO, people with fasting glucose levels from 6.1 to 6.9 mmol/L (110 to 125 mg/dL) are considered to have impaired fasting glucose. People with plasma glucose at or above 7.8 mmol/L (140 mg/dL), but not over 11.1 mmol/L (200 mg/dL), two hours after a 75 gram oral glucose load are considered to have impaired glucose tolerance.

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

PREVENTION

There is no known preventive measure for type 1 diabetes. Type 2 diabetes can often be prevented or delayed by maintaining a normal body weight, engaging in physical activity, and eating a healthy diet. Higher levels of physical activity (more than 90 minutes per day) reduce the risk of diabetes. Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish. Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help prevent diabetes. Tobacco smoking is also associated with an increased risk of diabetes and its complications, so smoking cessation can be an important preventive measure as well. Weight loss can prevent progression from prediabetes to diabetes type 2, decrease the risk of cardiovascular disease.

MANAGEMENT

Diabetes management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with dietary changes, exercise, weight loss, and use of appropriate medications (insulin, oral medications).

Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels. Per the American College of Physicians, the goal of treatment is an HbA$_{1C}$ level of 7-8%. Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, high blood pressure, metabolic syndrome obesity, and lack of regular exercise. Specialized footwear is widely used to reduce the risk of ulcers in at-risk diabetic feet although evidence for the efficacy of this remains equivocal.
1) **Lifestyle**

People with diabetes can benefit from education about the disease and treatment, dietary changes, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

2) **Medications**

   - **Glucose control**

Most medications used to treat diabetes act by lowering blood sugar levels through different mechanisms.

Type 1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs. Type 2 diabetes may also be treated with insulin at later stages. Some medications for type 2 diabetes are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists.

These include agents that increase insulin release (sulfonylureas), agents that decrease absorption of sugar from the intestines (acarbose), agents that inhibit dipeptidyl peptidase-4 (DPP-4) enzyme which inactivates incretins such as GLP-1 and GIP (Sitagliptin), agents that make the body more sensitive to insulin (Thiazolidinedione) and agents that increase the excretion of glucose in the urine (SGLT2 inhibitors).

   - **Surgery**

Weight loss surgery in those with obesity and type 2 diabetes is often an effective measure. Many are able to maintain normal blood sugar levels with little or no medications following surgery.
SEX HORMONE DISORDERS

Sex hormone disorders occur when there is either an overproduction or underproduction of the hormones responsible for sexual characteristics and development. In females, the main female hormone is estrogen which is primarily produced by the ovaries. Women also produce androgens. Testosterone and DHEAS are two of the androgens women produce. When these hormones are not in balance women may experience symptoms including menstrual cycle irregularities, hirsutism, acne and alopecia. In males, the main male hormone is testosterone. When males do not produce enough testosterone they may experience a decline in libido, erectile dysfunction, loss of muscle and loss of body hair.

Sex hormone disorders are resulted either due to excess production or due to the underproduction of sexual hormones which results in the improper development of sexual characteristics in a person. In females this may occur due to the decreased production of oestrogen and in males this may result due to the decreased production of testosterone. Which results in PCOS, Hirsutism, androgen excess, menopause in females and hypogonadism, erectile dysfuntion, gynecomastia in males. Women are found more than males with sex hormone disorders. These are hereditary and can be inherited from one generation to other generation.

- Intersex disorders
- Gonadal dysgenesis
- Hermaphroditism and androgen insensitivity syndromes
- Klinefelter and kallmann syndrome
- Menstrual function or fertility disorders
- Erectile dysfunction
- Hypogonadism and gynecomastia
- Hirsutism
- Menopause and perimenopause
- Reproductive hormone disorders
Disorders of sex development

Disorders of sex development (DSDs), also known as differences in sex development, diverse sex development and variations in sex characteristics (VSC)\(^2\), are medical conditions involving the reproductive system. More specifically, these terms refer to "congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical."

Overview

DSDs are medical conditions involving the way the reproductive system develops from infancy (and before birth) through young adulthood. There are several types of DSDs and their effect on the external and internal reproductive organs varies greatly.

A frequently-used social and medical adjective for people with DSDs is "intersex".\(^9\) Parents with DSD children and clinicians involved in DSD treatment usually try to make clear distinctions between biological sex, social gender, and sexual orientation. This helps reduce confusion about the differences between being intersex, being transgender, and being gay/lesbian.

The most common DSD is congenital adrenal hyperplasia (CAH), which results in a person with female (XX) chromosomes having genitals that look somewhat masculine. In mild cases, CAH results in a slightly enlarged clitoris, while in more severe cases it can be difficult to decide on observation whether a baby is male or female (ambiguous genitalia). CAH is caused by a problem with the adrenal glands and is usually treated by taking a daily medication to replace or supplement the missing adrenal hormones. (When this adrenal problem occurs in people with male (XY) chromosomes, the result is over-masculinization and premature puberty).

Another common DSD is androgen insensitivity syndrome (AIS), also known as "testicular feminising syndrome" in which a person with male (XY) chromosomes does
not respond to testosterone in the usual way. This results in a body that to some degree has a feminine appearance. In complete androgen insensitivity syndrome (CAIS) the result is a totally feminine appearance, including typical female breast development. Consequently, most young women with CAIS are unaware of their condition until the early teen years when they fail to menstruate. In the milder form, called partial androgen insensitivity syndrome (PAIS), the genitals can vary from mostly female to almost completely male. Some people with PAIS think of themselves as women or girls, others regard themselves as men or boys, and some consider themselves nonbinary.

One of the more uncommon DSDs is 5-alpha-reductase deficiency (5ARD). It is caused by a shortage early in life of an enzyme that converts testosterone into DHT. DHT is required for the development of external male genitalia. Therefore, in this condition, a person with male (XY) chromosomes has a body that appears female before puberty. After puberty begins, other testosterone-activating enzymes become available and the body soon takes on a masculine appearance, with the scrotum and penis usually reaching typical or nearly-typical size. If 5ARD is diagnosed at a young age, the child is often raised as a boy (a 1996 Brazilian study suggested that the majority of adults with this condition consider themselves men but this has been questioned in some more recent research).

- **Genital anatomy**

The penis (males) and clitoris (females) have a mutual origin, both arising from an embryonic structure called the primordial phallus. In typical males, the urethra is located at the tip of the penis, while in typical females the urethra is located below the base of the clitoris. It is also possible also to have a urethral opening located along the shaft; this condition is known as hypospadias.

Open-minded parenting, appropriate and conservative medical intervention, and age-appropriate child involvement in the treatment plan contribute greatly to successful outcomes for the entire range of DSDs.
1. HERMAPHRODITE

*Hermaphrodite* is used in older literature to describe any person whose physical characteristics do not neatly fit male or female classifications, but some people advocate to replace the term with intersex. Intersex describes a wide variety of combinations of what are considered male and female biology. Intersex biology may include, for example, ambiguous-looking external genitalia, karyotypes that include mixed XX and XY chromosome pairs (46XX/46XY, 46XX/47XXY or 45X/XY mosaic).

Clinically, medicine currently describes intersex people as having disorders of sex development, a term vigorously contested. This is particularly because of a relationship between medical terminology and medical intervention. Intersex civil society organizations, and many human rights institutions, have criticized medical interventions designed to make intersex bodies more typically male or female.

Some people who are intersex, such as some of those with androgen insensitivity syndrome, outwardly appear completely female or male, frequently without realizing they are intersex. Other kinds of intersex conditions are identified immediately at birth because those with the condition have a sexual organ larger than a clitoris and smaller than a penis.

Some humans were historically termed true hermaphrodites if their gonadal tissue contained both testicular and ovarian tissue, or pseudohermaphrodites if their external appearance (phenotype) differed from sex expected from internal gonads. This language has fallen out of favor due to misconceptions and pejorative connotations associated with the terms, and also a shift to nomenclature based on genetics.

Intersex is in some caused by unusual sex hormones; the unusual hormones may be caused by an atypical set of sex chromosomes. One possible pathophysiologic explanation of intersex in humans is a parthenogenetic division of a haploid ovum into two haploid ova. Upon fertilization of the two ova by two sperm cells (one carrying an X chromosome and the other carrying a Y chromosome), the two fertilized ova are then fused together resulting in a person having dual genitalial, gonadal (ovotestes)
and genetic sex. Another common cause of being intersex is the crossing over of the SRY from the Y chromosome to the X chromosome during meiosis. The SRY is then activated in only certain areas, causing development of testes in some areas by beginning a series of events starting with the upregulation of SOX9, and in other areas not being active (causing the growth of ovarian tissues). Thus, testicular and ovarian tissues will both be present in the same individual.

Fetuses before sexual differentiation are sometimes described as female by doctors explaining the process. This is technically not true. Before this stage, humans are simply undifferentiated and possess a Müllerian duct, a Wolffian duct, and a genital tubercle.

- **Protandry**: Where an organism is born as a male, and then changes sex to a female.
- **Protogyny**: Where the organism is born as a female, and then changes sex to a male.
- **Bidirectional Sex Changers**: where an organism has female and male reproductive organs, but act as either female or male during different stages in life.
- **Simultaneous hermaphrodites**: A simultaneous (or synchronous) hermaphrodite (or homogamous) is an adult organism that has both male and female sexual organs at the same time.\(^{[12]}\) Self-fertilization often occurs.
2. GONADAL DYSGENESIS

Gonadal dysgenesis (or "absolute genderless") is classified as any congenital developmental disorder of the reproductive system in the male or female. It is the defective development of the gonads in an embryo, with reproductive tissue replaced with functionless, fibrous tissue, termed streak gonads. Streak gonads are a form of aplasia, resulting in hormonal failure that manifests as sexual infantism and infertility, with no initiation of puberty and secondary sex characteristics.

Gonadal development is a genetically controlled process by the chromosomal sex (XX or XY) which directs the formation of the gonad (ovary or testis). Differentiation of the gonads requires a tightly regulated cascade of genetic, molecular and morphogenic events. At the formation of the developed gonad, steroid production influences local and distant receptors for continued morphological and biochemical changes. This results in the appropriate phenotype corresponding to the karyotype (46,XX for females and 46,XY for males).

Gonadal dysgenesis arises from the failure of signalling in this tightly regulated process during early foetal development.

Manifestations of gonadal dysgenesis are dependent on the aetiology and severity of the underlying defect.

Causes

- Pure gonadal dysgenesis 46,XX also known as XX gonadal dysgenesis
- Pure gonadal dysgenesis 46,XY also known as XY gonadal dysgenesis
- Mixed gonadal dysgenesis also known as partial gonadal dysgenesis, and 45,X/46,XY mosaicism
- Turner syndrome also known as 45,X or 45,X0
- Endocrine disruptions
Pathogenesis

■ 46,XX Gonadal Dysgenesis

46,XX gonadal dysgenesis is characteristic of female hypogonadism with a karyotype of 46,XX. Streak ovaries are present with non-functional tissues unable to produce the required sex steroid oestrogen. Low levels of oestrogen effect the HPG axis with no feedback to the anterior pituitary to inhibit the secretion of FSH and LH. FSH and LH are secreted at abnormal elevated levels. Improper levels of these hormones will cause a failure to initiate puberty, undergo menarche, and develop secondary sex characteristics. If sufficient functional ovarian tissue is present, limited menstrual cycles can occur.

The pathogenesis of 46,XX gonadal dysgenesis is unclear, as it can manifest from a variety of dysregulations. Interruption during ovarian development in embryogenesis can cause 46,XX gonadal dysgenesis with cases of abnormalities in the FSH receptor and mutations in steroidogenic acute regulatory protein (StAR protein) which regulates steroid hormone production.

■ 46,XY Gonadal Dysgenesis: Swyer Syndrome

46,XY gonadal dysgenesis is characteristic of male hypogonadism with karyotype 46,XY.

In embryogenesis, the development of the male gonads is controlled by the testis determining factor located on the sex-determining region of the Y chromosome (SRY). The male gonad is dependent on SRY and the signalling pathways initiated to several other genes to facilitate testis development.

The aetiology of 46,XY gonadal dysgenesis can be caused by mutations in the genes involved in testis development such as SRY, SOX9, WT1, SF1, and DHH. If a single or combination of these genes are mutated or deleted, downstream signalling is disrupted, leading to malformation of male external genitalia.

SRY acts on gene SOX9 which drives Sertoli cell formation and testis differentiation. An absence in SRY causes SOX9 to not be expressed at the appropriate time or
concentration, leading to a deficiency in testosterone and Anti-Müllerian hormone production. Inadequate levels of testosterone and Anti-Müllerian hormone disrupts the development of Wolffian ducts and internal genitalia that are key to male reproductive tract development. The lack of the male associated steroid hormones drives Müllerian duct development and perusal of the development of female genitalia.

Gonadal streaks replace the tissues of the testes, resembling ovarian stroma absent of follicles. 46,XY gonadal dysgenesis can remain unsuspected until delayed pubertal development is observed. Approximately 15% of cases of 46,XY gonadal dysgenesis carry de novo mutations in the SRY gene, with an unknown causation for the remaining portion of 46,XY gonadal dysgenesis patients.

■ **Mixed Gonadal Dysgenesis: 45,X/46,XY mosaicism**

Mixed gonadal dysgenesis, also known as X0/XY mosaicism or partial gonadal dysgenesis is a sex development disorder associated with sex chromosome aneuploidy and mosaicism of the Y chromosome. Mixed gonadal dysgenesis is the presence of two or more germ line cells. The degree of development of the male reproductive tract is determined by the ratio of germ line cells expressing the XY genotype. Manifestations of mixed gonadal dysgenesis are highly variable with asymmetry in gonadal development of testis and streak gonad, accounted for by the percentage of cells expressing XY genotype. The dysgenic testis can have adequate functional tissue to produce satisfactory levels of testosterone to cause masculinisation.

Mixed gonadal dysgenesis is poorly understood at the molecular level. The loss of the Y chromosome can occur from deletions, translocations, or migration failure of paired chromosomes during cell division. The chromosomal loss results in partial expression of the SRY gene, giving rise to abnormal development of the reproductive tract and altered hormones levels.

■ **Turner syndrome: Turner syndrome**
Turner syndrome, also known as 45,X or 45,X0, is a chromosomal abnormality characterised by a partial or completely missing second X chromosome giving a chromosomal count of 45, instead of the correct count of 46 chromosomes.

Dysregulation in meiosis signalling to germ cells during embryogenesis may result in nondisjunction and monosomy X from separation failure of chromosomes in either the parental gamete or during early embryonic divisions. The aetiology of Turner syndrome phenotype can be the result of haploinsufficiency, where a portion of critical genes are rendered inactive during embryogenesis. Normal ovarian development requires these vital regions of the X chromosome that are inactivated. Clinical manifestation include primary amenorrhea, hypergonadotropic hypogonadism, streak gonads, infertility and failure to develop secondary sex characteristics. Turner Syndrome is not diagnosed until a delayed onset of puberty with Müllerian structures found to be in infantile stage. Physical phenotypic characteristics include short stature, dysmorphic features and lymphedema at birth. Comorbidities include heart defects, vision and hearing problems, diabetes and low thyroid hormone production.

■ Endocrine Disruptions

Endocrine disruptors interfere with the endocrine system and hormones. Hormones are critical for the correct events in embryogenesis to occur. Foetal development relies on the proper timing of the delivery of hormones for cellular differentiation and maturation. Disruptions can cause sexual development disorders leading to gonadal dysgenesis.
3. ANDROGEN INSENSITIVITY SYNDROME

Androgen insensitivity syndrome (AIS) is an intersex condition that results in the partial or complete inability of the cell to respond to androgens. The unresponsiveness of the cell to the presence of androgenic hormones can impair or prevent the masculinization of male genitalia in the developing fetus, as well as impairing or preventing the development of male secondary sexual characteristics at puberty, but does not significantly impair female genital or sexual development. As such, the insensitivity to androgens is clinically significant only when it occurs in genetic males (i.e. individuals with a Y-chromosome, or more specifically, an SRY gene). Clinical phenotypes in these individuals range from a typical male habitus with mild spermatogenic defect or reduced secondary terminal hair, to a full female habitus, despite the presence of a Y-chromosome.

AIS is divided into three categories that are differentiated by the degree of genital masculinization: complete androgen insensitivity syndrome (CAIS) is indicated when the external genitalia are those of a typical female; mild androgen insensitivity syndrome (MAIS) is indicated when the external genitalia are those of a typical male, and partial androgen insensitivity syndrome (PAIS) is indicated when the external genitalia are partially, but not fully, masculinized. Androgen insensitivity syndrome is the largest single entity that leads to 46,XY undermasculinized genitalia.

Management of AIS is currently limited to symptomatic management; no method is currently available to correct the malfunctioning androgen receptor proteins produced by AR gene mutations. Areas of management include sex assignment, genitoplasty, gonadectomy in relation to tumor risk, hormone replacement therapy, genetic counseling, and psychological counseling.

Pathophysiology

- Androgens and the androgen receptor
The effects that androgens have on the human body (virilization, masculinization, anabolism, etc.) are not brought about by androgens themselves, but rather are the result of androgens bound to androgen receptors; the androgen receptor mediates the effects of androgens in the human body. Likewise, the androgen receptor itself is generally inactive in the cell until androgen binding occurs.

The following series of steps illustrates how androgens and the androgen receptor work together to produce androgenic effects:

1. Androgen enters the cell.
   a. Only certain organs in the body, such as the gonads and the adrenal glands, produce the androgen testosterone.
   b. Testosterone is converted into dihydrotestosterone, a chemically similar androgen, in cells containing the enzyme 5-alpha reductase.
   c. Both androgens exert their influence through binding with the androgen receptor.

2. Androgen binds with the androgen receptor.
   a. The androgen receptor is expressed ubiquitously throughout the tissues of the human body.
   b. Before it binds with an androgen, the androgen receptor is bound to heat shock proteins.
   c. These heat shock proteins are released upon androgen binding.
   d. Androgen binding induces a stabilizing, conformational change in the androgen receptor.
   e. The two zinc fingers of the DNA-binding domain are exposed as a result of this new conformation.
   f. AR stability is thought to be aided by type II coregulators, which modulate protein folding and androgen binding, or facilitate NH2/carboxyl-terminal interaction.

3. The hormone-activated androgen receptor is phosphorylated.
a. Receptor phosphorylation can occur before androgen binding, although the presence of androgen promotes hyperphosphorylation.

b. The biological ramifications of receptor phosphorylation are unknown.

4. The hormone-activated androgen receptor translocates to the nucleus.
   a. Nucleocytoplasmic transport is in part facilitated by an amino acid sequence on the AR called the nuclear localization signal.
   b. The AR's nuclear localization signal is primarily encoded in the hinge region of the AR gene.

5. Homodimerization occurs.
   a. Dimerization is mediated by the second (nearest the 3’ end) zinc finger.

6. DNA binding to regulatory androgen response elements occurs.
   a. Target genes contain (or are flanked by) transcriptional enhancer nucleotide sequences that interact with the first zinc finger.
   b. These areas are called androgen response elements.

7. Coactivators are recruited by the AR.
   a. Type I coactivators (i.e., coregulators) are thought to influence AR transcriptional activity by facilitating DNA occupancy, chromatin remodeling, or the recruitment of general transcription factors associated with RNA polymerase II holocomplex.

8. Target gene transcription ensues.

In this way, androgens bound to androgen receptors regulate the expression of target genes, thus produce androgenic effects.

Theoretically, certain mutant androgen receptors can function without androgens; in vitro studies have demonstrated that a mutant androgen receptor protein can induce transcription in the absence of androgen if its steroid binding domain is deleted. Conversely, the steroid-binding domain may act to repress the AR transactivation domain, perhaps due to the AR's unliganded conformation.
Management

Management of AIS is currently limited to symptomatic management; no method is currently available to correct the malfunctioning androgen receptor proteins produced by AR gene mutations.
4. HYPOGONADISM

**Hypogonadism** means diminished functional activity of the gonads—the testes or the ovaries—that may result in diminished production of sex hormones. Low androgen (e.g., testosterone) levels are referred to as hypoandrogenism and low estrogen (e.g., estradiol) as hypoestrogenism. These are responsible for the observed signs and symptoms. Hypogonadism can decrease other hormones secreted by the gonads including progesterone, DHEA, anti-Müllerian hormone, activin, and inhibin. Sperm development (spermatogenesis) and release of the egg from the ovaries (ovulation) may be impaired by hypogonadism, which, depending on the degree of severity, may result in partial or complete difficulty or inability to have children.

In January 2020, the American College of Physicians issued clinical guidelines for testosterone treatment in adult men with age-related low levels of testosterone. The guidelines are supported by the American Academy of Family Physicians. The guidelines include patient discussions regarding testosterone treatment for sexual dysfunction; annual patient evaluation regarding possible notable improvement and, if none, to discontinue testosterone treatment; physicians should consider intramuscular treatments, rather than transdermal treatments, due to costs and since the effectiveness and harm of either method is similar; and, testosterone treatment for reasons other than possible improvement of sexual dysfunction may not be recommended.

**Signs and symptoms**

Women with hypogonadism do not begin menstruating and it may affect their height and breast development. Onset in women after puberty causes cessation of menstruation, lowered libido, loss of body hair, and hot flashes. In men it causes impaired muscle and body hair development, gynecomastia, decreased height, erectile dysfunction, and sexual difficulties. If hypogonadism is caused by a disorder of the central nervous system (e.g., a brain tumor), then this is known as central hypogonadism. Signs and symptoms of central hypogonadism may involve headaches, impaired vision, double vision, milky discharge from the breast, and symptoms caused by other hormone problems.
■ Hypogonadotrophic hypogonadism

The symptoms of hypogonadotrophic hypogonadism, a subtype of hypogonadism, include late, incomplete or lack of development at puberty, and sometimes short stature or the inability to smell; in females, a lack of breasts and menstrual periods, and in males a lack of sexual development, e.g., facial hair, penis and testes enlargement, deepening voice.

Diagnosis

■ Men

Low testosterone can be identified through a simple blood test performed by a laboratory, ordered by a health care provider. Blood for the test must be taken in the morning hours, when levels are highest, as levels can drop by as much as 13% during the day and all normal reference ranges are based on morning levels. However, low testosterone in the absence of any symptoms does not clearly need to be treated. Normal total testosterone levels depend on the man's age but generally range from 240–950 ng/dL (nanograms per deciliter) or 8.3-32.9 nmol/L (nanomoles per liter). According to American Urological Association, the diagnosis of low testosterone can be supported when the total testosterone level is below 300 ng/dl. Some men with normal total testosterone have low free or bioavailable testosterone levels which could still account for their symptoms. Men with low serum testosterone levels should have other hormones checked, particularly luteinizing hormone to help determine why their testosterone levels are low and help choose the most appropriate treatment (most notably, testosterone is usually not appropriate for secondary or tertiary forms of male hypogonadism, in which the LH levels are usually reduced).

Treatment is often prescribed for total testosterone levels below 230 ng/dL with symptoms. If the serum total testosterone level is between 230 and 350 ng/dL, free or bioavailable testosterone should be checked as they are frequently low when the total is marginal.
The standard range given is based on widely varying ages and, given that testosterone levels naturally decrease as humans age, age-group specific averages should be taken into consideration when discussing treatment between doctor and patient. In men, testosterone falls approximately 1 to 3 percent each year.

- **Blood testing**

A position statement by the Endocrine Society expressed dissatisfaction with most assays for total, free, and bioavailable testosterone. In particular, research has questioned the validity of commonly administered assays of free testosterone by radioimmunoassay. The free androgen index, essentially a calculation based on total testosterone and sex hormone-binding globulin levels, has been found to be the worst predictor of free testosterone levels and should not be used. Measurement by equilibrium dialysis or mass spectroscopy is generally required for accurate results, particularly for free testosterone which is normally present in very small concentrations.

- **Women**

Testing serum LH and FSH levels are often used to assess hypogonadism in women, particularly when menopause is believed to be happening. These levels change during a woman's normal menstrual cycle, so the history of having ceased menstruation coupled with high levels aids the diagnosis of being menopausal. Commonly, the post-menopausal woman is not called hypogonadal if she is of typical menopausal age. Contrast with a young woman or teen, who would have hypogonadism rather than menopause. This is because hypogonadism is an abnormality, whereas menopause is a normal change in hormone levels. In any case, the LH and FSH levels will rise in cases of primary hypogonadism or menopause, while they will be low in women with secondary or tertiary hypogonadism.

Hypogonadism is often discovered during evaluation of delayed puberty, but ordinary delay, which eventually results in normal pubertal development, wherein reproductive function is termed constitutional delay. It may be discovered during an infertility evaluation in either men or women.
Treatment

Male primary or hypergonadotropin hypogonadism is often treated with testosterone replacement therapy if they are not trying to conceive. Adverse effects of testosterone replacement therapy include increased cardiovascular events (including strokes and heart attacks) and death. The FDA has required that testosterone pharmaceutical labels include warning information about the possibility of an increased risk of heart attacks and stroke. While historically, men with prostate cancer risk were warned against testosterone therapy, that has shown to be a myth.

Other side effects can include an elevation of the hematocrit to levels that require blood withdrawal (phlebotomy) to prevent complications from excessively thick blood. Gynecomastia (growth of breasts in men) sometimes occurs. Finally, some physicians worry that obstructive sleep apnea may worsen with testosterone therapy, and should be monitored.

Another treatment for hypogonadism is human chorionic gonadotropin (hCG). This stimulates the LH receptor, thereby promoting testosterone synthesis. This will not be effective in men who simply cannot make testosterone anymore (primary hypogonadism) and the failure of hCG therapy is further support for the existence of true testicular failure in a patient. It is particularly indicated in men with hypogonadism who wish to retain their fertility, as it does not suppress spermatogenesis like testosterone replacement therapy does.

For both men and women, an alternative to testosterone replacement is low-dose clomifene treatment, which can stimulate the body to naturally increase hormone levels while avoiding infertility and other side effects that can result from direct hormone replacement therapy.

Clomifene is a selective estrogen receptor modulator (SERM).
5. KALLMANN SYNDROME

Kallmann syndrome (KS) is a genetic disorder that prevents a person from starting or fully completing puberty. Kallmann syndrome is a form of a group of conditions termed hypogonadotropic hypogonadism. To distinguish it from other forms of hypogonadotropic hypogonadism, Kallmann syndrome has the additional symptom of a total lack of sense of smell (anosmia) or a reduced sense of smell. If left untreated, people will have poorly defined secondary sexual characteristics, show signs of hypogonadism, almost invariably are infertile and are at increased risk of developing osteoporosis. A range of other physical symptoms affecting the face, hands and skeletal system can also occur.

The underlying cause is a failure in the correct production or activity of gonadotropin-releasing hormone by the hypothalamus. This results in low levels of the sex hormones testosterone in males or oestrogen and progesterone in females. Diagnosis normally occurs during teenage years when puberty fails to start. Lifelong treatment for all sexes is normally required. Hormone replacement therapy (HRT) is the major form of treatment with the aim to replace the missing testosterone or oestrogen and progesterone. Specialised fertility treatments are also available.

- **Reproductive features**

  - Failure to start or fully complete puberty.
  - Lack of testicle development in men (size < 4 ml, whereas the normal range is between 12 and 25 ml).
  - Primary amenorrhoea (failure to start menstruation).
  - Poorly defined secondary sexual characteristics.
  - Micropenis in 5-10% of male cases.
  - Cryptorchidism (undescended testicles) at birth.
  - Low levels of the gonadotropins LH and FSH.
• Hypogonadism due to low levels of testosterone in men or oestrogen/progesterone in women.
• Infertility.

■ Non-reproductive features

• Total lack of sense of smell (anosmia) or markedly reduced sense of smell (hyposmia). This is the defining feature of Kallmann syndrome; it is not seen in other cases of HH. Approximately 50% of HH cases occur with anosmia and can be termed as Kallmann syndrome.
• Cleft palate, cleft lip or other midline cranio-facial defects.
• Neural hearing impairment
• Absence of one of the kidneys (unilateral renal agenesis)
• Skeletal defects including split hand/foot (ectrodactyly), shortened middle finger (metacarpal) or scoliosis
• Manual synkinesis (mirror movements of hands)
• Missing teeth (hypodontia)
• Poor balance or coordination due to cerebral ataxia.
• Eye defects such as coloboma or ptosis.

Increased incidence of color-blindness

The underlying cause of Kallmann syndrome or other forms of hypogonadotropic hypogonadism is a failure in the correct action of the hypothalamic hormone GnRH. The term isolated GnRH deficiency (IGD) has increasingly been used to describe this group of conditions as it highlights the primary cause of these conditions and distinguishes them from other conditions such as Klinefelter syndrome or Turner syndrome which share some similar symptoms but have a different etiology. The term hypogonadism describes a low level of circulating sex hormones; testosterone in males and oestrogen and progesterone in females. Hypogonadism can occur through a number of different mechanisms. The use of the term hypogonadotropic relates to the fact that the
hypogonadism found in HH is caused by a disruption in the production of the gonadotropin hormones normally released by the anterior pituitary gland known as luteinising hormone (LH) and follicle stimulating hormone (FSH). Failure in GnRH activity can otherwise be due to the absence of the GnRH releasing neurons inside the hypothalamus. HH can occur as an isolated condition with just the LH and FSH production being affected or it can occur in combined pituitary deficiency conditions.

In the first 10 weeks of normal embryonic development, the GnRH releasing neurons migrate from their original source in the nasal region and end up inside the hypothalamus. These neurons originate in an area of the developing head, the olfactory placode, that will give rise to the olfactory epithelium; they then pass through the cribriform plate, along with the fibres of the olfactory nerves, and into the rostral forebrain. From there they migrate to what will become the hypothalamus. Any problems with the development of the olfactory nerve fibres will prevent the progression of the GnRH releasing neurons towards the brain.

**Diagnosis**

- Early morning hormonal testing including FSH, LH, testosterone, oestrogen and prolactin.
- GnRH and/or hCG stimulation test to determine activity of hypothalamus and pituitary.
- Sperm test
- Liver function, renal function and inflammation marker testing.
- Karyotype to check for chromosomal abnormalities.

**Treatment**

For both males and females, the initial aim for treatment is the development of the secondary sexual characteristics normally seen at puberty. Once this has been achieved, continued hormone replacement therapy is required for both males and females.
to maintain sexual function, bone health, libido and general wellbeing. In males, testosterone replacement therapy is required for the maintenance of normal muscle mass.
6. KLINEFELTER SYNDROME

Klinefelter syndrome (KS), also known as 47, XXY is the set of symptoms that result from two or more X chromosomes in males. The primary features are infertility and small poorly functioning testicles. Often, symptoms may be subtle and many people do not realize they are affected. Sometimes, symptoms are more prominent and may include weaker muscles, greater height, poor coordination, less body hair, breast growth, and less interest in sex. Often it is only at puberty that these symptoms are noticed. Intelligence is usually normal; however, reading difficulties and problems with speech are more common. Symptoms are typically more severe if three or more X chromosomes are present (48,XXXY syndrome or 49,XXXXY syndrome).

Klinefelter syndrome occurs randomly. The extra X chromosome comes from the father and mother nearly equally. An older mother may have a slightly increased risk of a child with KS. The condition is not typically inherited from one's parents. The underlying mechanisms involves at least one extra X chromosome in addition to a Y chromosome such that the total chromosome number is 47 or more rather than the usual 46. KS is diagnosed by the genetic test known as a karyotype.

While no cure is known, a number of treatments may help. Physical therapy, speech and language therapy, counselling, and adjustments of teaching methods may be useful. Testosterone replacement may be used in those who have significantly lower levels. Enlarged breasts may be removed by surgery. About half of affected males have a chance of fathering children with the help of assisted reproductive technology, but this is expensive and not risk free. XXY males appear to have a higher risk of breast cancer than typical, but still lower than that of females. People with the condition have a nearly normal life expectancy.
7. TURNER SYNDROME

**Turner syndrome** (TS), also known 45,X, or 45,X0, is a genetic condition in which a female is partly or completely missing an X chromosome. Signs and symptoms vary among those affected. Often, a short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth. Typically, they develop menstrual periods and breasts only with hormone treatment, and are unable to have children without reproductive technology. Heart defects, diabetes, and low thyroid hormone occur more frequently. Most people with TS have normal intelligence. Many have troubles with spatial visualization that may be needed for mathematics. Vision and hearing problems occur more often.

Turner syndrome is not usually inherited; rather, it occurs as a result of a genetic defect arising during formation of the reproductive cells in a parent or in early cell division during development. No environmental risks are known, and the mother's age does not play a role. Turner syndrome is due to a chromosomal abnormality in which all or part of one of the X chromosomes is missing or altered. While most people have 46 chromosomes, people with TS usually have 45. The chromosomal abnormality may be present in just some cells in which case it is known as TS with mosaicism. In these cases, the symptoms are usually fewer and possibly none occur at all. Diagnosis is based on physical signs and genetic testing.

No cure for Turner syndrome is known. Treatment may help with symptoms. Human growth hormone injections during childhood may increase adult height. Estrogen replacement therapy can promote development of the breasts and hips. Medical care is often required to manage other health problems with which TS is associated.
8. PREMATURE OVARIAN FAILURE

Premature ovarian failure (POF) is the loss of function of the ovaries before age 40. A commonly cited triad for the diagnosis is amenorrhea, hypergonadotropism, and hypoestrogenism. If it has a genetic cause, it may be called gonadal dysgenesis.

The term "primary ovarian insufficiency" was first used in 1942 by Fuller Albright who first described the condition. About 5 to 10% of women with primary ovarian insufficiency conceive subsequent to the diagnosis without medical intervention.

Hormonally, POF is defined by abnormally low levels of estrogen and high levels of FSH, which demonstrate that the ovaries are no longer responding to circulating FSH by producing estrogen and developing fertile eggs. The ovaries will likely appear shrunken.

Causes

- Genetic disorders
- Autoimmune diseases
- Tuberculosis of the genital tract
- Smoking
- Radiation and/or chemotherapy
- Ovarian failure following hysterectomy
- Prolonged GnRH (Gonadatrophin Releasing Hormone) therapy
- Enzyme defects
- Resistant ovary
- Induction of multiple ovulation in infertility

Diagnosis

Serum follicle-stimulating hormone (FSH) measurement alone can be used to diagnose the disease.
Treatment

Currently no fertility treatment has officially been found to effectively increase fertility in women with POF, and the use of donor eggs with in-vitro fertilization (IVF) and adoption are popular as a means of achieving parenthood for women with POF.
9. DELAYED PUBERTY

Delayed puberty is when a person lacks or has incomplete development of specific sexual characteristics past the usual age of onset of puberty. The person may have no physical or hormonal signs that puberty has begun. In the United States, girls are considered to have delayed puberty if they lack breast development by age 13 or have not started menstruating by age 16. Boys are considered to have delayed puberty if they lack enlargement of the testicles by age 14. Delayed puberty affects about 2% of adolescents.

Most commonly, puberty may be delayed for several years and still occur normally, in which case it is considered constitutional delay of growth and puberty, a common variation of healthy physical development. Delay of puberty may also occur due to various causes such as malnutrition, various systemic diseases, or defects of the reproductive system (hypogonadism) or the body’s responsiveness to sex hormones.

Initial workup for delayed puberty not due to a chronic condition involves measuring serum FSH, LH, testosterone/estradiol, as well as bone age radiography.

If it becomes clear that there is a permanent defect of the reproductive system, treatment usually involves replacement of the appropriate hormones (testosterone/dihydrotestosterone for boys, estradiol and progesterone for girls).
10. PRECOCIOUS PUBERTY

**precocious puberty** is puberty occurring at an unusually early age. In most cases, the process is normal in every aspect except the unusually early age and simply represents a variation of normal development. In a minority of children with precocious puberty, the early development is triggered by a disease such as a tumor or injury of the brain. Even when there is no disease, unusually early puberty can have adverse effects on social behavior and psychological development, can reduce adult height potential, and may shift some lifelong health risks. Central precocious puberty can be treated by suppressing the pituitary hormones that induce sex steroid production. The opposite condition is delayed puberty.

The term is used with several slightly different meanings that are usually apparent from the context. In its broadest sense, and often simplified as **early puberty**, "precocious puberty" sometimes refers to any physical sex hormone effect, due to any cause, occurring earlier than the usual age, especially when it is being considered as a medical problem. Stricter definitions of "precocity" may refer only to central puberty starting before a statistically specified age based on percentile in the population (e.g., 2.5 standard deviations below the population mean), on expert recommendations of ages at which there is more than a negligible chance of discovering an abnormal cause, or based on opinion as to the age at which early puberty may have adverse effects. A common definition for medical purposes is onset before 8 years in girls or 9 years in boys.
11. AMENORRHEA

Amenorrhea is the absence of a menstrual period in a woman of reproductive age. Physiological states of amenorrhoea are seen, most commonly, during pregnancy and lactation (breastfeeding), the latter also forming the basis of a form of contraception known as the lactational amenorrhoea method. Outside the reproductive years, there is absence of menses during childhood and after menopause.

Amenorrhoea is a symptom with many potential causes. Primary amenorrhoea is defined as an absence of secondary sexual characteristics by age 14 with no menarche or normal secondary sexual characteristics but no menarche by 16 years of age. It may be caused by developmental problems, such as the congenital absence of the uterus, failure of the ovary to receive or maintain egg cells, or delay in pubertal development. Secondary amenorrhoea (menstrual cycles ceasing) is often caused by hormonal disturbances from the hypothalamus and the pituitary gland, from premature menopause or intrauterine scar formation. It is defined as the absence of menses for three months in a woman with previously normal menstruation, or six months for women with a history of oligomenorrhoea.
12. POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is a set of symptoms due to elevated androgens (male hormones) in females. Signs and symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin. Associated conditions include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer.

PCOS is due to a combination of genetic and environmental factors. Risk factors include obesity, a lack of physical exercise, and a family history of someone with the condition. Diagnosis is based on two of the following three findings: no ovulation, high androgen levels, and ovarian cysts. Cysts may be detectable by ultrasound. Other conditions that produce similar symptoms include adrenal hyperplasia, hypothyroidism, and high blood levels of prolactin.

PCOS has no cure. Treatment may involve lifestyle changes such as weight loss and exercise. Birth control pills may help with improving the regularity of periods, excess hair growth, and acne. Metformin and anti-androgens may also help. Other typical acne treatments and hair removal techniques may be used. Efforts to improve fertility include weight loss, clomiphene, or metformin. In vitro fertilization is used by some in whom other measures are not effective.
13. HIRSUTISM

Hirsutism is excessive body hair in men and women on parts of the body where hair is normally absent or minimal. It may refer to a "male" pattern of hair growth that may be a sign of a more serious medical condition, especially if it develops well after puberty. Cultural stigma against hirsutism can cause much psychological distress and social difficulty. Facial hirsutism often leads to the avoidance of social situations and to symptoms of anxiety and depression.

Hirsutism is usually the result of an underlying endocrine imbalance, which may be adrenal, ovarian, or central. It can be caused by increased levels of androgen hormones. The amount and location of the hair is measured by a Ferriman-Gallwey score. It is different from hypertrichosis, which is excessive hair growth anywhere on the body.

Treatments may include birth control pills that contain estrogen and progestin, antiandrogens, or insulin sensitizers.
14. ERECTILE DYSFUNCTION

Erectile dysfunction (ED), also known as impotence, is a type of sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual activity. ED can have psychological consequences as it can be tied to relationship difficulties and self-image.

A physical cause can be identified in about 80% of cases. These include cardiovascular disease, diabetes mellitus, neurological problems such as following prostatectomy, hypogonadism, and drug side effects. Psychological impotence is where erection or penetration fails due to thoughts or feelings; this is somewhat less frequent, on the order of about 10% of cases. In psychological impotence, there is a strong response to placebo treatment. The term erectile dysfunction is not used for other disorders of erection, such as priapism.

Treatment involves addressing the underlying causes, lifestyle modifications, and addressing psychosocial issues. In many cases, a trial of pharmacological therapy with a PDE5 inhibitor, such as sildenafil, can be attempted. In some cases, treatment can involve inserting prostaglandin pellets into the urethra, injecting smooth muscle relaxants and vasodilators into the penis, a penile implant, a penis pump, or vascular reconstructive surgery. It is the most common sexual problem in men.
15. GONADAL DYSGENESIS

Gonadal dysgenesis (or "absolute genderless") is classified as any congenital developmental disorder of the reproductive system in the male or female. It is the defective development of the gonads in an embryo, with reproductive tissue replaced with functionless, fibrous tissue, termed streak gonads. Streak gonads are a form of aplasia, resulting in hormonal failure that manifests as sexual infantism and infertility, with no initiation of puberty and secondary sex characteristics.

Gonadal development is a genetically controlled process by the chromosomal sex (XX or XY) which directs the formation of the gonad (ovary or testis).

Differentiation of the gonads requires a tightly regulated cascade of genetic, molecular and morphogenic events. At the formation of the developed gonad, steroid production influences local and distant receptors for continued morphological and biochemical changes. This results in the appropriate phenotype corresponding to the karyotype (46,XX for females and 46,XY for males).

Gonadal dysgenesis arises from the failure of signalling in this tightly regulated process during early foetal development.

Manifestations of gonadal dysgenesis are dependent on the aetiology and severity of the underlying defect.
1. EPILEPSY

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Periods of vigorous shaking, nearly undetectable spells</th>
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<td>Duration</td>
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<td>Causes</td>
<td>Unknown, brain injury, stroke, brain tumors, infections of the brain, birth defects</td>
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<td>Diagnostic method</td>
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<td>Differential diagnosis</td>
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<td>Treatment</td>
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Epilepsy is a group of neurological disorders characterized by recurrent epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable periods to long periods of vigorous shaking. These episodes can result in physical injuries, including occasionally broken bones. In epilepsy, seizures have a tendency to recur and, as a rule, have no immediate underlying cause. Isolated seizures that are provoked by a specific cause such as poisoning are not deemed to represent epilepsy. People with epilepsy may be treated differently in various areas of the world and experience varying degrees of social stigma due to their condition.

The cause of most cases of epilepsy is unknown. Some cases occur as the result of brain injury, stroke, brain tumors, infections of the brain, or birth defects through a process known as epileptogenesis. Known genetic mutations are directly linked to a small proportion of cases. Epileptic seizures are the result of excessive and abnormal neuronal activity in the cortex of the brain. The diagnosis involves ruling out other conditions that might cause similar symptoms, such as fainting, and determining if another cause of seizures is present, such as alcohol withdrawal or electrolyte problems. This may be partly done by imaging the brain and performing blood tests. Epilepsy can often be confirmed with an electroencephalogram (EEG), but a normal test does not rule out the condition.

Epilepsy that occurs as a result of other issues may be preventable. Seizures are controllable with medication in about 70% of cases; inexpensive anti-seizure medications are often available. In those whose seizures do not respond to medication, surgery, neurostimulation or dietary changes may then be considered. Not all cases of epilepsy are lifelong, and many people improve to the point that treatment is no longer needed.

**SIGNS AND SYMPTOMS**

Epilepsy is characterized by a long-term risk of recurrent seizures. These seizures may present in several ways depending on the part of the brain involved and the person's age.
**Seizures**

The most common type (60%) of seizures are convulsive. Of these, one-third begin as generalized seizures from the start, affecting both hemispheres of the brain. Two-thirds begin as focal seizures (which affect one hemisphere of the brain) which may then progress to generalized seizures. The remaining 40% of seizures are non-convulsive. An example of this type is the absence seizure, which presents as a decreased level of consciousness and usually lasts about 10 seconds.

Focal seizures are often preceded by certain experiences, known as auras. They include sensory (visual, hearing, or smell), psychic, autonomic, and motor phenomena. Jerking activity may start in a specific muscle group and spread to surrounding muscle groups in which case it is known as a Jacksonian march. Automatisms may occur, which are non-consciously-generated activities and mostly simple repetitive movements like smacking of the lips or more complex activities such as attempts to pick up something.

There are six main types of generalized seizures: tonic-clonic, tonic, clonic, myoclonic, absence and atonic seizures. They all involve loss of consciousness and typically happen without warning.

Tonic-clonic seizures occur with a contraction of the limbs followed by their extension along with arching of the back which lasts 10–30 seconds (the tonic phase). A cry may be heard due to contraction of the chest muscles, followed by a shaking of the limbs in unison (clonic phase). Tonic seizures produce constant contractions of the muscles. A person often turns blue as breathing is stopped. In clonic seizures there is shaking of the limbs in unison. After the shaking has stopped it may take 10–30 minutes for the person to return to normal; this period is called the "postictal state" or "postictal phase." Loss of bowel or bladder control may occur during a seizure. The tongue may be bitten at either the tip or on the sides during a seizure. In tonic-clonic seizure, bites to the sides are more common. Tongue bites are also relatively common in psychogenic non-epileptic seizures.

Myoclonic seizures involve spasms of muscles in either a few areas or all over. Absence seizures can be subtle with only a slight turn of the head or eye blinking. The person does not fall over and returns to normal right after it ends. Atonic seizures involve the loss of muscle activity for greater than one second. This typically occurs on both sides of the body.

About 6% of those with epilepsy have seizures that are often triggered by specific events and are known as reflex seizures. Those with reflex epilepsy have seizures that are only triggered by specific stimuli. Common triggers include flashing lights and sudden noises. In certain types of epilepsy, seizures happen more often during sleep, and in other types they occur almost only when sleeping.

**Post-ictal**

After the active portion of a seizure (the ictal state) there is typically a period of recovery during which there is confusion, referred to as the postictal period before a normal level of consciousness returns. It usually lasts 3 to 15 minutes but may last for hours. Other common symptoms include feeling tired, headache, difficulty speaking, and abnormal behavior. Psychosis after a seizure is relatively common, occurring in 6–10% of people. Often people do not remember what happened during this time. Localized weakness, known as Todd's
paralysis, may also occur after a focal seizure. When it occurs it typically lasts for seconds to minutes but may rarely last for a day or two.

- **Psychosocial**
  Epilepsy can have adverse effects on social and psychological well-being. These effects may include social isolation, stigmatization, or disability. They may result in lower educational achievement and worse employment outcomes. Learning disabilities are common in those with the condition, and especially among children with epilepsy. The stigma of epilepsy can also affect the families of those with the disorder. Certain disorders occur more often in people with epilepsy, depending partly on the epilepsy syndrome present. These include depression, anxiety, obsessive–compulsive disorder (OCD), and migraine. Attention deficit hyperactivity disorder affects three to five times more children with epilepsy than children without the condition. ADHD and epilepsy have significant consequences on a child's behavioral, learning, and social development. Epilepsy is also more common in children with autism.

**CAUSES**

Epilepsy can have both genetic and acquired causes, with interaction of these factors in many cases. Established acquired causes include serious brain trauma, stroke, tumors and problems in the brain as a result of a previous infection.\[^{45}\] In about 60% of cases the cause is unknown. Epilepsies caused by genetic, congenital, or developmental conditions are more common among younger people, while brain tumors and strokes are more likely in older people. Seizures may also occur as a consequence of other health problems; if they occur right around a specific cause, such as a stroke, head injury, toxic ingestion or metabolic problem, they are known as acute symptomatic seizures and are in the broader classification of seizure-related disorders rather than epilepsy itself.

- **Genetics**
  Genetics is believed to be involved in the majority of cases, either directly or indirectly. Some epilepsies are due to a single gene defect (1–2%); most are due to the interaction of multiple genes and environmental factors.

**MECHANISM**

Normally brain electrical activity is non-synchronous, as neurons do not normally fire in sync with each other, but rather fire in order as signals travel throughout the brain. Its activity is regulated by various factors both within the neuron and the cellular environment. Factors within the neuron include the type, number and distribution of ion channels, changes to receptors and changes of gene expression. Factors around the neuron include ion concentrations, synaptic plasticity and regulation of transmitter breakdown by glial cells. Chronic inflammation also appears to play a role.

- **Epilepsy**
  The exact mechanism of epilepsy is unknown, but a little is known about its cellular and network mechanisms. In epilepsy, the resistance of excitatory neurons to fire during this period is
decreased. This may occur due to changes in ion channels or inhibitory neurons not functioning properly. This then results in a specific area from which seizures may develop, known as a "seizure focus". Another mechanism of epilepsy may be the up-regulation of excitatory circuits or down-regulation of inhibitory circuits following an injury to the brain. These secondary epilepsies occur through processes known as epileptogenesis. Failure of the blood–brain barrier may also be a causal mechanism as it would allow substances in the blood to enter the brain.

Seizures
Seizures are often brought on by factors such as stress, alcohol abuse, flickering light, or a lack of sleep, among others. The term seizure threshold is used to indicate the amount of stimulus necessary to bring about a seizure. Seizure threshold is lowered in epilepsy. In epileptic seizures a group of neurons begin firing in an abnormal, excessive, and synchronized manner. This results in a wave of depolarization known as a paroxysmal depolarizing shift. Normally, after an excitatory neuron fires it becomes more resistant to firing for a period of time. This is due in part to the effect of inhibitory neurons, electrical changes within the excitatory neuron, and the negative effects of adenosine.

DIAGNOSIS
The diagnosis of epilepsy is typically made based on observation of the seizure onset and the underlying cause. An electroencephalogram (EEG) to look for abnormal patterns of brain waves and neuroimaging (CT scan or MRI) to look at the structure of the brain are also usually part of the workup. For adults, the testing of electrolyte, blood glucose and calcium levels is important to rule out problems with these as causes. An electrocardiogram can rule out problems with the rhythm of the heart. A lumbar puncture may be useful to diagnose a central nervous system infection. Urine biochemistry and blood testing looking for metabolic disorders

DIFFERENTIAL DIAGNOSIS
Diagnosis of epilepsy can be difficult. A number of other conditions may present very similar signs and symptoms to seizures, including syncope, hyperventilation, migraines, narcolepsy, panic attacks and psychogenic non-epileptic seizures (PNES). In particular a syncope can be accompanied by a short episode of convulsions. Nocturnal frontal lobe epilepsy, often misdiagnosed as nightmares, was considered to be a parasomnia but later identified to be an epilepsy syndrome. Attacks of the movement disorder paroxysmal dyskinesia may be taken for epileptic seizures.

PREVENTION
While many cases are not preventable, efforts to reduce head injuries, provide good care around the time of birth, and reduce environmental parasites such as the pork tapeworm may be effective.
**MANAGEMENT**

Epilepsy is usually treated with daily medication once a second seizure has occurred, while medication may be started after the first seizure in those at high risk for subsequent seizures. Supporting people's self management of their condition may be useful. In drug-resistant cases different management options may be looked at including a special diet, the implantation of a neurostimulator, or neurosurgery.

- **First aid**
  Rolling a person with an active tonic-clonic seizure onto their side and into the recovery position helps prevent fluids from getting into the lungs. Putting fingers, a bite block or tongue depressor in the mouth is not recommended as it might make the person vomit or result in the rescuer being bitten. Efforts should be taken to prevent further self-injury.
  If a seizure lasts longer than 5 minutes or if there are more than two seizures in an hour without a return to a normal level of consciousness between them, it is considered a medical emergency known as status epilepticus. This may require medical help to keep the airway open and protected; a nasopharyngeal airway may be useful for this. At home the recommended initial medication for seizure of a long duration is midazolam placed in the mouth. Diazepam may also be used rectally. In hospital, intravenous lorazepam is preferred. If two doses of benzodiazepines are not effective, other medications such as phenytoin are recommended.

- **Medications**
  The mainstay treatment of epilepsy is anticonvulsant medications.
  The choice of anticonvulsant is based on seizure type, epilepsy syndrome, other medications used, other health problems, and the person's age and lifestyle. A single medication is recommended initially; if this is not effective, switching to a single other medication is recommended. Two medications at once is recommended only if a single medication does not work.
  There are a number of medications available including phenytoin, carbamazepine and valproate. Evidence suggests that phenytoin, carbamazepine, and valproate may be equally effective in both focal and generalized seizures. Valproate is recommended first-line for generalized seizures with lamotrigine being second-line. In those with absence seizures, ethosuximide or valproate are recommended; valproate is particularly effective in myoclonic seizures and tonic or atonic seizures.

- **Surgery**
  Epilepsy surgery may be an option for people with focal seizures that remain a problem despite other treatments.

- **Diet**
  There is promising evidence that a ketogenic diet (high-fat, low-carbohydrate, adequate-protein) decreases the number of seizures and eliminate seizures in some.
1. PARKINSON’S DISEASE (PD)

Parkinson's disease

| Synonyms | Parkinson disease, idiopathic or primary parkinsonism, hypokinetic rigid syndrome, paralysis agitans |

Figure: 1.1 Illustration of Parkinson's disease

Specialty Neurology
Symptoms Shaking, rigidity, slowness of movement, difficulty walking
Complications Dementia, depression, anxiety
INTRODUCTION

Parkinson’s disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. The symptoms generally come on slowly over time. Early in the disease, the most obvious are shaking, rigidity, slowness of movement, and difficulty with walking. Thinking and behavioral problems may also occur. Dementia becomes common in the advanced stages of the disease. Depression and anxiety are also common occurring in more than a third of people with PD. Other symptoms include sensory, sleep, and emotional problems. The main motor symptoms are collectively called "parkinsonism", or a "parkinsonian syndrome".

The cause of Parkinson's disease is generally unknown, but believed to involve both genetic and environmental factors. Those with a family member affected are more likely to get the disease themselves. There is also an increased risk in people exposed to certain pesticides and among those who have had prior head injuries, while there is a reduced risk in tobacco smokers and those who drink coffee or tea. The motor symptoms of the disease result from the death of cells in the substantia nigra, a region of the midbrain. This results in not enough dopamine in these areas. The reason for this cell death is poorly understood, but involves the build-up of proteins into Lewy bodies in the neurons. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used to rule out other diseases.

There is no cure for Parkinson's disease, with treatment directed at improving symptoms. Initial treatment is typically with the antiparkinson medication levodopa (L-DOPA), with dopamine agonists being used once levodopa becomes less effective. As the disease progresses and neurons continue to be lost, these medications become less effective while at the same time they produce a complication marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness at improving symptoms. Surgery to place microelectrodes for deep brain stimulation has been used to reduce motor symptoms in severe cases where drugs are ineffective. Evidence for treatments for the non-movement-related symptoms of PD, such as sleep disturbances and emotional problems, is less strong.

CLASSIFICATION

The movement difficulties found in PD are called parkinsonism and a number of different disorders feature parkinsonism. "Parkinsonism" is defined as bradykinesia (slowness in initiating voluntary movements, with progressive reduction in speed and range of repetitive actions such as

**Usual onset** Age over 60  
**Causes** Unknown  
**Risk factors** Pesticide exposure, head injuries  
**Diagnostic method** Based on symptoms  
**Differential diagnosis** Dementia with Lewy bodies, progressive supranuclear palsy, essential tremor, antipsychotic use  
**Treatment** Medications, surgery  
**Medication** L-DOPA, dopamine agonists
voluntary finger-tapping) in combination with one of three other physical signs: muscular (lead-pipe or cogwheel) rigidity, tremor at rest, and postural instability.

**SIGNS AND SYMPTOMS**

The most recognizable symptoms in Parkinson's disease are movement ("motor") related. Non-motor symptoms, which include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations), and sensory (especially altered sense of smell) and sleep difficulties, are also common. Some of these non-motor symptoms may be present at the time of diagnosis.

- **Motor**
  
  Four motor symptoms are considered cardinal in PD: tremor, slowness of movement (bradykinesia), rigidity, and postural instability.

  The most common presenting sign is a coarse slow tremor of the hand at rest which disappears during voluntary movement of the affected arm and in the deeper stages of sleep. It typically appears in only one hand, eventually affecting both hands as the disease progresses.\[^{20}\]
  
  Frequency of PD tremor is between 4 and 6 hertz (cycles per second). A feature of tremor is *pill-rolling*, the tendency of the index finger and thumb to touch and perform together a circular movement. The term derives from the similarity between the movement of people with PD and the early pharmaceutical technique of manually making pills.

  Bradykinesia (slowness of movement) is found in every case of PD, and is due to disturbances in motor planning of movement initiation, and associated with difficulties along the whole course of the movement process, from planning to initiation to execution of a movement. Performance of sequential and simultaneous movement is impaired. Bradykinesia is the most handicapping symptom of Parkinson’s disease leading to difficulties with everyday tasks such as dressing, feeding, and bathing. It leads to particular difficulty in carrying out two independent motor activities at the same time and can be made worse by emotional stress or concurrent illnesses. Paradoxically patients with Parkinson's disease can often ride a bicycle or climb stairs more easily than walk on a level. While most physicians may readily notice bradykinesia, formal assessment requires a patient to do repetitive movements with their fingers and feet.

  Rigidity is stiffness and resistance to limb movement caused by increased muscle tone, an excessive and continuous contraction of muscles. In parkinsonism the rigidity can be uniform ("lead-pipe rigidity") or ratchety ("cogwheel rigidity"). The combination of tremor and increased tone is considered to be at the origin of cogwheel rigidity. Rigidity may be associated with joint pain; such pain being a frequent initial manifestation of the disease. In early stages of Parkinson's disease, rigidity is often asymmetrical and it tends to affect the neck and shoulder muscles prior to the muscles of the face and extremities. With the progression of the disease, rigidity typically affects the whole body and reduces the ability to move.

  Postural instability is typical in the later stages of the disease, leading to impaired balance and frequent falls, and secondarily to bone fractures, loss of confidence, and reduced mobility. Instability is often absent in the initial stages, especially in younger people, especially prior to
the development of bilateral symptoms. Up to 40% of people diagnosed with PD may experience falls and around 10% may have falls weekly, with the number of falls being related to the severity of PD.

Other recognized motor signs and symptoms include gait and posture disturbances such as festination (rapid shuffling steps and a forward-flexed posture when walking with no flexed arm swing). Freezing of gait (brief arrests when the feet seem to get stuck to the floor, especially on turning or changing direction), a slurred monotonous quiet voice, mask-like facial expression, and handwriting that gets smaller and smaller are other common signs.

- **Neuropsychiatric**

Parkinson's disease can cause neuropsychiatric disturbances, which can range from mild to severe. This includes disorders of cognition, mood, behavior, and thought. The most common cognitive deficit in PD is executive dysfunction, which can include problems with planning, cognitive flexibility, abstract thinking, rule acquisition, inhibiting inappropriate actions, initiating appropriate actions, working memory, and control of attention. Other cognitive difficulties include slowed cognitive processing speed, impaired recall and impaired perception and estimation of time. Behavior and mood alterations are more common in PD. The most frequent mood difficulties are depression, apathy, and anxiety.

**DIAGNOSIS**

A physician will initially assess for Parkinson's disease with a careful medical history and neurological examination. People may be given levodopa, with any resulting improvement in motor impairment helping to confirm the PD diagnosis. The finding of Lewy bodies in the midbrain on autopsy is usually considered final proof that the person had PD. Others are slowness of movement (bradykinesia) plus either rigidity, resting tremor, or postural instability.

- **Imaging**

Computed tomography (CT) scans of people with PD usually appear normal. MRI has become more accurate in diagnosis of the disease over time, specifically through iron-sensitive T2* and SWI sequences at a magnetic field strength of at least 3T. Dopamine-related activity in the basal ganglia can be directly measured with PET and SPECT scans.

**PREVENTION**

Exercise in middle age may reduce the risk of Parkinson's disease later in life. Caffeine also appears protective with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee. People who smoke cigarettes or use smokeless tobacco are less likely than non-smokers to develop PD. Antioxidants, such as vitamins C and E, have been proposed to protect against the disease.
MANAGEMENT

There is no cure for Parkinson's disease, but medications, surgery, and physical treatment can provide relief. The main families of drugs useful for treating motor symptoms are levodopa (always combined with a dopa decarboxylase inhibitor and sometimes also with a COMT inhibitor), dopamine agonists and MAO-B inhibitors.

Figure: 1.2 Pharmacological treatment of Parkinson's disease
MEDICATIONS

I) Levodopa
II) COMT inhibitors
III) Dopamine agonists
IV) MAO-B inhibitors
V) Surgery

REHABILITATION

Exercise programs are recommended in people with Parkinson's disease. There is some evidence that speech or mobility problems can improve with rehabilitation. Regular physical exercise with or without physical therapy can be beneficial to maintain and improve mobility, flexibility, strength, gait speed, and quality of life.

PALLIATIVE CARE

Palliative care should be involved earlier, rather than later in the disease course. Palliative care specialists can help with physical symptoms, emotional factors such as loss of function and jobs, depression, fear, and existential concerns.
2. STROKE

Previously known as cerebrovascular accident, stroke or cerebral infarct is a sudden impairment of cerebral circulation in one or more of the blood vessels supplying the brain. It interrupts or diminishes oxygen supply, causing serious damage or necrosis in brain tissues.

Transient, reversible, progressive, or completed Stroke is classified according to how it progresses:

- Transient ischemic attack (TIA), the least severe type, is caused by a temporary interruption of blood flow, usually in the carotid and vertebrobasilar arteries.
- Reversible ischemic attack lasts more than 24 hours and up to 2 weeks, but the patient fully recovers.
- Progressive stroke, also called stroke-in-evolution or thrombus-in-evolution, begins with a slight neurologic deficit and worsens in a day or two.
- Completed stroke, the most severe type, causes maximum neurologic deficits at the onset.

CAUSES

Factors that increase the risk of stroke include:

- history of TIA
- atherosclerosis
- hypertension
- arrhythmias, especially atrial fibrillation
- electrocardiogram changes
- rheumatic heart disease
- diabetes mellitus
- gout
- orthostatic hypotension
- cardiac enlargement
- high serum triglyceride levels
- lack of exercise
- hormonal contraceptive use
- drug abuse
- smoking
- family history of cerebrovascular disease
- sickle cell disease.

Ranking stroke causes

Major causes of stroke include:

- Thrombosis
- Embolism
- Hemorrhage.

i.) Thrombosis

Thrombosis is the most common cause of stroke in middle-aged and elderly people. It usually results from an obstruction in the extracerebral vessels, but sometimes it’s intracerebral. The risk increases with obesity, smoking, hormonal contraceptive use, and surgery.
ii.) Embolism
The second most common cause of stroke, embolism is a blood vessel occlusion caused by a fragmented clot, a tumor, fat, bacteria, or air. It can occur at any age, especially in patients with a history of rheumatic heart disease, endocarditis, posttraumatic valvular disease, or atrial fibrillation or other cardiac arrhythmias. It also occurs after open-heart surgery. Embolism usually develops rapidly—in 10 to 20 seconds—and without warning. The left middle cerebral artery is usually the embolus site.

iii.) Hemorrhage
Hemorrhage, the third most common cause of stroke, may also occur suddenly at any age. It arises from chronic hypertension or aneurysms, which cause a sudden rupture of a cerebral artery. Increasing cocaine use by younger people has also increased the number of hemorrhagic strokes because of the severe hypertension caused by this drug.

Thrombosis, embolus, and hemorrhage affect the body in different ways. Thrombosis causes congestion and edema in the affected vessel as well as ischemia in the brain tissue supplied by the vessel.
An embolus cuts off circulation in the cerebral vasculature by lodging in a narrow portion of the artery, causing necrosis and edema. If the embolus is septic and the infection extends beyond the vessel wall, encephalitis may develop. If the infection stays within the vessel wall, an aneurysm may form, which could lead to the sudden rupture of an artery, or cerebral hemorrhage.
In hemorrhage, a brain artery bursts, diminishing blood supply to the area served by the artery. Blood also accumulates deep within the brain, causing even greater damage by further compromising neural tissue.

Getting complicated
Among the many possible complications of stroke are unstable blood pressure from loss of vasomotor control, fluid imbalances, malnutrition, infections such as pneumonia, and sensory impairment, including vision problems. Altered LOC, aspiration, contractures, and pulmonary emboli may also occur.

DIAGNOSIS/ INVESTIGATION

These tests are used to diagnose stroke:
- Cerebral angiography details disruption or displacement of the cerebral circulation by occlusion or hemorrhage. It’s the test of choice for examining the entire cerebral circulation.
- Digital subtraction angiography evaluates the patency of the cerebral vessels and identifies their position in the head and neck. It also detects and evaluates lesions and vascular abnormalities.
- CT scan detects structural abnormalities, edema, and lesions, such as nonhemorrhagic infarction and aneurysms. It differentiates stroke from other disorders, such as primary metastatic tumor and subdural, intracerebral, or epidural hematoma. Patients with TIA commonly have a normal CT scan.
- PET scan provides data on cerebral metabolism and cerebral blood flow changes, especially in ischemic stroke.
o Single-photon emission tomography identifies cerebral blood flow and helps diagnose cerebral infarction.
o MRI and magnetic resonance angiography evaluate the lesion’s location and size. MRI doesn’t distinguish hemorrhage, tumor, or infarction as well as a CT scan, but it provides superior images of the cerebellum and brain stem.
o Transcranial Doppler studies evaluate the velocity of blood flow through major intracranial vessels, which can indicate the vessels’ diameter.
o Cerebral blood flow studies measure blood flow to the brain and help detect abnormalities.
o Ophthalmoscopy may show signs of hypertension and atherosclerotic changes in the retinal arteries.
o EEG may detect reduced electrical activity in an area of cortical infarction and is especially useful when CT scan results are inconclusive. It can also differentiate seizure activity from stroke.
o Oculoplethysmography indirectly measures ophthalmic blood flow and carotid artery blood flow.

Ischemic stroke

![Ischemic stroke diagram]

**Figure: 2.1** common sites of cardiac thrombosis and the resulting sites of embolism and infarction
TREATMENT/ MANAGEMENT

Medical treatment for stroke commonly includes physical rehabilitation, dietary and drug regimens to help decrease risk factors, and measures to help the patient adapt to specific deficits, such as speech impairment and paralysis.

❖ Drug therapy

Drugs commonly used for stroke therapy include:

- thrombolytic therapy such as recombinant tissue plasminogen activator given within the first 3 hours of an ischemic stroke to restore circulation to the affected brain tissue and limit the extent of brain injury
- anticonvulsants such as phenytoin (Dilantin) to treat or prevent seizures
- stool softeners to avoid straining, which increases intracranial pressure
- corticosteroids such as dexamethasone to minimize cerebral edema
- anticoagulants, such as heparin, warfarin (Coumadin), and ticlopidine, to reduce the risk of thrombotic stroke
- analgesics such as codeine to relieve headache that may follow hemorrhagic stroke.

❖ Surgery

Depending on the stroke’s cause and extent, the patient may also undergo surgery. A craniotomy may be done to remove a hematoma, an endarterectomy to remove atherosclerotic plaque from the inner arterial wall, or extracranial-intracranial bypass to circumvent an artery that’s blocked by occlusion or stenosis. Ventricular shunts may be necessary to drain cerebrospinal fluid if hydrocephalus occurs.
1. DEPRESSION

**Depression** is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being. A depressed mood is a normal temporary reaction to life events such as loss of a loved one. It is also a symptom of some physical diseases and a side effect of some drugs and medical treatments. Depressed mood is also a symptom of some mood disorders such as major depressive disorder or dysthymia.

People with a depressed mood may be notably sad, anxious, or empty; they may also feel notably hopeless, helpless, dejected, or worthless. Other symptoms expressed may include senses of guilt, irritability, or anger. Further feelings expressed by these individuals may include feeling ashamed or an expressed restlessness. These individuals may notably lose interest in activities that they once considered pleasurable or experience either loss of appetite or overeating. Experiencing problems concentrating, remembering general facts or details, otherwise making decisions or experiencing relationship difficulties may also be notable factors in these individuals' depression and may also lead to their attempting or actually dying by suicide.

The difference between a depressed mood and Major Depressive Disorder is length of time, ranging from very temporary such as a day to a month, and Major Depressive Disorder which is long-term and life-impacting. The depressive mood can be overcome by lifestyle changes or conversations, whereas Major Depressive Disorder generally requires major intervention with a combination of SSRIs or Dopamine therapy and long-term psychiatric treatments.

Depression is one of the major causes or risk factors of suicide among adolescents, and more than half of the suicide victims in this age group are diagnosed with depressive orders before their demise. Depression among teenagers is also a leading cause of educational and social impairments, substance abuse, obesity, and increased risk of smoking. Expressed insomnia, excessive sleeping, fatigue, and vocalizing general aches, pains, and digestive problems and a reduced energy may also be present in individuals experiencing depression.

**FACTORS/ CAUSES**

- **Life events**

  Adversity in childhood, such as bereavement, neglect, mental abuse, physical abuse, sexual abuse, and unequal parental treatment of siblings can contribute to depression in adulthood. Childhood physical or sexual abuse in particular significantly correlates with the likelihood of experiencing depression over the life course.

  Life events and changes that may precipitate depressed mood include (but are not limited to): childbirth, menopause, financial difficulties, unemployment, stress (such as from work, education, family, living conditions etc.), a medical diagnosis (cancer, HIV, etc.), bullying, loss of a loved one, natural disasters, social isolation, rape, relationship troubles, jealousy, separation, and catastrophic injury. Adolescents may be especially prone to experiencing depressed mood following social rejection, peer pressure and bullying. In addition, culture shock and homesickness are one of the main factors influencing international students. To be more precise, students who experience homesickness might feel alienation from their surroundings, anxiety and depression, especially when they face problems. This can be coupled with low self-esteem, which may make them less confident in public and in social situations.
• **Personality**
High scores on the personality domain neuroticism make the development of depressive symptoms as well as all kinds of depression diagnoses more likely, and depression is associated with low extraversion. Other personality indicators could be: temporary but rapid mood changes, short term hopelessness, loss of interest in activities that used to be a part of one's life, sleep disruption, withdrawal from previous social life, appetite changes, and difficulty concentrating.

• **Gender identity and sexuality**
Studies have shown that those who fall into minorities due to either their gender identity or sexual orientation (such as those that identify as LGBT), are more prone to depression.

• **Medical treatments**
Depression may also be iatrogenic (the result of healthcare), such as drug induced depression. Therapies associated with depression include interferon therapy, beta-blockers, Isotretinoin, contraceptives, cardiac agents, anticonvulsants, antimigraine drugs, antipsychotics, and hormonal agents such as gonadotropin-releasing hormone agonist.

• **Substance-induced**
Several drugs of abuse can cause or exacerbate depression, whether in intoxication, withdrawal, and from chronic use. These include alcohol, sedatives (including prescription benzodiazepines), opioids (including prescription pain killers and illicit drugs such as heroin), stimulants (such as cocaine and amphetamines), hallucinogens, and inhalants.

• **Non-psychiatric illnesses**
Depressed mood can be the result of a number of infectious diseases, nutritional deficiencies, neurological conditions and physiological problems, including hypoandrogenism (in men), Addison's disease, Cushing's syndrome, hypothyroidism, Lyme disease, multiple sclerosis, Parkinson's disease, chronic pain, stroke, diabetes, and cancer.

• **Psychiatric syndromes**
A number of psychiatric syndromes feature depressed mood as a main symptom. The mood disorders are a group of disorders considered to be primary disturbances of mood. These include major depressive disorder (MDD; commonly called major depression or clinical depression) where a person has at least two weeks of depressed mood or a loss of interest or pleasure in nearly all activities; and dysthymia, a state of chronic depressed mood, the symptoms of which do not meet the severity of a major depressive episode. Another mood disorder, bipolar disorder, features one or more episodes of abnormally elevated mood, cognition and energy levels, but may also involve one or more episodes of depression. When the course of depressive episodes follows a seasonal pattern, the disorder (major depressive disorder, bipolar disorder, etc.) may be described as a seasonal affective disorder. Outside the mood disorders: borderline personality disorder often features an extremely intense depressive mood; adjustment disorder with depressed mood is a mood disturbance appearing as a psychological response to an identifiable event or stressor, in which the resulting emotional or behavioral symptoms are significant but do not meet the criteria for a major depressive episode; and posttraumatic stress disorder, a mental disorder that sometimes follows trauma, is commonly accompanied by depressed mood. Depression is sometimes associated with substance use disorders. Both legal and illegal drugs can cause a substance use disorder.
• **Historical legacy**
Researchers have begun to conceptualize ways in which the historical legacies of racism and colonialism may create depressive conditions.

• **Combination of many factors**
The depressed mood can be a combination of many things. A significant life event could possibly trigger onset while other factors are still present. The brain could be lacking optimal stimulation of dopamine or serotonin, and an individual could be abusing alcohol in order to relax after a stressful day of work. All of these factors could total to a depressed mood, while just one of them alone may not cause the mood adjustment. The root cause of depression generally does not have one single factor, but rather a combination of many.

**DIAGNOSIS OR INVESTIGATION OR ASSESSMENT**
The Seasonal Pattern Assessment Questionnaire can be used to screen for seasonal affective disorder. Semi structured interviews such as the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) and the Structured Clinical Interview for DSM-IV (SCID) are used for diagnostic confirmation of depression.

**MANAGEMENT**
Depressed mood may not require professional treatment, and may be a normal temporary reaction to life events, a symptom of some medical condition, or a side effect of some drugs or medical treatments. A prolonged depressed mood, especially in combination with other symptoms, may lead to a diagnosis of a psychiatric or medical condition which may benefit from treatment.
# 1. SCHIZOPHRENIA

<table>
<thead>
<tr>
<th>Specialty</th>
<th>psychiatry, Psychology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>False beliefs, confused thinking, hearing voices others do not</td>
</tr>
<tr>
<td>Usual onset</td>
<td>Typically early adulthood</td>
</tr>
<tr>
<td>Duration</td>
<td>Chronic</td>
</tr>
<tr>
<td>Causes</td>
<td>Environmental and genetic factors</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Family history, cannabis use, problems during pregnancy, being raised in a city, older father</td>
</tr>
<tr>
<td>Diagnostic method</td>
<td>Based on observed behavior, reported experiences, and reports of others familiar with the person</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Substance misuse, Huntington's disease, mood disorders, autism</td>
</tr>
<tr>
<td>Treatment</td>
<td>Counselling, job training</td>
</tr>
<tr>
<td>Medication</td>
<td>Antipsychotics</td>
</tr>
</tbody>
</table>

**Schizophrenia** is a mental disorder characterized by abnormal social behavior and failure to understand reality. Common symptoms include false beliefs, unclear or confused thinking, hearing voices that others do not, reduced social engagement and emotional expression, and a lack of motivation. People with schizophrenia often have additional mental health problems such as anxiety, depressive, or substance-use disorders. Symptoms typically come on gradually, begin in young adulthood, and last a long time.

The causes of schizophrenia include environmental and genetic factors. Possible environmental factors include being raised in a city, cannabis use during adolescence, certain infections, parental age and poor nutrition during pregnancy. Genetic factors include a variety of common and rare genetic variants. Diagnosis is based on observed behavior, the person's reported experiences and reports of others familiar with the person. During diagnosis a person's culture must also be taken into account. As of 2013 there is no objective test. Schizophrenia does not imply a "split personality" or "dissociative identity disorder" – conditions with which it is often confused in public perception.

The mainstay of treatment is antipsychotic medication, along with counselling, job training and social rehabilitation. It is unclear whether typical or atypical antipsychotics are better. In those who do not improve with other antipsychotics clozapine may be tried. In more serious situations where there is risk to self or others involuntary hospitalization may be necessary, although hospital stays are now shorter and less frequent than they once were.

**SIGNS AND SYMPTOMS**

Individuals with schizophrenia may experience hallucinations (most reported are hearing voices), delusions (often bizarre or persecutory in nature), and disorganized thinking and speech. The last
Schizophrenia may range from loss of train of thought, to sentences only loosely connected in meaning, to speech that is not understandable known as word salad. Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgment are all common in schizophrenia. Distortions of self-experience such as feeling as if one's thoughts or feelings are not really one's own to believing thoughts are being inserted into one's mind, sometimes termed passivity phenomena, are also common. There is often an observable pattern of emotional difficulty, for example lack of responsiveness. Impairment in social cognition is associated with schizophrenia, as are symptoms of paranoia. Social isolation commonly occurs. Difficulties in working and long-term memory, attention, executive functioning, and speed of processing also commonly occur. In one uncommon subtype, the person may be largely mute, remain motionless in bizarre postures, or exhibit purposeless agitation, all signs of catatonia. People with schizophrenia often find facial emotion perception to be difficult. It is unclear if the phenomenon called "thought blocking", where a talking person suddenly becomes silent for a few seconds to minutes, occurs in schizophrenia.

People with schizophrenia may have a high rate of irritable bowel syndrome but they often do not mention it unless specifically asked. Psychogenic polydipsia, or excessive fluid intake in the absence of physiological reasons to drink, is relatively common in people with schizophrenia.

- **Symptom organization**
  Schizophrenia is often described in terms of positive and negative (or deficit) symptoms. *Positive symptoms* are those that most individuals do not normally experience, but are present in people with schizophrenia. They can include delusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations, typically regarded as manifestations of psychosis. Hallucinations are also typically related to the content of the delusional theme. Positive symptoms generally respond well to medication. *Negative symptoms* are deficits of normal emotional responses or of other thought processes, and are less responsive to medication. They commonly include flat expressions or little emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. Negative symptoms appear to contribute more to poor quality of life, functional ability, and the burden on others than positive symptoms do. People with greater negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited.

- **Cognitive dysfunction**
  Deficits in cognitive abilities are widely recognized as a core feature of schizophrenia. The deficits impacting the cognitive function are found in a large number of areas: working memory, long-term memory, verbal declarative memory, semantic processing, episodic memory, attention, learning (particularly verbal learning). Deficits in verbal memory are the most pronounced in individuals with schizophrenia, and are not accounted for by deficit in attention. Verbal memory impairment has been linked to a decreased ability in individuals with schizophrenia to semantically encode...
Onset
The onset of the disease is usually later in women than in men. Those who go on to develop schizophrenia may experience transient or self-limiting psychotic symptoms and the non-specific symptoms of social withdrawal, irritability, dysphoria, and clumsiness before the onset of the disease. Children who go on to develop schizophrenia may also demonstrate decreased intelligence, decreased motor development (reaching milestones such as walking slowly), isolated play preference, social anxiety, and poor school performance.

CAUSES
A combination of genetic and environmental factors play a role in the development of schizophrenia.

Genetic
Many genes are known to be involved in schizophrenia, each of small effect and unknown transmission and expression.

Environment
Environmental factors associated with the development of schizophrenia include the living environment, drug use, and prenatal stressors. Maternal stress has been associated with an increased risk of schizophrenia, possibly in association with reelin.

Substance use
About half of those with schizophrenia use drugs or alcohol excessively. Amphetamine, cocaine, and to a lesser extent alcohol, Cannabis can be a contributory factor in schizophrenia.

Developmental factors
Factors such as hypoxia and infection, or stress and malnutrition in the mother during fetal development, may result in a slight increase in the risk of schizophrenia later in life.

PATHOGENESIS (MECHANISMS)
A number of attempts have been made to explain the link between altered brain function and schizophrenia. One of the most common is the dopamine hypothesis, which attributes psychosis to the mind's faulty interpretation of the misfiring of dopaminergic neurons.

Psychological
Despite a demonstrated appearance of blunted affect, recent findings indicate that many individuals diagnosed with schizophrenia are emotionally responsive, particularly to stressful or negative stimuli, and that such sensitivity may cause vulnerability to symptoms or to the disorder. Some evidence suggests that the content of delusional beliefs and psychotic experiences can reflect emotional causes of the disorder, and that how a person interprets such
experiences can influence symptomatology. The use of "safety behaviors" (acts such as gestures or the use of words in specific contexts) to avoid or neutralize imagined threats may actually contribute to the chronicity of delusions. Further evidence for the role of psychological mechanisms comes from the effects of psychotherapies on symptoms of schizophrenia.

- **Neurological**

  Reductions in brain volume are most pronounced in grey matter structures, and correlate with duration of illness, although white matter abnormalities have also been found. A progressive increase in ventricular volume as well as a progressive reduction in grey matter in the frontal, parietal, and temporal lobes has also been observed. These differences have been linked to the neurocognitive deficits often associated with schizophrenia. Because neural circuits are altered, it has alternatively been suggested that schizophrenia could be thought of as a neurodevelopmental disorder with psychosis occurring as a possibly preventable late stage. There has been debate on whether treatment with antipsychotics can itself cause reduction of brain volume.

  Particular attention has been paid to the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that phenothiazine drugs, which block dopamine function, could reduce psychotic symptoms. It is also supported by the fact that amphetamines, which trigger the release of dopamine, may exacerbate the psychotic symptoms in schizophrenia. The influential dopamine hypothesis of schizophrenia proposed that excessive activation of D2 receptors was the cause of (the positive symptoms of) schizophrenia. Although postulated for about 20 years based on the D2 blockade effect common to all antipsychotics, it was not until the mid-1990s that PET and SPET imaging studies provided supporting evidence. While dopamine D2/D3 receptors are elevated in schizophrenia, the effect size is small, and only evident in medication naive schizophrenics. On the other hand, presynaptic dopamine metabolism and released is elevated despite no difference in dopamine transporter. The altered synthesis of dopamine in the nigrostriatal system have been confirmed in several human studies. Hypoactivity of dopamine D1 receptor activation in the prefrontal cortex has also been observed. The hyperactivity of D2 receptor stimulation and relative hypoactivity of D1 receptor stimulation is thought to contribute to cognitive dysfunction by disrupting signal to noise ratio in cortical microcircuits. The dopamine hypothesis is now thought to be simplistic, partly because newer antipsychotic medication (atypical antipsychotic medication) can be just as effective as older medication (typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect.

  Interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in schizophrenia, largely because of the abnormally low levels of glutamate receptors found in the postmortem brains of those diagnosed with schizophrenia, and the discovery that glutamate-blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition. Reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function, and glutamate can affect dopamine function, both of which have been implicated in schizophrenia; this has suggested an important mediating (and possibly causal) role of glutamate pathways in the condition. But positive symptoms fail to respond to glutamatergic medication. Closely related to evidence of glutamate dysfunction in schizophrenia is the observed changes GABAergic transmission. Post-Mortem studies demonstrate decreased expression of GAD67, GAT-1 and
GABA_A receptor subunits in the prefrontal cortex, although this appears to be restricted to a certain subsets of parvalbumin containing GABAergic neurons. While in vivo imaging of GABAergic signaling appears to be moderately reduced, this may be dependent upon treatment and disease stage.

**PATHOGENESIS (MECHANISMS)**
Studies using neuropsychological tests and brain imaging technologies such as fMRI and PET to examine functional differences in brain activity have shown.

**DIFFERENTIAL DIAGNOSIS**
Psychotic symptoms may be present in several other mental disorders, including bipolar disorder, borderline personality disorder, drug intoxication, and drug-induced psychosis. Delusions ("non-bizarre") are also present in delusional disorder, and social withdrawal in social anxiety disorder, avoidant personality disorder and schizotypal personality disorder. Schizotypal personality disorder has symptoms that are similar but less severe than those of schizophrenia. Schizophrenia occurs along with obsessive-compulsive disorder (OCD) considerably more often than could be explained by chance, although it can be difficult to distinguish obsessions that occur in OCD from the delusions of schizophrenia. A few people withdrawing from benzodiazepines experience a severe withdrawal syndrome which may last a long time. It can resemble schizophrenia and be misdiagnosed as such.

A more general medical and neurological examination may be needed to rule out medical illnesses which may rarely produce psychotic schizophrenia-like symptoms, such as metabolic disturbance, systemic infection, syphilis, AIDS dementia complex, epilepsy, limbic encephalitis, and brain lesions. Stroke, multiple sclerosis, hyperthyroidism, hypothyroidism, and dementias such as Alzheimer's disease, Huntington's disease, frontotemporal dementia, and the Lewy body dementias may also be associated with schizophrenia-like psychotic symptoms.

**PREVENTION**
Cognitive behavioral therapy may reduce the risk of psychosis in those at high risk after a year. Another preventative measure is to avoid drugs that have been associated with development of the disorder, including cannabis, cocaine, and amphetamines.

**MANAGEMENT**
The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports. Some evidence indicates that regular exercise has a positive effect on the physical and mental health of those with schizophrenia.

- **Medication**
The first-line psychiatric treatment for schizophrenia is antipsychotic medication, which can reduce the positive symptoms of psychosis in about 7 to 14 days. Antipsychotics, however, fail to significantly improve the negative symptoms and cognitive dysfunction.
• **Psychosocial**

A number of psychosocial interventions may be useful in the treatment of schizophrenia including: family therapy, assertive community treatment, supported employment, cognitive remediation, skills training, token economic interventions, and psychosocial interventions for substance use and weight management. Family therapy or education, which addresses the whole family system of an individual, may reduce relapses and hospitalizations.
1. ALZHEIMER’S DISEASE (AD)

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer's disease.

Synonyms
Alzheimer disease, Alzheimer's

**Figure: 1.1** comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right). Characteristics that separate the two are pointed out.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Neurology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Difficulty in remembering recent events, problems with language, disorientation, mood swings</td>
</tr>
<tr>
<td>Usual onset</td>
<td>Over 65 years old</td>
</tr>
<tr>
<td>Duration</td>
<td>Long term</td>
</tr>
<tr>
<td>Causes</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Genetics, head injuries, depression, hypertension</td>
</tr>
<tr>
<td>Diagnostic method</td>
<td>Based on symptoms and cognitive testing after ruling out other possible causes</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Normal aging</td>
</tr>
<tr>
<td>Medication</td>
<td>Acetylcholinesterase inhibitors, NMDA receptor antagonists (small benefit)</td>
</tr>
</tbody>
</table>

Alzheimer's disease (AD), also referred to simply as Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and worsens over time. It is the cause of 60–70% of cases of dementia. The most common early symptom is difficulty in remembering recent...
events (short-term memory loss). As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues. As a person's condition declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death.[10] Although the speed of progression can vary, the typical life expectancy following diagnosis is three to nine years.

The cause of Alzheimer's disease is poorly understood. About 70% of the risk is believed to be genetic with many genes usually involved. Other risk factors include a history of head injuries, depression, or hypertension. The disease process is associated with plaques and tangles in the brain. A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes. Initial symptoms are often mistaken for normal ageing. Examination of brain tissue is needed for a definite diagnosis. Mental and physical exercise, and avoiding obesity may decrease the risk of AD; however, evidence to support these recommendations is not strong. There are no medications or supplements that have been shown to decrease risk.

No treatments stop or reverse its progression, though some may temporarily improve symptoms. Affected people increasingly rely on others for assistance, often placing a burden on the caregiver; the pressures can include social, psychological, physical, and economic elements. Exercise programmes may be beneficial with respect to activities of daily living and can potentially improve outcomes. Behavioural problems or psychosis due to dementia are often treated with antipsychotics, but this is not usually recommended, as there is little benefit with an increased risk of early death.

SIGNS AND SYMPTOMS

- Stages of Alzheimer's disease:

Effects of ageing on memory but not AD

- Forgetting things occasionally
- Misplacing items sometimes
- Minor short-term memory loss
- Not remembering exact details

Early stage Alzheimer's

- Not remembering episodes of forgetfulness
- Forgets names of family or friends
- Changes may only be noticed by close friends or relatives
- Some confusion in situations outside the familiar

Middle stage Alzheimer's

- Greater difficulty remembering recently learned information
- Deepening confusion in many circumstances
- Problems with sleep

Pathophysiology B.Pharmacy II semester

JAIPUR COLLEGE OF PHARMACY, JAIPUR
By: K S Dhakad (Asst. Professor- Pharmacology)  

**Alzheimer’s Disease (AD)**

- Trouble knowing where they are

<table>
<thead>
<tr>
<th>Late stage Alzheimer’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Poor ability to think</td>
</tr>
<tr>
<td>• Problems speaking</td>
</tr>
<tr>
<td>• Repeats same conversations</td>
</tr>
<tr>
<td>• More abusive, anxious, or paranoid</td>
</tr>
</tbody>
</table>

I) **Pre-dementia**

The first symptoms are often mistakenly attributed to ageing or stress. Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before a person fulfils the clinical criteria for diagnosis of AD. These early symptoms can affect the most complex activities of daily living. The most noticeable deficit is short term memory loss, which shows up as difficulty in remembering recently learned facts and inability to acquire new information. Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings, and concept relationships) can also be symptomatic of the early stages of AD. Apathy can be observed at this stage, and remains the most persistent neuropsychiatric symptom throughout the course of the disease. Depressive symptoms, irritability and reduced awareness of subtle memory difficulties are also common. The preclinical stage of the disease has also been termed mild cognitive impairment (MCI). This is often found to be a transitional stage between normal ageing and dementia. MCI can present with a variety of symptoms, and when memory loss is the predominant symptom, it is termed "amnestic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease.

II) **Early**

In people with AD, the increasing impairment of learning and memory eventually leads to a definitive diagnosis. In a small percentage, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems. AD does not affect all memory capacities equally. Older memories of the person's life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat or how to drink from a glass) are affected to a lesser degree than new facts or memories. Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, leading to a general impoverishment of oral and written language. In this stage, the person with Alzheimer's is usually capable of communicating basic ideas adequately. While performing fine motor tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present, but they are commonly unnoticed. As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities.

III) **Moderate**

Progressive deterioration eventually hinders independence, with subjects being unable to perform most common activities of daily living. Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions (paraphasias). Reading and writing skills are also progressively lost. Complex motor sequences become less coordinated as time passes and AD progresses, so the risk of falling increases. During this phase,
By: K S Dhakad (Asst. Professor - Pharmacology)  
Alzheimer’s Disease (AD)

memory problems worsen, and the person may fail to recognise close relatives. Long-term memory, which was previously intact, becomes impaired. Behavioural and neuropsychiatric changes become more prevalent. Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving. Sundowning can also appear. Approximately 30% of people with AD develop illusionary misidentifications and other delusional symptoms. Subjects also lose insight of their disease process and limitations (anosognosia). Urinary incontinence can develop. These symptoms create stress for relatives and carers, which can be reduced by moving the person from home care to other long-term care facilities.

IV) Advanced
During the final stages, the patient is completely dependent upon caregivers. Language is reduced to simple phrases or even single words, eventually leading to complete loss of speech. Despite the loss of verbal language abilities, people can often understand and return emotional signals. Although aggressiveness can still be present, extreme apathy and exhaustion are much more common symptoms. People with Alzheimer's disease will ultimately not be able to perform even the simplest tasks independently; muscle mass and mobility deteriorates to the point where they are bedridden and unable to feed themselves. The cause of death is usually an external factor, such as infection of pressure ulcers or pneumonia, not the disease itself.

CAUSE

- Genetic
- Cholinergic hypothesis
- Amyloid hypothesis
- Tau hypothesis
- Other hypotheses

The cause for most Alzheimer's cases is still mostly unknown except for 1% to 5% of cases where genetic differences have been identified. Several competing hypotheses exist trying to explain the cause of the disease.

i.) Genetic
The genetic heritability of Alzheimer's disease (and memory components thereof), based on reviews of twin and family studies, ranges from 49% to 79%. Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age 65.

Most cases of Alzheimer's disease do not exhibit autosomal-dominant inheritance and are termed sporadic AD, in which environmental and genetic differences may act as risk factors. The best known genetic risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE).

ii.) Cholinergic hypothesis
cholinergic hypothesis, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective.

Pathophysiology B.Pharmacy II semester

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iii.) Amyloid hypothesis
The *amyloid hypothesis* postulated that extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age. Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. While apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.

iv.) Tau hypothesis
The *tau hypothesis* proposes that tau protein abnormalities initiate the disease cascade. When this occurs, the microtubules disintegrate, destroying the structure of the cell's cytoskeleton which collapses the neuron's transport system. AD is also considered a tauopathy due to abnormal aggregation of the tau protein. Every neuron has a cytoskeleton, an internal support structure partly made up of structures called microtubules. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back. A protein called *tau* stabilises the microtubules when phosphorylated, and is therefore called a microtubule-associated protein. In AD, tau undergoes chemical changes, becoming hyperphosphorylated; it then begins to pair with other threads, creating neurofibrillary tangles and disintegrating the neuron's transport system.

This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.

v.) Other hypotheses
A neurovascular hypothesis has been proposed which states that poor functioning of the blood–brain barrier may be involved.

The cellular homeostasis of biometals such as ionic copper, iron, and zinc is disrupted in AD, though it remains unclear whether this is produced by or causes the changes in proteins. These ions affect and are affected by tau, APP, and APOE, and their dysregulation may cause oxidative stress that may contribute to the pathology.

Smoking is a significant AD risk factor. Systemic markers of the innate immune system are risk factors for late-onset AD.

There is tentative evidence that exposure to air pollution may be a contributing factor to the development of Alzheimer's disease.

**PATHOPHYSIOLOGY**

Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Degeneration is also present in brainstem nuclei like the locus coeruleus. Studies using MRI and PET have documented reductions in the size of specific brain regions in people with AD as they progressed from mild cognitive impairment to Alzheimer's disease, and in comparison with similar images from healthy older adults.
Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD. Plaques are dense, mostly insoluble deposits of beta-amyloid peptide and cellular material outside and around neurons.

- **Disease mechanism**

Exactly how disturbances of production and aggregation of the beta-amyloid peptide give rise to the pathology of AD is not known. The amyloid hypothesis traditionally points to the accumulation of beta-amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation of glucose by neurons.

Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response. There is increasing evidence of a strong interaction between the neurons and the immunological mechanisms in the brain. Obesity and systemic inflammation may interfere with immunological processes which promote disease progression.

**DIAGNOSIS**

Alzheimer's disease is usually diagnosed based on the person's medical history, history from relatives, and behavioural observations. The presence of characteristic neurological and neuropsychological features and the absence of alternative conditions is supportive. Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. Moreover, it may predict conversion from prodromal stages (mild cognitive impairment) to Alzheimer's disease. Assessment of intellectual functioning including memory testing can further characterise the state of the disease.

**PREVENTION**

There is no definitive evidence to support that any particular measure is effective in preventing AD. However Intellectual activities such as playing chess or regular social interaction have been linked to a reduced risk of AD. certain modifiable factors, such as diet, cardiovascular risk, pharmaceutical products, or intellectual activities among others, and a population's likelihood of developing AD.

- **Medication**

Although cardiovascular risk factors, such as hypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of AD, statins, which are cholesterol lowering drugs, have not been effective in preventing or improving the course of the disease.
People who engage in intellectual activities such as reading, playing board games, completing crossword puzzles, playing musical instruments, or regular social interaction show a reduced risk for Alzheimer's disease. This is compatible with the cognitive reserve theory, which states that some life experiences result in more efficient neural functioning providing the individual a cognitive reserve that delays the onset of dementia manifestations. Education delays the onset of AD syndrome without changing the duration of the disease. Learning a second language even later in life seems to delay getting Alzheimer disease. Physical activity is also associated with a reduced risk of AD. Physical exercise is associated with decreased rate of dementia.

Diet
People who maintain a healthy, Japanese, or Mediterranean diet have a reduced risk of AD. A Mediterranean diet may improve outcomes in those with the disease. Those who eat a diet high in saturated fats and simple carbohydrates (mono- and disaccharide) have a higher risk. There is limited evidence that light to moderate use of alcohol, particularly red wine, is associated with lower risk of AD. There is tentative evidence that caffeine may be protective. A number of foods high in flavonoids such as cocoa, red wine, and tea may decrease the risk of AD.

MANAGEMENT
There is no cure for Alzheimer's disease; available treatments offer relatively small symptomatic benefit but remain palliative in nature. Current treatments can be divided into pharmaceutical, psychosocial and caregiving. Five medications are currently used to treat the cognitive problems of AD: four are acetylcholinesterase inhibitors (tacrine, rivastigmine, galantamine and donepezil) and the other (memantine) is an NMDA receptor antagonist. Glutamate is an excitatory neurotransmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors. Excitotoxicity occurs not only in Alzheimer's disease, but also in other neurological diseases such as Parkinson's disease and multiple sclerosis. Memantine is a noncompetitive NMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate. Atypical antipsychotics are modestly useful in reducing aggression and psychosis in people with Alzheimer's disease,
### 2. PEPTIC ULCER DISEASE

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Upper abdominal pain, belching, vomiting, weight loss, poor appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>Bleeding, perforation, blockage of the stomach</td>
</tr>
<tr>
<td>Causes</td>
<td><em>Helicobacter pylori</em>, non-steroidal anti-inflammatory drugs, tobacco smoking, Crohn disease</td>
</tr>
<tr>
<td>Diagnostic method</td>
<td>Based on symptoms, confirmed by endoscopy or barium swallow[^1]</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Stomach cancer, coronary heart disease, inflammation of the stomach lining, gallbladder inflammation</td>
</tr>
<tr>
<td>Treatment</td>
<td>Stopping smoking, stopping NSAIDs, stopping alcohol, medications[^1]</td>
</tr>
<tr>
<td>Medication</td>
<td>Proton pump inhibitor, H2 blocker, antibiotics</td>
</tr>
</tbody>
</table>

**Peptic ulcer disease (PUD)** is a break in the inner lining of the stomach, the first part of the small intestine, or sometimes the lower esophagus. An ulcer in the stomach is called a **gastric ulcer**, while one in the first part of the intestines is a **duodenal ulcer**. The most common symptoms of a duodenal ulcer are waking at night with upper abdominal pain and upper abdominal pain that improves with eating. With a gastric ulcer, the pain may worsen with eating. The pain is often described as a burning or dull ache. Other symptoms include belching, vomiting, weight loss, or poor appetite. About a third of older people have no symptoms. Complications may include bleeding, perforation, and blockage of the stomach. Bleeding occurs in as many as 15% of cases.

Common causes include the bacteria *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs). Other, less common causes include tobacco smoking, stress due to serious illness, Behcet disease, Zollinger-Ellison syndrome, Crohn disease, and liver cirrhosis. Older people are more sensitive to the ulcer-causing effects of NSAIDs. The diagnosis is typically suspected due to the presenting symptoms with confirmation by either endoscopy or barium swallow. *H. pylori* can be diagnosed by testing the blood for antibodies, a urea breath test, testing the stool for signs of the bacteria, or a biopsy of the stomach. Other conditions that produce similar symptoms include stomach cancer, coronary heart disease, and inflammation of the stomach lining or gallbladder inflammation.

Diet does not play an important role in either causing or preventing ulcers. Treatment includes stopping smoking, stopping use of NSAIDs, stopping alcohol, and taking medications to decrease stomach acid. The medication used to decrease acid is usually either a proton pump inhibitor (PPI) or an H2 blocker, with four weeks of treatment initially recommended. Ulcers due to *H. pylori* are treated with a combination of medications, such as amoxicillin, clarithromycin, and a PPI. Antibiotic resistance is increasing and thus treatment may not always be effective.[^4] Bleeding ulcers may be treated by endoscopy, with open surgery typically only used in cases in which it is not successful.

[^1]: [1]
[^4]: [4]
SIGNS AND SYMPTOMS

Signs and symptoms of a peptic ulcer can include one or more of the following:

- Abdominal Pain, classically epigastric, strongly correlated with mealtimes. In case of duodenal ulcers, the pain appears about three hours after taking a meal and wakes the person from sleep;
- Bloating and abdominal fullness;
- Waterbrash (a rush of saliva after an episode of regurgitation to dilute the acid in esophagus, although this is more associated with gastroesophageal reflux disease);
- Nausea and copious vomiting;
- Loss Of Appetite and weight loss, in gastric ulcer;
- Weight gain, in duodenal ulcer, as the pain is relieved by eating;
- Hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer or from damage to the esophagus from severe/continuing vomiting.
- Melena (tarry, foul-smelling feces due to presence of oxidized iron from hemoglobin);
- Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis and extreme, stabbing pain, and requires immediate surgery.

A history of heartburn or gastroesophageal reflux disease (GERD) and use of certain medications can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAIDs (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase and most glucocorticoids (e.g., dexamethasone and prednisolone).

A burning or gnawing feeling in the stomach area lasting between 30 minutes and 3 hours. This pain can be misinterpreted as hunger, indigestion, or heartburn. Pain is usually caused by the ulcer, but it may be aggravated by the stomach acid. It can commonly be temporarily relieved by eating foods that buffer stomach acid or by taking anti-acid medication.

COMPLICATIONS

- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening.
- Perforation (a hole in the wall of the gastrointestinal tract) following a gastric ulcer often leads to catastrophic consequences if left untreated.
- Perforation (a hole in the wall of the gastrointestinal tract) following a gastric ulcer often leads to catastrophic consequences if left untreated.
- Cancer is included in the differential diagnosis (elucidated by biopsy), Helicobacter pylori as the etiological factor making it

CAUSE

- **H. pylori**

_Helicobacter pylori_ is one of the major causative factors of peptic ulcer disease. It secretes urease to create an alkaline environment, which is suitable for its survival. It expresses
blood group antigen adhesin (BabA) and outer inflammatory protein adhesin (OipA), which enables it to attach to the gastric epithelium.

- **NSAIDs**
  Taking nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin can increase the risk of peptic ulcer disease by four times compared to non-users.
  Risk of bleeding increases if NSAIDs are combined with selective serotonin reuptake inhibitor (SSRI), corticosteroids, antimineralocorticoids, and anticoagulants. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (COX-1), which is essential for the production of these prostaglandins. Besides this, NSAIDs also inhibit stomach mucosa cells proliferation and mucosal blood flow, reducing bicarbonate and mucus secretion, which reduces the integrity of the mucosa.
  Another type of NSAIDs, called COX-2 selective anti-inflammatory drugs (such as celecoxib), preferentially inhibit COX-2, which is less essential in the gastric mucosa. This reduces the probability of getting peptic ulcers.

- **Stress**
  Stress due to serious health problems, which are also known as stress ulcers.

- **Diet**
  Dietary factors, such as spice consumption, were hypothesized to cause ulcers. Caffeine and coffee, also commonly thought to cause or exacerbate ulcers, alcohol consumption increases risk when associated with *H. pylori* infection.

- **Other**
  Other causes of peptic ulcer disease include gastric ischaemia, drugs, metabolic disturbances, cytomegalovirus (CMV), upper abdominal radiotherapy, Crohn's disease, and vasculitis. Gastrinomas (Zollinger–Ellison syndrome), or rare gastrin-secreting tumors.

**DIAGNOSIS**

The diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer.

Confirmation of the diagnosis is made with the help of tests such as endoscopies or barium contrast x-rays. An esophagastroduodenoscopy (EGD), a form of endoscopy, also known as a gastroscopy, is carried out on people in whom a peptic ulcer is suspected.

The diagnosis of *Helicobacter pylori* can be made by:
- Urea breath test (noninvasive and does not require EGD)
- Direct detection of urease activity in a biopsy specimen by rapid urease test.
- Stool antigen test;
- Histological examination and staining of an EGD biopsy

**DIFFERENTIAL DIAGNOSIS**

Conditions that may appear similar include:
By: K S Dhakad (Asst. Professor- Pharmacology)

**Epilepsy & Peptic Ulcer**

- Gastritis
- Stomach cancer
- Gastroesophageal reflux disease
- Pancreatitis
- Hepatic congestion
- Cholecystitis
- Biliary colic
- Inferior myocardial infarction
- Referred pain (pleurisy, pericarditis)
- Superior mesenteric artery syndrome

**PREVENTION**

Prevention of peptic ulcer disease for those who are taking NSAIDs can be achieved by adding a proton pump inhibitor (PPI), an H$_2$ antagonist, or misoprostol. NSAIDs of the COX-2 inhibitors type may reduce the rate of ulcers when compared to non-selective NSAIDs.

**MANAGEMENT**

- **Eradication therapy**
  Once the diagnosis of *H. pylori* is confirmed, the first-line treatment would be a triple regimen in which pantoprazole and clarithromycin are combined with either amoxicillin or metronidazole. This treatment regimen can be given for 7–14 days.

- **NSAIDs induced ulcers**
  NSAID-associated ulcers heal in 6 to 8 weeks provided the NSAIDs are withdrawn with the introduction of proton pump inhibitors (PPI).

- **Bleeding**
  For those with bleeding peptic ulcers, fluid replacement with crystalloids should be given to maintain volume in the blood vessels. Tranexamic acid and antifibrinolytic agents are not useful in treating peptic ulcer disease. Intravenous PPIs can suppress stomach bleeding more quickly than oral ones.